28 February 2019
EMA/208498/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lynparza

International non-proprietary name: olaparib

Procedure No. EMEA/H/C/003726/II/0020

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

ADR	Adverse drug reaction
AE(s)	Adverse event(s)
AML	Acute myeloid leukaemia
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under plasma concentration-time curve
AUCss	Area under plasma concentration-time curve during any dosing interval at steady state
bd	Twice daily
BGI *gBRCA* test	Analysis of the *BRCA1* and *BRCA2* genes performed by the BGI Clinical Laboratory in China (Shenzen)
BICR	Blinded independent central review
BoR	Best overall response
BRCA	Breast cancer susceptibility gene (in accordance with scientific convention, gene and mutation is italicised whereas protein is not italicised)
BRCAm	*gBRCA* or s*BRCA-mutated*
BRCAwt/VUS	*gBRCA* and s*BRCA* wildtype/variant of uncertain significance
CDx	Companion diagnostic
CDS	Core Data Sheet
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
Cmax (Cmax ss)	Maximum plasma concentration (at steady state)
Cmin (Cmin ss)	Minimum plasma concentration (at steady state)
CR	Complete response
CrCL	Creatinine clearance
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Common Technical Document
CTSQ	Cancer Therapy Satisfaction Questionnaire
CYP	Cytochrome P450
DCO	Data cut-off
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
DoR	Duration of Response
DSBs	(DNA) double-strand breaks
ECOG	Eastern Cooperative Oncology Arm
eCRF	Electronic case report form
EFR	Evaluable for response
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ER	Estrogen receptor
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIGO	Fédération Internationale de Gynécologie Obstérique (International Federation of Gynaecology and Obstetrics)
FTIM	First time in man
gBRCAm	Germline *BRCA-mutated*
gBRCAwt/VUS	Germline *BRCA* wildtype/variant of uncertain significance
GVP	Good Pharmacovigilance Practices
h	Hours
Hb	Haemoglobin
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRD	Homologous recombination deficient/deficiency
HRQoL	Health-related quality of life
HRR	Homologous recombination repair

ICH	International Council for Harmonisation
IND	Investigational new drug
IVIVC	*in vitro-in vivo* correlation
ITT	Intention-to-treat
iv	Intravenous
IVRS	Interactive voice response system
MATE	Human Multi-Drug And Toxin Extrusion Transporter
MCV	Mean corpuscular volume
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MTP	Multiple testing procedure
N	Total number of patients
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NDA	New Drug Application
NE	Not estimable
NR	Not reported
OAT	Organic anion transporter
OATP	Organic anion-transporting polypeptide
OCT	Organic cation-transporter
ORR	Objective response rate
OS	Overall survival
PARP	Polyadenosine 5'diphosphoribose polymerase
PBPK	Physiologically-based pharmacokinetic
PD	Pharmacodynamics
PFS	Progression-free survival
PFS2	Time from start of randomisation to second progression or death
P-gp	P-glycoprotein
PgR	Progesterone receptor
PK	Pharmacokinetics
POC	Proof-of-concept
PPE	Palmar-plantar erythrodysaesthesia
PR	Partial response
PRO	Patient reported outcomes
PSR	Platinum-sensitive relapsed
PT	Preferred term
QC	Quality control
qd	Once daily
QLQ-C30	Quality of Life Questionnaire Core 30 item module
QoL	Quality of life
QSR	Quality Systems Regulation
QT	Electrocardiogram interval measured from the beginning of the QRS complex to the end of the T wave
QTcF	QT interval corrected for heart rate using Fridericia correction
QTcI	QT interval corrected for heart rate using individual-specific correction
RECIST	Response Evaluation Criteria in Solid Tumours
RMP	Risk management plan
SAE	Serious adverse event
SAP	Statistical analysis plan
sBRCA	Somatic *BRCA* (*BRCA* variant found in the tumour but not in the germline)
sBRCA VUS	Somatic *BRCA* variant of uncertain significance
sBRCAm	Somatic *BRCA*-mutated
sd	Standard deviation
SEER	Surveillance, Epidemiology and End Results
SOC	System organ class
SmPC	Summary of Product Characteristics
sNDA	Supplemental new drug application
tBRCAm	Tumour *BRCA*-mutated
tBRCAwt/VUS	Tumour *BRCA* wild type/variant of uncertain signifance
TEAE	Treatment emergent adverse event
TFST	Time to first subsequent therapy or death (defined as time from randomisation to start of first subsequent therapy or death [ie, following discontinuation of randomised study treatment])
TNBC	Triple negative breast cancer

TNT	Triple Negative Trial
TIM-1	TNO Intestinal Model
TSST	Time to second subsequent therapy or death (defined as time from randomisation to the start of second subsequent therapy or death)
TTP	Time to progression
UGT	UDP-glucuronosyltransferase
ULN	Upper limit of normal
vs	Versus
VUS	Variants of uncertain significance
WBC	White blood cell
wt	Wildtype

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 12 March 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 tablets as a monotherapy for the treatment of adult patients with BRCA1/2-mutated HER2 negative metastatic breast cancer who have previously been treated with chemotherapy; these patients could have received chemotherapy in the neoadjuvant, adjuvant or metastatic setting. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC for Lynparza tablets are updated. Section 4.8 of the SmPC for the Lynparza capsules and relevant sections of the package leaflet have been updated accordingly. Furthermore, RMP version 16 has also been provided.

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 CW/1/2011 on the granting of a class waiver.

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 applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant requested Scientific Advice to the CHMP related to clinical aspects of the dossier.

The MAH received scientific advice pertaining to clinical aspects of the dossier from the CHMP on 21/01/2010 (EMA/CHMP/SAWP/61318/2010) related to an early study design that the MAH did not pursue and follow-up scientific advice on 25/07/2013 (EMEA/H/SA/1215/2/FU/1/2013/II) in regard to new design of the study.

In the second scientific advice, the CHMP advised that HER2-positive patients be excluded from this trial as there are other therapeutic options that have a demonstrated survival benefit in the relapsed setting and the proportion of patients with BRCA 1/2-mutated and HER2-positive breast cancer is considered very small, to which the applicant agreed. Only hormone receptor positive patients who failed at least one hormonal treatment or were unsuitable for hormonal therapy were allowed into the trial. The MAH proposed to include ER and/or PgR+ patients after progression on one or more lines of endocrine treatment. Including ER/PR positive patients after progression on one endocrine treatment while subsequent anti-hormonal agents can be active, was considered acceptable at the discretion of the treating physician, as a switch to another anti-hormonal agent was not considered feasible due to short or no response to 1st-line treatment, although this could be subjective.

The Applicant was asked to define in more detail in the protocol “suitable for single-agent chemotherapy”, e.g. in relation to different lines of chemotherapy. In the first-line metastatic setting, for example, this could mean poor tolerability or early relapse on prior adjuvant anthracycline/taxane therapy.

The CHMP highlighted the need to study a homogenous population for ease of assessment, such as limiting to second and third line patients. However, feasibility to do as such was considered challenging and therefore, applicant also included first line patients.

Regarding the physician’s choice of capecitabine, vinorelbine, or eribulin as a comparator arm in the OlympiAD study, the CHMP questioned the absence of a platinum therapy as a treatment option. In the first-line metastatic setting, and especially in case of BRCA1 mutations, it was considered likely that many clinicians would opt for cisplatin or carboplatin alone or in combination with gemcitabine or paclitaxel, especially in symptomatic or early progressive disease. Enrolment criteria would exclude these patients.

Whilst resistance to prior platinum-based therapy as exclusion criterion was accepted due to expected cross-resistance to PARP inhibitors, it was harder to accept, and not understood, that platinum therapy is not an option as a comparator.

The use of the more common dose of capecitabine of 1000 mg/m^2 was recommended. However, a dose of 2500 mg/m^2 was used in OlympiAD, to be consistent with the prescribing information.

PFS as a primary endpoint for OlympiAD was proposed due to the relatively small target population and the expected crossover to alternative PARP inhibitors after progression in the control arm, and due to other sequential treatment options. The CHMP recommended that patients be followed for PFS2; PFS2 as assessed by investigators is a secondary endpoint in OlympiAD.

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	12 March 2018
Start of procedure:	31 March 2018
CHMP Co-Rapporteur Assessment Report	1 June 2018
CHMP Rapporteur Assessment Report	25 May 2018
PRAC Rapporteur Assessment Report	5 June 2018
PRAC members comments	6 June 2018
Updated PRAC Rapporteur Assessment Report	8 June 2018
PRAC Outcome	14 June 2018
CHMP members comments	18 June 2018
Updated CHMP Rapporteur(s) (Joint) Assessment Report	22 June 2018
Request for supplementary information (RSI)	28 June 2018
CHMP Rapporteur Assessment Report	21 August 2018
PRAC Rapporteur Assessment Report	24 August 2018
PRAC members comments	29 August 2018
Updated PRAC Rapporteur Assessment Report	27 August 2018
PRAC Outcome	6 September 2018
CHMP members comments	10 September 2018
Updated CHMP Rapporteur Assessment Report	14 September 2018
2nd Request for supplementary information (RSI)	20 September 2018
CHMP Rapporteur Assessment Report	22 October 2018
PRAC Rapporteur Assessment Report	16 November 2018
PRAC members comments	21 November 2018
PRAC Outcome	29 November 2018
CHMP members comments	3 December 2018
Updated CHMP Rapporteur Assessment Report	7 December 2018
3rd Request for supplementary information (RSI)	13 December 2018
CHMP Rapporteur Assessment Report	14 February 2019
CHMP members comments	26 February 2019
Opinion	28 February 2019

2. Scientific discussion

2.1. Introduction

2.1.1. Disease or condition

The claimed indication is for the treatment of adult patients with BRCA1/2-mutated HER2 negative metastatic breast cancer who have previously been treated with chemotherapy.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Breast cancer is a life-threatening disease and is the second leading cause of cancer death among women and the fourth leading cause of cancer death overall[1].

In 2018, it is estimated that there will be 268,670 newly diagnosed breast cancer cases in the US, and approximately 41,400 people will die from breast cancer[1]. Across 40 European countries, the estimated age-adjusted annual incidence in 2012 was 92.8/100,000 and the mortality 23.1/100,000[2].

2.1.3. Biologic features

Approximately 5% of breast cancers are associated with a germline mutation in the BRCA1 and/or BRCA2 gene with approximately 3% associated with the BRCA2 gene (generally hormone receptor positive). The presence of BRCA1 mutations is associated with a lifetime risk of breast cancer ranging from 60% to 70% (Antoniou et al 2003). BRCA2 mutations are associated with a lifetime risk of breast cancer between 40% to 60% in women and 5% to 10% in men.

Approximately 70% of BRCA1 mutated breast cancer present as triple negative breast cancer (TNBC). In contrast, breast cancer patients carrying mutations in the BRCA2 gene are more likely to be positive for expression of the estrogen receptor (ER) and PgR and only approximately 20% are TNBC[3].

Although there are phenotypic differences in breast cancers resulting from gBRCA1 or gBRCA2 mutations, their important commonality is that mutations in either gene could result in development of tumours that are deficient in homologous recombination.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

The diagnosis of breast cancer is based on clinical examination in combination with imaging, and confirmed by pathological assessment. Disease stage is assessed according to the TNM system (ESMO clinical practice guideline). Although treatable, metastatic breast cancer (MBC) remains an incurable disease with a median overall survival (OS) of approximately 3 years and a 5-year survival of only approximately 25%[4],[5].

[1] American Cancer Society 2018
[2] EUCAN 2017
[3] Mavaddat et al 2012
[4] Cardoso F, Spence D, Mertz S et al. Global analysis of advanced/metastatic breast cancer: decade report (2005–2015). Breast 2018; 39:131–138.
[5] Howlader N, Noone AM, Krapcho M et al. (eds). SEER Cancer Statistics Review, 1975–2013. Bethesda, MD: National Cancer Institute. http://seer.cancer.gov/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER web site, April 2016.

2.1.5. Management

The selection of appropriate therapy for advanced breast cancer comprising locally advanced and metastatic breast cancer is complex because of the many treatment options and biologic heterogeneity of the disease (ABC4 consensus guidelines). The potential treatment options are determined in accordance with ER and PR and HER2 status of the tumour. Treatment options for patients presenting with metastatic breast cancer may also be influenced by what adjuvant therapy was used, how soon after adjuvant therapy the patient relapses, and by sites of metastasis.

For patients with HER2-negative metastatic breast cancer, there is no preferred first-line chemotherapy. Sequential monotherapy with single agent capecitabine, vinorelbine, or eribulin are among the preferred choices in metastatic breast cancer patients previously treated with an anthracycline and a taxane in the adjuvant or metastatic setting and for whom further hormonal treatments are not indicated[6]. Additional choices include gemcitabine, platinum agents, taxanes and liposomal anthracyclines[7]. Combination chemotherapy is reserved for patients with rapid clinical progression, life-threatening visceral metastases, or need for rapid symptom and/or disease control[6,7].

Currently, single agent chemotherapy after previous exposure to anthracyclines and taxanes has a median progression free survival (PFS) of approximately 4 months and an overall survival (OS) of 9 to 16 months when given early in the metastatic setting.

There is no targeted therapy available to date for the treatment of TNBC. The prognosis for patients with TNBC and/or those who carry gBRCA1 mutations with metastatic disease may even be worse than the overall metastatic breast cancer population. According to current NCCN guidelines (2018), carboplatin is considered as one of recommended regimens for recurrent or metastatic disease. In advanced TNBC patients (regardless of BRCA status) previously treated with anthracyclines with or without taxanes in the (neo)adjuvant setting, carboplatin showed comparable efficacy and a more favourable toxicity profile, compared with docetaxel, and is considered, therefore, an important treatment option. However in patients with BRCA-associated advanced TNBC or endocrine-resistant advanced breast cancer a platinum regimen is considered as a preferred option, if not previously administered[7].

For the treatment of hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer, CDK4/6 inhibitors have been recently approved in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy.

Everolimus, an mTOR inhibitor, is also approved for the treatment of hormone receptor-positive, HER2 negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor.

There are currently no treatments approved in the European Union (EU) specifically for BRCAm patients with metastatic breast cancer and these patients are treated according to their hormone receptor and HER2 status.

About the product

Olaparib is a potent inhibitor of human poly (ADP-ribose) polymerase enzymes (PARP-1, PARP-2, and PARP-3), and has been shown to inhibit the growth of selected tumour cell lines in vitro and tumour growth in vivo either as a standalone treatment or in combination with established chemotherapies.

PARPs are required for the efficient repair of DNA single strand breaks and an important aspect of PARP-induced repair requires that after chromatin modification, PARP auto-modifies itself and dissociates from

[6] NCCN 2017
[7] ESMO ABC4

the DNA to facilitate access for base excision repair (BER) enzymes. When olaparib is bound to the active site of DNA-associated PARP it prevents the dissociation of PARP and traps it on the DNA, thus blocking repair. In replicating cells this also leads to the formation of DNA double-strand breaks (DSBs) when replication forks meet the PARP-DNA adducts. In normal cells, homologous recombination repair (HRR) pathway is effective at repairing these DNA DSBs. In cancers that lack functional components of HRR such as BRCA1 or 2, DNA DSBs cannot be repaired accurately or effectively. Instead, alternative and error-prone pathways are activated, such as the classical non-homologous end joining (NHEJ) pathway, leading to increased genomic instability. After a number of rounds of replication, genomic instability can reach insupportable levels and result in cancer cell death, as cancer cells already have a high DNA damage load relative to normal cells. In the absence of BRCA1 or BRCA2 mutations, HRR pathway may be compromised by other mechanisms, although the causative aberrancy and penetrance are not fully elucidated. Absence of fully functional HRR pathway is one of the key determinants of platinum sensitivity in ovarian and other cancers.

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

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

The proposed target patient population in this application is focused on BRCAm HER2-negative metastatic breast cancer. The pivotal study included patients with gBRCAm TNBC as well as BRCAm ER and/or PgR+ patients.

The applicant claimed the use of the already approved tablet formulation in the following proposed indication: “Lynparza is indicated as monotherapy for the treatment of adult patients with BRCA1/2-mutated HER2 negative metastatic breast cancer who have previously been treated with chemotherapy. These patients could have received chemotherapy in the neoadjuvant, adjuvant or metastatic setting.”

The recommended indication is:

“Lynparza is indicated as monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2 negative locally advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments (see section 5.1).

Patients with hormone receptor (HR)-positive breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy”

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.

It is recommended that treatment be continued until progression of the underlying disease or unacceptable toxicity. There are no data on retreatment with Lynparza following subsequent relapse (see section 5.1).

Patients must have confirmation of a deleterious or suspected deleterious gBRCA1/2 mutation before Lynparza treatment is initiated. gBRCA1/2 mutation status should be determined by an experienced laboratory using a validated test method. Data demonstrating clinical validation of tumour BRCA1/2 tests in breast cancer are not currently available.

Genetic counselling for patients tested for mutations in BRCA1/2 genes should be performed according to local regulations.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity / environmental risk assessment

The MAH provided an updated ERA. The $PEC_{surfacewater}$ is calculated based on the sum of the PECsurfacewater calculated for both the ovarian cancer (0.026 µg/L) and breast cancer (0.090 µg/L) indications

Table 1: Summary of main study results

Substance (INN / Invented Name):			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	**OECD107 (study 06-0182/C)**	**1.55**	Not > 4.5: **not PBT**
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	1.55	Not B
	BCF	NA	
Persistence	DT_{50} or ready biodegradability	DT50, total system, 20°C = 259 (S1) & 251 (S2) DT50, total system, 12°C = 553 (S1) & 536 (S2)	vP
Toxicity	NOEC or CMR	NA	
PBT-statement :	The compound is not considered as PBT nor vPvB.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	**If Fpen=0.01** **if Fpen=0.0001094**	**4.0 µg/L** **0.44 µg/L**	**Then < 0.01 µg/L**
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	**Modified OECD 106 (study 12-0285/A)**	*High Organic Carbon (HOC) sediment mean* **K_d =111** **K_{oc} = 1986** *Low Organic Carbon (LOC) sediment* mean **K_d = 3.8** **K_{oc} = 27487**	*KFoc values indicated that [^{14}C]Olaparib was of* ***low mobility in the HOC sediment*** *(KFoc 500-2000), and* ***immobile in the LOC sediment*** *(KFc>5000)*
Ready Biodegradability Test	**OECD 301F (study 06-0182/J)**	*Negligible biodegradation* (day 28: **<6%**)	*Not readily biodegradable*
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	**OECD 308 (study 08-0028/C)**	DT50, water, 20°C = 3.2 (S1) & 7.4 (**S2**) DT50, sediment = no degradation or dissipation observed. DT50, total system, 20°C	*2 sediments:* ***S1:*** *silty clay high OC* ***S2:*** *sand, low OC* *Shifting Transformation products: <10%*

		= 259 (**S1**) & 251 (**S2**) DT50, total system, 12°C = 553 (**S1**) & 536 (**S2**)			*Olaparib is very persistent* *Sediment toxicity study triggered.*
Adsoprtion/desorption to sludge	**OPPTS 835.1110 (study 08-0028/B)**	$Kd_{sludge(ads)}$ = **25**			*[^{14}C]AZD2281 did not show significant adsorption to sewage sludge and therefore, is not predicted to adsorb to bio-solids during wastewater treatment. A Kd value of 25 was calculated assuming a linear adsorption isotherm*
Hydrolysis	**OECD 111 (study 06-0182/D)**	<10 % (5 days) at pH 5, 7 and 9 Hydrolytically stable			*Hydrolytically stable (less than 10% hydrolysis over 120 hours at environmental relevant pHs)*
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	**OECD 201 (study 06-0182/F)**	NOEC	83	mg/L	*EC_{50} = > 83 mg/L*
Daphnia sp. Reproduction Test	**OECD 211 (study 06-0182/H)**	NOEC	0.32	µg/L	*21 day LOEC = 1.0 mg/L*
Fish, Early Life Stage Toxicity Test/*Species*	**OECD 210 (study 06-0182/I)**	NOEC	0.32	µg/L	*32 day LOEC 1.0 mg/L*
Activated Sludge, Respiration Inhibition Test	**OECD 209 (study 06-0182/E)**	NOEC	100	µg/L	*3 hour EC_{50} > 100 mg/L*
PNECmicroorganism = 10 000 µg/L **PNECsurfacewater** = 32 µg/L **PECgroundwater** = 0.011 µg/L and **PNECgroundwater** = 32 µg/L **PECsurfacewater/PNECmicroorganism = 4.4 × 10^{-6} (then <0.1):** Olaparib is unlikely to present a risk to microorganisms **PECsurfacewater/PNECsurfacewater = 1.4 × 10^{-3} (then <1):** Olaparib is unlikely to present a risk to organisms in surface water **PECgroundwater/PNECgroundwater** = 3.4 × 10^{-4} (then <1): Olaparib is unlikely to present a risk to the groundwater environment					
Phase IIb Studies					
Toxicity to *Chironomus riparius*	**OECD 218 (study 08-0028/D)**	*28 d NOEC = 0.6 mg/kg dry sediment and;* *28 d LOEC = 1.25 mg/kg dry sediment, based on development rate*			
PECsediment = PECsurface water × Kdsediment (111) PECsediment = 0.044 μg/L × 111 L/kg = 4.9 µg/kg **PNECsediment = NOEC from the chironomus test / 100** PNECsediment = 600 µg/kg / 100 = 6 µg/kg **PEC/PNECsediment = 0.82 (then <1):** no further testing is required					

2.2.2. Conclusion on the non-clinical aspects

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

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

Table 2: Tabular overview of clinical studies

Study number (description)	Design	Efficacy endpoint	Total number of patients	Number of *BRCAm* breast cancer patients[a]	Status
Phase I studies: Tolerability and preliminary efficacy					
D0810C00002 (first time in man study)	First time in human with efficacy expansion at 200 mg bd	BoR, DoR, PFS	98	7 (local testing)	Complete
D0810C00024 (formulation comparison study)	Comparative bioavailability of two oral formulations of olaparib in patients with advanced solid tumours with efficacy expansion in *gBRCAm* ovarian and breast cancer patients	Tumour shrinkage, BoR, ORR, PFS	196	14 (local testing)	Complete
Phase II studies					
D0810C00008 (proof-of-concept study)	Open-label, single-arm, POC study to assess the efficacy and safety of olaparib 400 mg bd (capsule) in *gBRCAm* advanced breast cancer patients.	ORR, DoR, BoR, tumour shrinkage, PFS	54	27 (local testing)	Complete
D0810C00020 (relapsed ovarian and breast cancer monotherapy study)	Open-label, non-randomised study of olaparib in patients with known hereditary *gBRCAm* or non-hereditary ovarian cancer and patients with known *gBRCAm* or triple negative breast cancer	BoR, ORR, PFS, OS, DoR, DCR	90	26 (local testing)	Complete
D0810C00042 (advanced *gBRCAm* tumours study)	Open-label, non-randomised study of olaparib in patients with advanced *gBRCAm* tumours	Response rate, ORR, PFS, OS, DoR, DCR	298	62 (local testing)	Complete
Phase III studies					
D0819C00003 (pivotal study)	Open-label, controlled trial in *gBRCAm* patients with metastatic HER2-negative breast cancer	PFS, OS, PFS2, ORR, DCR, HRQoL	302	~302 (local & centralised testing)	Ongoing for extended OS follow-up

[a] *BRCA* mutation status was determined by various methods dependent on the study: (1) local germline testing, as recorded on CRFs at study enrolment, (2) prospective or retrospective centralised testing of blood samples at the Myriad Genetic Laboratories Inc (using either the Integrated BRAC*Analysis*® or BRACAnalysis CDx® test) or BGI Clinical Laboratory (Shenzen) to determine germline (*gBRCA*) mutation status. Further information relating to these testing methods is presented in Section 4.1.4.

bd twice daily; BoR best overall response; *BRCA* breast cancer susceptibility gene; DCR disease control rate; DoR duration of response; *gBRCA* germline *BRCA* mutation; PFS progression-free survival; PFS2 time to second progression or death; ORR Objective response rate; OS overall survival.

Source: OlympiAD CSR, Module 5.3.5.1, Study 20 CSR, Module 5.3.5.2; Study 42 CSR, Module 5.3.5.2; Study D0810C00008, Module 5.3.3.2; Study 24 CSR, Module 5.3.3.2 and Study 02 CSR, Module 5.3.3.2.

2.3.2. Pharmacokinetics

No new clinical PK study was submitted to support the proposed indication in BRCAm patients with HER2-negative metastatic breast cancer. A population PK analysis (Olaparib MS-05) performed using an earlier developed model and including sparse data collected in patient with breast cancer OlympiAD was provided.

Population PK analysis (Olaparib-MS-05)

Objectives

The objectives of this analysis were to: 1) characterise olaparib PK in patients with metastatic breast cancer in OlympiAD study; 2) obtain individual PK parameter estimates with plasma concentrations available; 3) explore and model (if feasible) the relationship between olaparib plasma exposure and selected efficacy and safety variables.

Methods

A total of 302 patients were randomised 2:1 (olaparib: physician's choice chemotherapy) into the OlympiAD study. Plasma samples for PK were collected in a sub-group of patients randomised to olaparib treatment group, at Day 1 Cycle 2 at following time window, Pre-dose, between 0 and 0.5 hour post-dose, between 0.5 and 1.5 hour post-dose, between 3 and 6 hours post-dose, and between 6 and 12 hours post-dose. The final PK data sets comprised 174 olaparib plasma concentrations from 36 olaparib-treated subjects. Of 36 subjects, 7 subjects had dose reduction from 300 mg bd to 250, 200 and 50 mg during the course of olaparib treatment.

The population PK model from Olaparib-MS-02 and Olaparib-MS-03 served as basis for the model development, but was further refined where deemed necessary. Patient covariate relationships were examined in a stepwise procedure to examine the impact of individual patient characteristics on olaparib PK. Individual PK parameters as well as exposure estimates for subsequent exposure-response assessment were derived based on the final PK model. The average AUC, Cmax, Cmin of 2 olaparib dose administrations during the safety event day, abbreviated as dAUC, dCmax, dCmin, respectively, were used as exposure on the safety event day for the safety exposure- response analysis. Since efficacy or safety events may associate with exposure from the beginning of olaparib treatment to the event day, an overall measure of exposure in mean AUC was used, using average olaparib concentration from the start of olaparib dose administrations to the efficacy or safety event day multiplied by dose interval (12 hours), abbreviated as average cumulative AUC (acAUC), was used for exposure-response analysis for both safety and efficacy events. The exposure metric acAUC is similar to steady state AUC, but considers the dose interruption and reduction over the period of olaparib treatment.

The relationship between olaparib exposure and safety/efficacy was explored graphically and modeled if supported by data.

Results

The exposure to olaparib in the Phase III study OlympiAD was determined using population PK analysis (N=36) and the estimated Gmean (coefficient of variation %) for Cmax,ss, AUCss and Cmin,ss after 300 mg tablet bd were 6.41 µg/mL (41%), 41.2 µg.h/mL (42%) and 1.17 (87%) µg.h/mL.

The model structure for plasma concentration data from OlympiAD was the same as the previous models (Olaparib-MS-02 and Olaparib-MS-03): a linear 2-compartment model with sequential zero and first-order absorption rates and first-order elimination. Covariates including age, body weight, gender, race, tablet strength, hepatic and renal function markers were evaluated in the population analysis, and none of them were identified as significant covariates impacting olaparib PK. The estimates of geometric mean steady-state exposure in AUCss, Cmax,ss and Cmin,ss in patients with metastatic breast cancer were similar to those from patients with ovarian cancer in SOLO2 study.

The relationships between exposure and efficacy (progression free survival [PFS], overall survival [OS] and time from randomisation to second progression or death [PFS2]) was examined with Kaplan-Meier

plots stratified by tertiles of exposure and showed no pattern that would suggest response differs at the exposures analysed in this study. No testing via modelling was performed.

Graphical exploratory analyses were conducted to explore the exposure-safety analysis for anaemia, fatigue and haemoglobin (Hb). No significant exposure-safety relationship was found, except a weak relationship between olaparib exposure in acAUC and Hb levels. A relationship was observed between olaparib exposure in acAUC and haemoglobin concentrations, and can be described by an indirect response model. The model predicted a small decrease in haemoglobin concentrations with the increase in olaparib exposure and model simulation indicated a negligible change haemoglobin concentration for the majority of olaparib exposures observed.

A comparison of steady state olaparib exposure for the capsule and tablet formulations determined using population PK analysis is provided below.

Table 3: Comparison of steady state olaparib exposure for the capsule and tablet formulations determined using population PK analysis

PK parameter	Summary statistic	Capsule 400 mg bd: pooled PK analysis[a]: Olaparib-MS-01	Tablet 300 mg bd SOLO2 study: Olaparib –MS-03	Tablet 300 mg bd OlympiAD study: Olaparib –MS-05	Tablet 300 mg bd: pooled PK analysis: Olaparib –MS-02
$C_{max,ss}$ (µg/mL)	n Gmean (range) [GCV]	68 5.73 (1.57–14.2)	94 7.12 (3.9-15) [26.9]	36 6.41 (2.16-17.7) [40.9]	131 9.10 (4.26-25.5) [38.7]
AUC_{ss} (µg.h/mL)	n Gmean (range) [GCV]	68 48.1 (8.57–154)	94 40.7 (17-120) [39.5]	36 41.2 (17.6-140) [42.0]	131 59.7 (25.5-183) [49.7]
$C_{min,ss}$ (µg/mL)	n Gmean (range) [GCV]	68 1.26 (0.08–8.08)	94 1.15 (0.28-6.2) [72.3]	36 1.17 (0.11-8.00) [87.0]	131 1.95 (0.35-11.5) [86.5]

a For Olaparib-MS-01 pooled population PK analysis GCV were not reported. Data for studies 1, 2, 12 and 24 are shown.

AUC_{ss} area under the plasma concentration-time curve during a dosing interval; bd twice daily; $C_{max,ss}$ maximum plasma concentration at steady state; $C_{min,ss}$ minimum plasma concentration; Gmean Geometric mean; GCV Geometric coefficient of variation %; PK pharmacokinetic.

Data source: Table 6 Olaparib-MS-01 Module 5.3.3.5, Table 9 Olaparib-MS-02 Module 5.3.3.5, Table 4 Olaparib-MS-05 Module 5.3.3.5, and Table 13 Olaparib-MS-03 Module 5.3.3.5.

2.3.3. Pharmacodynamics

Mechanism of action

Olaparib is a potent inhibitor of human poly (ADP ribose) polymerase enzymes (PARP 1, PARP 2, and PARP 3), and has been shown to inhibit the growth of selected tumour cell lines in vitro and tumour growth in vivo either as a standalone treatment or in combination with established chemotherapies.

PARPs are required for the efficient repair of DNA single strand breaks and an important aspect of PARP induced repair requires that after chromatin modification, PARP auto modifies itself and dissociates from the DNA to facilitate access for base excision repair (BER) enzymes. When olaparib is bound to the active site of DNA associated PARP it prevents the dissociation of PARP and traps it on the DNA, thus blocking repair. In replicating cells this leads to DNA double strand breaks (DSBs) when replication forks meet the

PARP DNA adduct. In normal cells, homologous recombination repair (HRR), which requires functional BRCA1 and 2 genes, is effective at repairing these DNA DSBs. In the absence of functional BRCA1 or 2, DNA DSBs cannot be repaired via HRR. Instead, alternative and error prone pathways are activated, such as the non-homologous end joining (NHEJ) pathway, leading to increased genomic instability. After a number of rounds of replication, genomic instability can reach insupportable levels and result in cancer cell death, as cancer cells have a high DNA damage load relative to normal cells (See SmPC Section 5.1).

Primary and secondary pharmacology

Effect of olaparib on the QT interval

The relationship between QT interval corrected for heart rate (QTc) and plasma concentrations was evaluated in Studies 04 and 07. Following the 300 mg bd tablet dose olaparib had no clinically significant effect on QT interval (QT interval corrected for heart rate using Fridericia's correction [QTcF] and QT interval corrected for heart rate using individual-specific correction [QTcI]).

Germline BRCA diagnostic testing

Patients were required to have documented evidence of a deleterious or suspected deleterious mutation in either BRCA1 or BRCA2 to be enrolled into the OlympiAD study. Evidence of a qualifying BRCA mutation could be from either an existing BRCA mutation result generated by local testing or from prospective testing performed by BGI or by Myriad using either the Integrated BRACAnalysis test (also referred to as the Myriad CLIA *gBRCA* test) or the BRACAnalysis CDx test (also referred to as the Myriad CDx *gBRCA* test).

Table 4: Number of samples in analysis sets in OlympiAD

	FAS N	CRF *gBRCA* status			BGI *gBRCA* status			Myriad CLIA status			Myriad CDx *gBRCA* status		
Study arm:		*gBRCAm*	Non-*gBRCAm*	Not reported[a]	*gBRCAm*	Non-*gBRCAm*	Not tested[b]	*gBRCAm*	Non-*gBRCAm*	Not tested[c]	*gBRCAm*	Non-*gBRCAm*	Not tested[c]
Olaparib	205	117	0	88	32	0	173	109	2	94	202	2	1
Chemo	97	50	0	47	9	0	88	59	0	38	95	0	2
Total	302	167	0	135	41	0	261	168	2[d]	132	297	2	3

a Local sites were only required to report prior gBRCA status where it was being used to guide randomisation.
b BGI testing was only performed for cases screened in China.
c Testing at Myriad was performed in the CLIA lab until 7th July 2015. After this date testing switched to the CDx lab.
d Includes 1 variant with a qualified interpretation (See Below/Unclassified) due to unclear evidence around pathogenicity.

In total, 2126 subjects were screened for entry into OlympiAD. Within patients meeting the clinical study eligibility criteria, 167 subjects were randomised based on an existing local *gBRCAm* result, 65 based on a Myriad *gBRCAm* CLIA result, 29 based on a Myriad *gBRCAm* CDx result and 41 based on a *gBRCAm* result from BGI testing. Among 302 randomised patients with gBRCA1/2 mutations, the gBRCAm status was confirmed by the Myriad BRACAnalysis CDx assay in 297 patients.

Previously reported data have shown an association between the mutated gBRCA1 or BRCA2 gene and disease histology, with gBRCA1 mutations being associated with TNBC and BRCA2 mutations being associated with HR+ disease[8]. These reported associations were also seen in the HR+ and TNBC patients in OlympiAD. The mutation types as gBRCAm by Myriad testing were reported.

[8] Mavaddat et al 2012

Table 5: BRCA mutation types in breast cancer observed in OlympiAD

Mutation type	Breast cancer (n=297)	HR+ (n=151)	TNBC (n=146)
Frameshift	62.3%	62.9%	61.6%
Nonsense	20.2%	21.2%	19.2%
Missense	7.7%	6.6%	8.9%
Large Rearrangement	4.4%	2.6%	6.2%
Other mutation types	6.1%	6.6%	5.5%
BRCA1	55.2%	30.4%	80.8%
BRCA2	43.4%	68.9%	17.1%
BRCA1 & *BRCA2*	1.4%	0.7%	2.1%
BRCA1 RING domain	10.8%	7.9%	13.7%
BRCA1 exon 11	23.2%	9.9%	37.0%

Exploratory analysis of tumour samples

Patients who entered screening part 2 of the OlympiAD study were requested to provide tumour tissue material for exploratory analyses if such material was available. There was no mandatory re-biopsy required in cases where patients did not have tumour material available. Only 161 of the overall 302 patients (53%) were able to provide a tumour sample.

A comparison between gBRCA and tBRCA results identified that the deleterious or suspected deleterious mutation present in the germline was detected in the tumour in 141/143 cases (in 1 case, 2 mutations were reported in the germline and both mutations were also reported in the tumour sample).

Locus-specific LOH data were reported in 125 of the 143 tBRCA tested patients (87.4%). Overall, tumour LOH was observed for 118/125 (94.4%) deleterious mutations observed in the germline.

BRCA analysis using the Myriad myChoice HRD plus test generated a valid homologous recombination deficiency (HRD) score in 130 samples. Of these, 108 (83.1%) had a HRD score ≥ 42 and the HRD scores <42 were seen in 16.3%. A higher proportion of negative HRD scores in the hormone receptor positive (HR+) patients (13/59 [22%]) versus the triple negative breast cancer (TNBC) patients (8/70 [11%]) was reported. A higher proportion of patients with TNBC had mutations in TP53 (86%) than with HER2-/HR+ (22%).

2.3.4. PK/PD relationship and modelling

Analysis of tumour samples

Study 07, a Phase I open-label study to identify an effective biological dose to be used for further clinical studies of olaparib by using biomarkers of PARP activity to delineate a PARP inhibitory concentration response curve for the selected doses of olaparib in breast tumour, was submitted with the initial MA application.

Intermediate and high risk breast cancer patients were randomly allocated to 1 of 5 dose cohorts (10 mg bd, 30 mg bd, 100 mg bd, 200 mg bd, and 400 mg bd) and received treatment for 4 or 5 days prior to surgery. Overall, 60 patients were randomized, 12 in each dose cohort, and all patients completed treatment.

Tumour biopsy samples were obtained before surgery from 60 intermediate and high risk breast cancer patients. Determination of concentrations of olaparib in tumour biopsies showed that measurable concentrations (>40 ng/g) were present in all but one of the samples collected from patients dosed at 30, 100, 200 and 400 mg bd. The extent of PARP inhibition in tumour samples ranged from about 20% to 80% compared with baseline and no clear relationship with dose could be showed.

Exposure/response (E-R) analysis for efficacy event in OlympiAD trial (DCO (25 September 2017))

The final E-R analysis data set for efficacy events included 36 subjects. There were only 12, 11 and 13 patients at the lower, middle and upper tertiles of acAUC exposure.

Kaplan-Meier survival estimate plots stratified by tertiles of acAUC for PFS2 and OS are shown below.

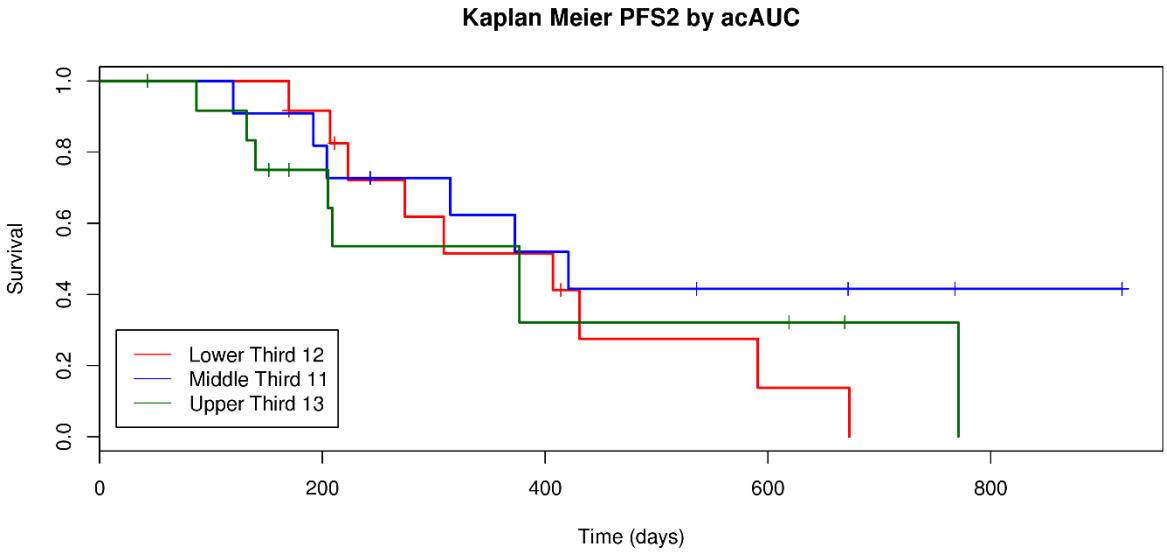


Figure 1 Kaplan-Meier survival estimates for PFS2 stratified by tertiles of acAUC

Note: acAUC Average cumulative AUC; PFS Progression free survival.

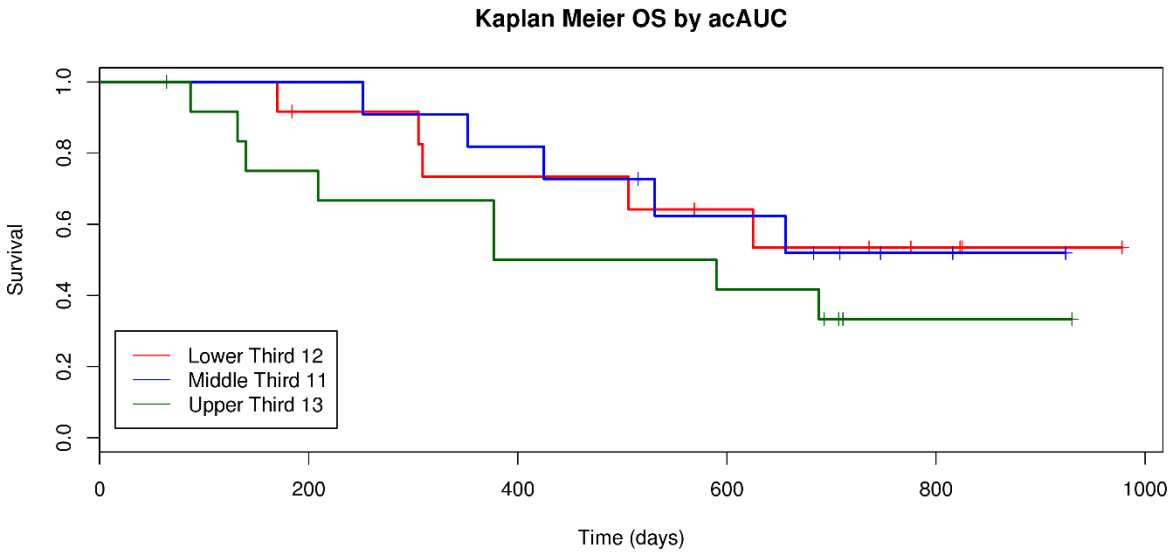


Figure 2 Kaplan-Meier survival estimates for OS stratified by tertiles of acAUC

The PKPD analysis in Olaparib-MS-02 did not show any significant exposure-safety relationship, except for haemoglobin (Hb) level where increased olaparib exposure was associated with a reduction in Hb level. The PKPD analyses of OlympiAD and SOLO2 in the Phase III studies also showed an exposure response relationship for Hb. In Olaparib-MS-05, the simulations from the Hb model indicated a very small change in mean Hb concentration time course until olaparib exposure approached the upper bound of 95% CI of predicted AUCss (100 µg.h/mL). The predicted mean Hb concentrations around the upper bound of 95% CI of the predicted AUCss were still above 10g/dL. No significant concentration dependent relationship was found for nausea, vomiting, platelet count, dysguesia, constipation, dyspepsia, or neutropenia.

2.3.5. Discussion on clinical pharmacology

The applicant claims the use of olaparib tablets in the treatment of patients with BRCA-Mutated HER2-Negative Metastatic Breast Cancer metastatic breast cancer.

With regards to PK data, the MAH submitted an overview of the pharmacokinetics of the tablet formulation and a population PK analysis (Olaparib MS-05) performed using an earlier developed model and including sparse data collected in patient with breast cancer OlympiAD. The PK properties (ADME) of olaparib were presented and assessed satisfactorily in previous applications related to the use of olaparib in the treatment of ovarian cancer. The biopharmaceutical performances of the capsule and tablet formulation were elucidated. The tablet showed higher bioavailability (approximately doubled) and less variablebehaviour. In the pivotal phase 3 study supporting the breast cancer indication, only the currently approved tablet formulation was used. No formal PK study was performed in the target population (claimed indication). However, sparse sampling data were collected for the purpose of population-PK analysis. The results of the population PK analysis should be interpreted with caution due to the small number of evaluable patients (N=36) in this analysis.

The exposure to olaparib following administration of 300mg bd tablet formulation observed in the Phase III study OlympiAD (Olaparib-MS-05, N=36) was comparable to that in SOLO2 (Olaparib-MS-03, N=94) and was within the range previously predicted for the capsule formulation at 400mg bd (Olaparib-MS-01). However, it was slightly lower (AUCss was 32% lower) than the one observed in the pooled Phase I tablet population PK analysis due to study variability (Olaparib-MS-02). A comparison of steady-state olaparib exposure for the capsule and tablet formulations determined using the population PK analysis (Olaparib-MS-01, Olaparib-MS-02 and Olaparib MS-03) was provided. In addition, potential causes of the apparent differences in olaparib exposure between the SOLO2 study and the pooled tablet analysis were further investigated and it appeared that this difference was due to variability between studies. Section 5.2 of the SmPC has been updated to reflect that patient gender was also not a significant covariate.

For the applied indication i.e. germline breast cancer susceptibility genes (gBRCA1/2) mutated human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer, patients must have confirmation of a deleterious or suspected deleterious gBRCA1/2 mutation before Lynparza treatment is initiated. gBRCA1/2 mutation status should be determined by an experienced laboratory using a validated test method (see SmPC section 4.2). Genetic counselling for patients tested for mutations in gBRCA1/2 genes should be performed according to local regulations.

Data in regard to analytical and clinical validation in breast cancer patients of the in-vitro diagnostic tests proposed to be used for the detection of deleterious or suspected deleterious BRCA1/2 mutations in tumours have not been provided. It is reflected in section 4.2 of the SmPC that data demonstrating clinical validation of tumour BRCA1/2 tests in breast cancer are not currently available.

Exploratory analysis of tumour samples in study OlympiAD showed that a higher proportion of patients with TNBC had mutations in TP53 (86%) than with HER2-/HR+ (22%) which is consistent with results from other studies and suggest a potential mechanistic rationale for investigating TP53 mutation in

patients with BRCAm tumours. In high-grade serous ovarian cancer (HGSOC), mutations in TP53 are nearly universal and exploratory analysis of results from the Study 19, the phase II double-blind, randomised, placebo-controlled, multicentre study conducted in advanced platinum-sensitive HGSOC, suggested a role of disruptive p53 mutations in predicting OS in patients treated with olaparib.

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 different histological types of breast tumours, including those with specific mutations and large genomic rearrangements in BRCA1, BRCA2 and other HRR-related genes.

In terms of exposure-efficacy relationship no definitive conclusion can be made due to a limited number of samples.

2.3.6. Conclusions on clinical pharmacology

No new biopharmaceutical or clinical pharmacology study were provided to support the proposed indication in BRCAm in patients with HER2-negative metastatic breast cancer which is considered acceptable. Available pharmacology data on olaparib provides sufficient characterisation of the key PK characteristics of olaparib and provides sufficient data in support of an adequate labelling for special populations and DDI.

The germline BRCA1/2 mutation status was centrally confirmed in blood samples in the majority of patients randomised in the pivotal study and exploratory analyses of available tumour samples were conducted. The MAH is recommended to further investigate predictive and prognostic biomarkers.

2.4. *Clinical efficacy*

2.4.1. Dose response study

No dose response study was submitted (see discussion on clinical efficacy).

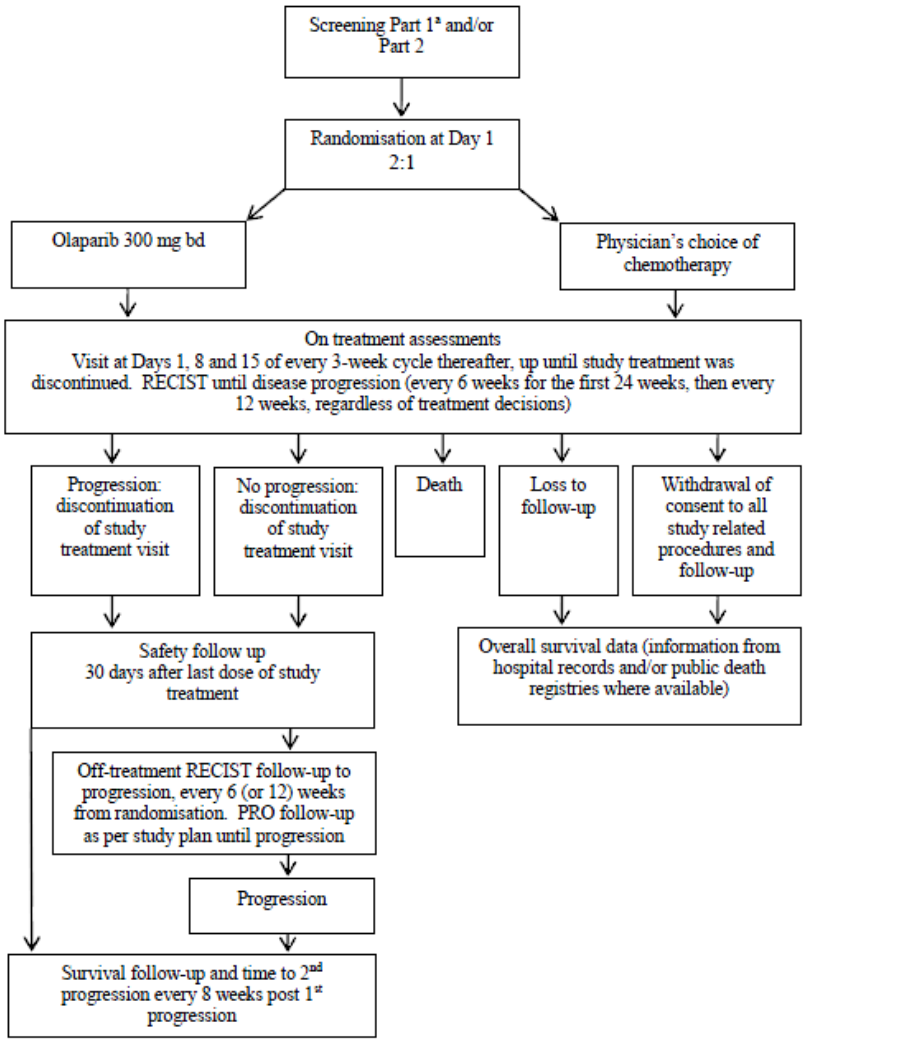
2.4.2. Main study

Study D0819C00003 (OlympiAD)

A Phase III, open label, randomised, controlled, multi-centre study to assess the efficacy and safety of Olaparib Monotherapy Versus Physician's Choice Chemotherapy in the Treatment of Metastatic Breast Cancer Patients with Germline BRCA1/2 Mutations

Methods

This was a Phase III, open-label, randomised, controlled, multi-centre study of patients with metastatic breast cancer and gBRCAm, designed to assess the efficacy and safety of single agent olaparib versus standard of care (study physician's choice of capecitabine, vinorelbine or eribulin).



[a] Only required if a patient's *gBRCAm* status was unknown.

Abbreviations: *gBRCAm*, germline breast cancer susceptibility gene mutated; PRO, patient reported outcomes; RECIST, Response Evaluation Criteria in Solid Tumors version 1.1.

Figure 3: Study design, study OlympiAD

Study participants

Main inclusion criteria

Patients were required to fulfil all of the following criteria to be eligible for inclusion in the study (patients with unknown BRCA mutation status were required to fulfil inclusion criteria 1, 3, 4, 9, 10 and 11 prior to BRCA mutation testing):

1. Patients had to be male or female ≥18 years of age with histologically or cytologically confirmed breast cancer with evidence of metastatic disease.

2. Documented mutation in BRCA1 or BRCA2 that was predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function. Patients with BRCA1 and/or BRCA2 mutations that were considered to be non-detrimental were not eligible for the study.

3. Patients must have received treatment with an anthracycline (eg, doxorubicin, epirubicin) unless contraindicated and a taxane (eg, paclitaxel, docetaxel) in either a neoadjuvant/adjuvant or metastatic setting.

4. Patients who had received platinum (cisplatin or carboplatin, either as monotherapy or in combination) for advanced breast cancer were eligible to enter the study provided there had been no evidence of disease progression during the platinum chemotherapy.

5. Patients who had received prior platinum based chemotherapy were eligible if platinum was given either as potentially curative treatment for a prior non-breast cancer (eg, ovarian cancer) with no evidence of disease for ≥5 years prior to study entry or as adjuvant/neoadjuvant treatment for breast cancer provided at least 12 months had elapsed between the last dose of platinum-based treatment and randomisation.

6. Patients with ER and/or PgR positive disease were required to have received and progressed on at least 1 endocrine therapy (adjuvant or metastatic), or had disease that the treating physician believed to be inappropriate for endocrine therapy.

7. At least 1 lesion (measurable and/or non-measurable) that could be accurately assessed at baseline by CT (MRI where CT was contraindicated) and was suitable for repeated assessment as per RECIST version 1.1.

8. Patients were required to have normal organ and bone marrow function measured within 28 days prior to administration of study treatment as defined below:

-Haemoglobin ≥10.0 g/dL with no blood transfusions (packed red blood cells and platelet transfusions) in the past 28 days

-Absolute neutrophil count (ANC) ≥1.5x109/L

-Platelet count ≥100x10^9/L

-Total bilirubin ≤1.5x institutional upper limit of normal (ULN)

-Aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase)/alanine aminotransferase (ALT) (serum glutamic-pyruvic transaminase) ≤2.5x institutional ULN unless liver metastases are present in which case they must be ≤5xULN

-Serum or plasma creatinine ≤1.5x institutional ULN

9. Eastern Cooperative Oncology Group (ECOG) performance status 0-1 within 21 days of randomisation.

10. Postmenopausal or hysterectomised; women of childbearing potential were eligible with a negative urine or serum pregnancy test documenting evidence of non-childbearing status

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. Formalin fixed, paraffin embedded tumour sample from the primary tumour if available.

For inclusion in the optional exploratory genetic research and/or the optional tumour biopsy research, patients were required to fulfil the following criteria:

-Provision of informed consent for genetic research

-Provision of informed consent for tumour biopsy research

Main exclusion criteria

Any of the following was regarded as a criterion for exclusion from the study (patients with an unknown BRCA mutation status were required to fulfil exclusion criteria 3, 5, 6, 8, 9, 11, 13, 14, 15, 16, 18, and 19 prior to BRCA mutation testing):

1. BRCA1 and/or BRCA2 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. Cytotoxic chemotherapy or non-hormonal targeted therapy within 21 days of Cycle 1 Day 1 was not permitted. It was required that endocrine therapy had been discontinued 7 or more days before Cycle 1 Day 1. Palliative radiotherapy was to have been completed 14 or more days before Cycle 1 Day 1. It was permitted that the patient received a stable dose of bisphosphonates or denosumab for bone metastases, before and during the study, as long as these were started at least 5 days prior to study treatment.

3. Patients with HER2-positive disease (3+ by IHC or ISH amplified ≥2.0)

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

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

6. Patients with second primary cancer; exceptions: adequately treated non-melanoma skin cancer, curatively treated in situ cancer of the cervix, ductal carcinoma in situ, stage 1 grade 1 endometrial carcinoma, or other solid tumours including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for ≥5 years prior to study entry.

7. Resting electrocardiogram (ECG) with QT interval corrected for heart rate (QTc) >470 msec detected on 2 or more time points within a 24-hour period, or family history of long QT syndrome. If an ECG demonstrated QTc >470 msec, a patient would be eligible only if a repeat ECG demonstrated QTc ≤470 msec

8. Patients must not have received more than 2 prior lines of cytotoxic chemotherapy for metastatic disease. Prior treatments with hormonal therapy and non-hormonal targeted therapy were allowed and not counted as a prior line of cytotoxic chemotherapy. For the purposes of this protocol, the combination of an aromatase inhibitor and everolimus was not considered cytotoxic chemotherapy

9. Concomitant use of known potent cytochrome P450 (CYP) 3A inhibitors such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfinavir. For further details refer to CSP Appendix I

10. Persistent toxicities (≥CTCAE grade 2) caused by previous cancer therapy, excluding alopecia and CTCAE grade 2 peripheral neuropathy

11. Patients with myelodysplastic syndrome (MDS)/treatment-related acute myeloid leukaemia

12. Major surgery within 2 weeks of starting study treatment: patients were to have recovered from any effects of any major surgery

13. Immunocompromised patients, eg, patients who were known to be serologically positive for human immunodeficiency virus

14. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples included, but were not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive bilateral lung disease on high resolution CT scan or any psychiatric disorder that would limit ability to comply with study procedures and any other medical condition that, in the opinion of the Investigator, placed the patient at unacceptable risk of toxicity

15. Patients with a history of treated central nervous system (CNS) metastases were eligible, provided they met all of the following criteria: disease outside the CNS was present; no clinical evidence of

progression since completion of CNS-directed therapy; minimum of 2 weeks between completion of radiotherapy and Cycle 1 Day 1 and recovery from significant (grade ≥3) acute toxicity with no ongoing requirement for >10 mg of prednisone per day or an equivalent dose of other corticosteroid

16. Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication

17. Pregnant or breast feeding women

18. Previous allogeneic bone marrow transplant

19. Whole blood transfusions in the last 120 days prior to enrolment into the study, which had the potential to interfere with gBRCA testing (packed red blood cells and platelet transfusions were acceptable: for timing, refer to inclusion criterion number 8).

Treatments

Olaparib

The planned dose of 300 mg bd comprised two 150 mg tablets bd. The 100 mg tablets were used to manage dose reductions.

Chemotherapy

Dosing and treatment regimen information for capecitabine, vinorelbine and eribulin were included in the local package inserts supplied with the drug.

-Oral capecitabine 2500 mg/m^2 to be taken daily (divided in 2 doses) for 14 days, repeated every 21 days

-Intravenous (IV) vinorelbine 30 mg/m^2 on Day 1 and Day 8, repeated every 21 days

-Intravenous eribulin mesylate 1.4 mg/m^2 or eribulin (active substance) 1.23 mg/m^2 on Day 1 and Day 8, repeated every 21 days.

Study centre personnel were instructed to follow the prescribing information for toxicity management and dose reduction. Standard or reduced doses of capecitabine could be used after the first cycle as per standard clinical practice. No switch to olaparib was permitted in this study.

Other medication considered necessary for the patient's safety and well-being could be given at the discretion of the Investigator(s). The administration of all medication (including study drugs) was recorded in the eCRFs until 30 days following the last CSP treatment.

Objectives

Primary objective

The primary objective of the study was to determine the efficacy of single agent olaparib versus physician's choice chemotherapy (capecitabine, vinorelbine or eribulin) by progression-free survival (PFS) using blinded independent central review (BICR) data assessed by Response Evaluation Criteria in Solid Tumors (RECIST version 1.1).

Secondary objectives

1. To compare the efficacy of single agent olaparib versus physician's choice chemotherapy (capecitabine, vinorelbine or eribulin) by assessment of OS, time to second progression or death (PFS2) and ORR using BICR data assessed by RECIST version 1.1.

2. To assess the effect of olaparib on the Health-related Quality of Life (HRQoL) as measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item module (EORTC QLQ-C30) global quality of life (QoL) scale.

3. To assess the 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 future BRCA mutation assays (gene sequencing and large rearrangement analysis).

4. To determine the exposure to olaparib in patients receiving olaparib monotherapy.

5. To assess the safety and tolerability of single agent olaparib versus physician's choice chemotherapy (capecitabine, vinorelbine or eribulin).

Exploratory objectives

1. To explore the impact of olaparib on symptoms and HRQoL as measured by the EORTC QLQ-C30 disease related multi-item symptom and functional scales.

2. To explore patients' treatment satisfaction (as measured by the Satisfaction with Therapy scale of the Cancer Therapy Questionnaire [CTSQ] and the other subscales and items of the CTSQ) with olaparib, compared to physician's choice chemotherapy.

3. To investigate the health economic impact of treatment and the disease on hospital related resource use.

4. To explore methods of estimating OS adjusting for the impact of the physician's choice chemotherapy group receiving subsequent PARP inhibitors or imbalances between the treatment arms for other potentially active agents.

5. To explore whether resistance mechanisms to olaparib can be identified through analysis of tumour and blood samples – archival tumour (mandatory if available), blood samples at baseline and on disease progression (mandated) and serial biopsies at baseline and disease progression (optional).

6. To determine the frequency of and describe the nature of BRCA mutation(s) in tumour samples and to compare this with gBRCA mutation status.

7. Future exploratory research into factors that may influence development of cancer and/or response to treatment (where response is defined broadly to include efficacy, tolerability or safety) may be performed on the collected and stored archival tumour samples (mandatory if available), blood samples at baseline and on disease progression (mandated) and serial biopsies at baseline and disease progression (optional).

8. To collect and store DNA according to each country's local and ethical procedures for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to study treatments and/or susceptibility to disease (optional).

Outcomes / endpoints

Primary endpoint

PFS: the time from randomisation until the date of objective radiological disease progression according to RECIST version 1.1, or to death (by any cause in the absence of disease progression), regardless of

whether the patient withdraws from randomised therapy or receives another cancer therapy prior to disease progression.

Secondary endpoints

OS: the time from the date of randomisation until death due to any cause.

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.

ORR: the number of responders (CR or PR) divided by the number of patients in the treatment group in the EFR analysis set (ITT population with measurable disease at baseline).

EORTC QLQ-C30: A 30-question patient reported outcome measure of HRQoL commonly used in oncology.

Global QoL scale: A measure of overall health and QoL consisting of 2 items from the QLQ-C30.

TFST and TSST were also analysed as supportive endpoints for PFS and PFS2, respectively:

Time to first subsequent therapy (TFST): the time from randomisation to the earlier of first subsequent cancer therapy start date following study treatment discontinuation or death.

Time to second subsequent therapy (TSST): the time from randomisation to the earlier of the second subsequent therapy start date following study treatment discontinuation, or death.

Sample size

The primary endpoint of the study was PFS. Approximately 310 patients were to be randomised. The study was sized assuming a true treatment effect was a PFS HR of 0.635, assuming 90% power and 2.5% alpha (1-sided), with 2:1 randomisation (olaparib: physician's choice of chemotherapy). Assuming PFS was exponentially distributed, a PFS HR of 0.635 equated to a 2.3-month improvement in median PFS over an assumed 4-month median PFS for the control arm.

Assuming that the study accrual period was approximately 22 months, 230 progression events were anticipated to be observed approximately 27 months after the first patient was randomised in the study. Patients were planned to be followed until the final analysis of PFS2 and OS (when approximately 190 death events occurred). This was anticipated to be 39 months after the first patient was randomised in the study.

Randomisation

First patient enrolled: 27 March 2014

Data cut-off date: 9 December 2016

Prior to randomisation to olaparib or chemotherapy, the Investigator was required to declare his or her choice of chemotherapy (capecitabine, vinorelbine, or eribulin). Randomisation was performed via an interactive voice response system/interactive web response system (IVRS/IWRS) Centralised Randomisation Centre.

Moreover, randomisation was stratified by whether patients:

- had received prior chemotherapy regimens for metastatic breast cancer (yes/no),

- were ER and/or PgR positive versus ER and PgR negative,

- had prior platinum treatment for breast cancer (yes/no).

Blinding (masking)

Due to different routes and schedules of administration of the treatment options in the physician's choice of chemotherapy arm as well as their different toxicity profiles, this study could not be blinded. Given the open label design of the study, rigorous methodology was employed to ensure robustness of the primary endpoint assessment, with a primary analysis of radiological PFS based on BICR of all patient screening and on-study scans.

Statistical methods

In OlympiAD, the primary population defined in the protocol for analysis of all efficacy endpoints included all randomised patients (ie, the full analysis set [FAS]). Thus, all primary and secondary efficacy and HRQoL data were summarised and analysed on an intention to treat (ITT) basis.

In addition, subset analyses to the main analyses of PFS, PFS2, OS, and ORR were performed in those patients whose gBRCAm status was confirmed by the Myriad CDx test.

Sensitivity analyses

The sensitivity analyses included assessments of possible evaluation time bias (if scans were not performed at the protocol scheduled time points), attrition bias (the possibility that the rate and nature of censoring resulted in bias), and ascertainment bias (assessing discrepancies between investigator assessed vs BICR assessment of PFS; hereafter referred to as investigator assessment of PFS).

Multiplicity adjustments

In an effort to control the type I error at 2.5% (1-sided) for key label claims, a multiple testing procedure (MTP) was employed across primary (PFS) and key secondary (PFS2 and OS) endpoints.

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 was to recycle the test mass to the endpoint not yet rejected in the hierarchy.

Interim analysis of OS was carried out at the time of the primary analysis of PFS, and final OS was tested again when 64% of deaths occurred, given that significant PFS and PFS2 results were observed at the primary analysis.

Primary analysis of progression-free survival

The primary analysis of PFS was based on the BICR of the radiological scans. A sensitivity analysis of PFS based on Investigator-recorded assessments was also to be carried out. Progression-free survival was to be analysed when approximately 230 progression events had occurred, based on the BICR data. Patients who had not progressed or died at the time of analysis were censored at the time of the latest date of assessment from their last evaluable RECIST version 1.1 assessment.

Progression-free survival was analysed using a log-rank test stratified by whether a patient had received prior chemotherapy regimens for metastatic breast cancer (yes/no), ER and/or PgR positive versus ER and PgR negative, and prior platinum for breast cancer (yes/no), for generation of the p-value and using the Breslow approach for handling ties.

Although it was expected that there would be enough PFS events in each strata to allow a meaningful analysis, if a stratum for either treatment arm contains less than 5 events, then a pooling strategy had to

be employed to remove one or more stratification factors from the primary analysis. Stratification factors were to be removed in the following order until were at least 5 events in each stratum for either treatment arm: prior platinum for breast cancer (yes/no), ER and/or PgR positive versus ER and PgR negative, prior chemotherapy regimens for metastatic breast cancer (yes/no).

The HR (olaparib versus chemotherapy), 95% CI and p-value were to be presented (an HR of less than 1 favoured olaparib). A Kaplan-Meier plot of PFS was to be presented by treatment arm. Summaries of the number and percentage of patients experiencing a PFS event and the type of event (RECIST or death) were to be provided along with median PFS for each treatment arm. The assumption of proportionality was assessed. Proportionality was to be tested firstly by producing plots of complementary log-log (survival function) versus log (time) and if these raised concerns, a Cox proportional hazards model including a time-dependent covariate would be fitted to assess the extent to which this represents random variation.

The estimated PFS rates at 6 months and 12 months were to be summarised (using the Kaplan-Meier curve) and presented by treatment arm.

Patient reported outcome (PRO)

PRO endpoints in this open-label trial were not included in the multiplicity adjustment hierarchy so there is no hypothesis specified.

The primary assessment of HRQoL focused on comparing mean changes from baseline in the global quality of life (QoL) score (EORTC QLQ-C30) between the treatment arms in the FAS (ITT) set. A visit response of deterioration was defined as a decrease of 10 points or more from baseline, or where the patient was too heavily affected by symptoms of the disease under investigation to complete the HRQoL at the visit. Data were descriptive and plots were used to visualise the adjusted mean global QoL/health status score over time for each treatment arm. 95% CI and p-value were presented for the overall adjusted mean estimate.

A supportive analysis of time to deterioration of HRQoL was also performed, using the same methodology and model as for the analysis of the primary endpoint (PFS) A Kaplan-Meier plot of time to deterioration of HRQoL and a summary of median time to deterioration of HRQoL were presented by treatment arm.

To support the primary assessment of HRQoL other items of interest, data from the CTSQ-16 scores of treatment satisfaction (as measured by the 'Satisfaction with Therapy' scale and the other sub-scales and items of the CTSQ-16) and well as overall compliance rate were summarised.

For each subscale, if less than 50% of the subscale items were missing, then the subscale score was divided by the number of non-missing items and multiplied by the total number of items on the subscales (Fayers et al 1999). If at least 50% of the items were missing, then that subscale was treated as missing. Missing single items were treated as missing. If there was evidence that the missing data were systematic, missing values were handled to ensure that any possible bias was minimised.

Results

Participant flow

This study included a 2-part screening. In Part 1, 1918 patients with unknown BRCA status were screened using the Myriad test to determine their BRCA status prior to enrolment. In Part 2, all other patients who had known BRCA status underwent a confirmatory test post-randomisation.

At the time of DCO for the primary analysis (9 December 2016), 36 (17.6%) and 3 (3.3%) patients in the olaparib arm and physician's choice of chemotherapy arm, respectively, were still receiving study treatment.

In the FAS, the majority of patients who discontinued study treatment did so due to disease progression. A small proportion of patients discontinued treatment due to an AE (4.9% on the olaparib arm versus 7.7% on the physician's choice of chemotherapy arm).

Table 6: Patient disposition (all patients) (DCO 9 December 2016)

	Number (%) of patients		
	Olaparib 300 mg bd	**Physician's choice chemotherapy**	**Total**
Patients enrolled[a]			344
Patients randomised	205 (100)	97 (100)	302 (100)
Patients who were not randomised[b]			42
Patient decision			2 (4.8)
Eligibility criteria not fulfilled			38 (90.5)
Other			2 (4.8)
Full analysis set[c]	205 (100)	97 (100)	302 (100)
Patients who received study treatment	205 (100)	91 (93.8)	296 (98.0)
Number who received olaparib (AZD2281)	205 (100)	0	205 (67.9)
Number who received capecitabine	0	41 (42.3)	41 (13.6)
Number who received vinorelbine	0	16 (16.5)	16 (5.3)
Number who received eribulin	0	34 (35.1)	34 (11.3)
Patients who did not receive study treatment	0	6 (6.2)	6 (2.0)
Patients ongoing study treatment at data cut-off[d]	36 (17.6)	3 (3.3)	39 (13.2)
Patients who discontinued study treatment[d, f]	169 (82.4)	88 (96.7)	257 (86.8)
Patient decision	7 (3.4)	9 (9.9)	16 (5.4)
Adverse event	10 (4.9)	6 (6.6)	16 (5.4)
Objective disease progression	149 (72.7)	68 (74.7)	217 (73.3)
Other	3 (1.5)	5 (5.5)	8 (2.7)
Patients continuing study off treatment at data cut-off[c, e]	68 (33.2)	41 (42.3)	109 (36.1)
Patients who prematurely withdrew from the study before data cut-off[c, e]	101 (49.3)	53 (54.6)	154 (51.0)
Patient decision	5 (2.4)	7 (7.2)	12 (4.0)
Death	94 (45.9)	46 (47.4)	140 (46.4)
Patient lost to follow-up	1 (0.5)	0	1 (0.3)
Other	1 (0.5)	0	1 (0.3)

[a] Main informed consent received.
[b] Percentages for reasons patients were not randomised are calculated from the number of patients who were not randomised.
[c] Percentages were calculated from number of patients randomised.
[d] Percentages were calculated from number of patients who received treatment.
[e] May have included patients who never received study treatment.
[f] Included patients who withdrew consent from the study as well as patients who stopped study treatment but continued to be followed for progression and overall survival.
bd, twice daily

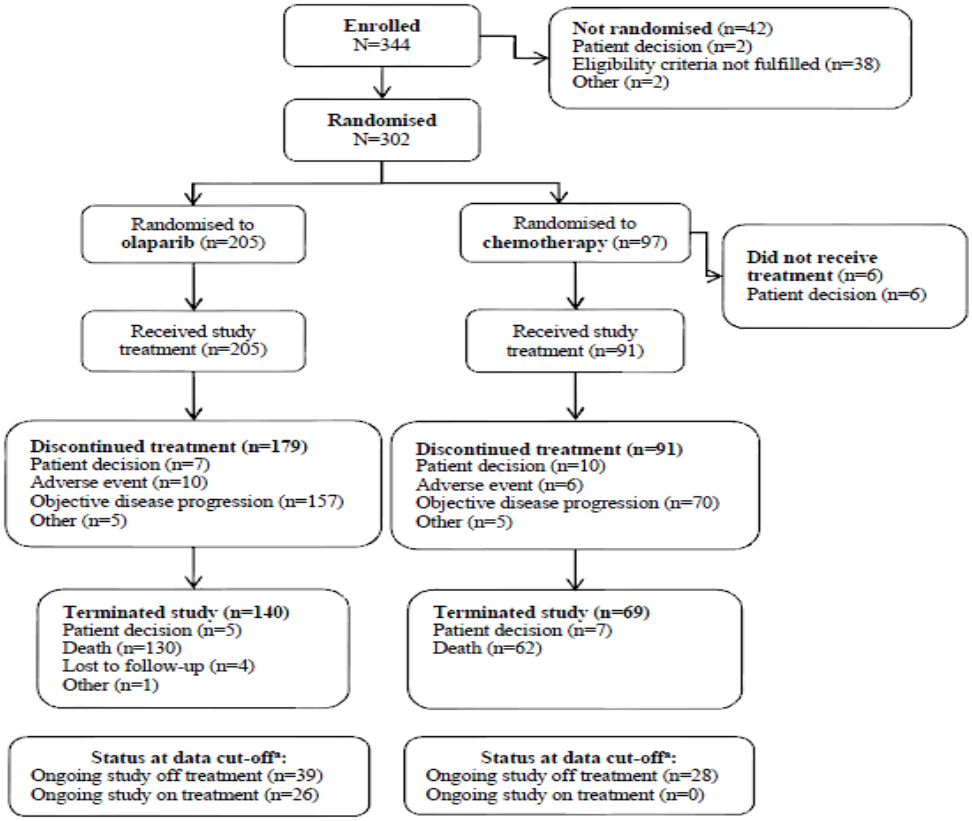


Figure 4: Patient disposition at data cut-off for final OS analysis (all patients) (DCO 25 September 2017)

Recruitment

The study was open for enrolment at 206 study centres in 19 countries: Bulgaria (8 centres), China (15 centres), Czech Republic (3 centres), France (5 centres), Hungary (7 centres), Italy (7 centres), Japan (9 centres), South Korea (8 centres), Mexico (7 centres), Peru (8 centres), Poland (10 centres), Romania (6 centres), Russia (12 centres), Spain (10 centres), Switzerland (3 centres), Taiwan (6 centres), Turkey (11 centres), United Kingdom (7 centres), United States (64 centres).

The first patient was enrolled into the study on 27 March 2014 and the last patient was enrolled into the study on 30 October 2015.

Conduct of the study

Protocol amendments

The original CSP was dated 8 November 2013. Important amendments to the original CSP, including their effective date with respect to patient recruitment, are shown in Table 3 with other significant changes to study conduct.

Table 7: 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: Substantive changes		
Amendment 1 (12 August 2014)	Text describing patient survival procedures was revised (Section 5.1; Table 2).	To specify time points when patients should be contacted for survival data.
	Text was revised to update the number of PFS events required for the interim and final analyses (Section 5.1).	To update the number of progression events that will define the timing of PFS analyses.
	Family history of cancer added to the study schedule (Table 2).	To collect data to potentially inform and refine future recommendations for tailoring genetic testing.
	Revision of inclusion criterion number 10 to specify the requirement for serum or plasma creatinine (Section 5.3.1).	Extension of creatinine analysis and to meet local laboratories' routine requirements.
	Secondary objective number 4 was added, to include the exposure to olaparib in patients receiving olaparib monotherapy (Section 4.2).	Collection of PK samples to allow concentration-effect modelling.
	Text added to describe collection of PK samples (Section 5.1; Table 2; Section 5.3).	Collection of PK samples to allow concentration-effect modelling.
	Text was added to include PK blood sampling collection procedures (Section 5.5.4).	Collection of PK samples to allow concentration-effect modelling.
	Text added to clarify analysis of plasma concentration-time data (Section 5.7.4.6).	Collection of PK samples to allow concentration-effect modelling.
	The number of required progression events was updated and clarification of the timings of the interim and final analyses of OS and PFS2 was made (Section 5.7.3; Section 5.7.7; Section 5.7.8).	To update the number of progression events required to have 90% power to detect a significant treatment effect. To specify OS and PFS2 analyses time points.
	Text was revised to allow repeat olaparib interruptions and dose reductions under certain conditions.	Clarification of dose management.
	The definition of best overall RECIST response was revised (Section 5.7.3; Section 5.7.4.3).	Clarification that RECIST responses that occurred on subsequent cancer therapy should be excluded from the derivation of best overall response.
	Text describing multiplicity strategy for primary and key secondary endpoints was revised.	To clarify the multiple testing procedure and to allow for the inclusion of an interim PFS analysis. To specify the significance levels to test PFS, PFS2 and OS against at the interim and final PFS analysis time points to ensure that the overall type I error was controlled at a 2.5% 1-sided level.
	Revision of text describing analysis of the primary endpoint (Section 5.7.3).	To update the number of progression events that defined the timing of the PFS analyses. To ensure that the primary analysis was stratified according to how patients were stratified in the randomisation as per the study design and to specify that if any patients were stratified incorrectly, a sensitivity analysis would be carried out using the correct data from the eCRF.
	Revision of text describing analysis of the PFS2 endpoint (Section 5.7.4.1).	To specify that PFS2 would be analysed at both interim and final PFS analysis time points, to give further detail regarding the presentation of PFS2 data and to refer to the supportive endpoint by its recognised name, TSST.
	Revision of text describing analysis of the OS endpoint	To specify that OS would be analysed at both interim and final PFS analysis time points.
	Text describing interim analysis methods was revised	An interim analysis with low p-value allocation was added to allow an earlier termination of the study in case the treatment differential was much larger than anticipated. An Independent Data Monitoring Committee was set to perform this analysis and to monitor safety and efficacy data on a regular basis.
	Text describing the determination of sample size was revised (Section 5.7.7).	To update the number of progression events required to have 90% power to detect a significant treatment effect, given the assumptions stated and allowing for an interim PFS analysis.
	Text describing the role of the Independent Data Monitoring Committee was revised (Section 5.7.9).	An Independent Data Monitoring Committee was to perform the interim analysis and to monitor safety and efficacy data on a regular basis.

Protocol Amendment 2: Substantive changes		
Amendment 2 (21 August 2015)	The planned interim analysis was removed from the study (Section 5.7.8).	Interim analysis was not to be performed in recognition of the regulatory landscape, to ensure robust event rates and address issues with crossover (to off-label drug in light of commercial availability of olaparib) which would dilute a potential effect on the secondary endpoints, particularly OS.
	Text describing the management of olaparib toxicity was revised.	Revised guidelines for the management of olaparib toxicity.
	Text describing the management of haematological toxicity was revised.	Revised guidelines for the management of haematological toxicity and anaemia.
	Text describing reasons for study withdrawal was revised (Section 5.3.4.2).	Added a Sponsor decision as a reason for patient withdrawal from the study.
	Text describing patient survival procedures was revised.	Removed interim analysis and added a window for survival contact.
	Text was revised to include the evaluable for response (EFR) analysis set (Section 5.7.2.3).	To define an additional analysis set used for the objective response rate, in line with the SAP.
	Formal statistical analyses to be conducted and pre-planned sensitivity analyses, was revised to include QoL assessments (Section 5.7.4.5).	To specify that QoL data were to be formally analysed.
	Text describing the multiplicity strategy for primary and key secondary endpoints was revised.	To remove the indications of the interim analysis from the protocol text and to use O'Brien-Fleming boundaries to preserve the type I error.
	Text describing analysis of the primary endpoint was revised to include status of progressive disease at time of randomisation as a subgroup (Section 5.7.3).	To specify an additional subgroup analysis.
Protocol Amendment 3: Substantive changes		
Amendment 3 (10 September 2015)	Text describing the analysis of PFS was revised to remove the first analysis of PFS (Section 5.7.3).	To specify that PFS would only be analysed when approximately 230 progression events had occurred

[a] All protocol amendments were approved by AstraZeneca before being submitted to a regulatory authority and/or an Institutional Review Board/Independent ethics committee.

Abbreviations: AE, adverse event; *BRCA*, breast cancer susceptibility gene; CYP3A, cytochrome P450 3A; ECG, electrocardiogram; eCRF, electronic case report form; OS, overall survival; PFS, progression free survival; PFS2, time from randomisation to second progression or death; PK, pharmacokinetic; PRO, patient reported outcomes; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors version 1.1; SAP, statistical analysis plan; SPC, Summary of Product Characteristics; TSST, time to start of second subsequent cancer therapy or death.

Changes to planned analyses

Table 8: Changes to planned analysis

Key details of change (section of this report affected)	Reason for change
Additional summaries of duration of response, time to onset of response and disease control rate were added. (see CSP Sections 11.1.2.3 and 12.2.3.3 and SAP Section 6)	To support the analysis
An additional supportive analysis of time to HRQoL deterioration was added. (see CSP Sections 11.3 and 12.2.3.4 and SAP Section 6)	To provide details and analyses of the PRO endpoints
The formula for calculating the log-rank statistic was corrected to the formula for the stratified log-rank statistic. (see CSP Section 12.2.2 and SAP Section 6)	To update the formula to be appropriate for the primary analysis
A novel mutation subgroup analysis was added. (see CSP Section 12.2.2 and SAP Section 6)	To support the PMA submission
The model used to analyse change from baseline in HRQoL score was updated to include an interaction term for baseline global QoL score and visit. (see CSP Section 12.2.3.4 and SAP Section 6)	To have a data cut-off at a point when most of the patients had discontinued and no longer had HRQoL assessments
An additional category 'no evidence of disease' was added for best objective response in case of any BICR reviewers concluding no disease at baseline. (CSP Sections 11.1.2.3 and 12.2.3.3 and SAP Section 6)	To provide a category for BICR reviewers concluding no disease at baseline
Potential exploratory analyses of OS to adjust for the impact of receiving a subsequent PARP inhibitor were extended to PFS2. (CSP Section 12.2.4 and SAP Section 6)	To further understand the potential impact of receiving a subsequent PARP inhibitor

Abbreviations: CSP, clinical study protocol; HRQoL, health-related quality of life; PMA, pre-marketing approval; QoL, quality of life; SAP, statistical analysis plan.

Protocol deviations

Overall, the proportion of patients with at least 1 important protocol deviation was 4.0%, and balanced between the treatment arms: 3.9% on olaparib and 4.1% on physician's choice of chemotherapy. In total, 14 important protocol deviations were reported (9 and 5 in the olaparib arm and physician's choice of chemotherapy arm, respectively). The most common important deviation observed in both treatment arms was exclusion criteria met: 5 patients (2.4%) in the olaparib arm and 4 (4.1%) in the physician's choice of chemotherapy arm.

Table 9: Important protocol deviations (FAS)

	Number (%) of patients		
Important protocol deviation[a]	Olaparib 300 mg bd (N=205)	Physician's choice chemotherapy (N=97)	Total (N=302)
Number of patients with at least 1 important deviation	8 (3.9)	4 (4.1)	12 (4.0)
Exclusion criteria met: Cytotoxic chemotherapy, non-hormonal targeted or endocrine therapy, palliative radiotherapy, bisphosphonates or denosumab for bone metastases within a disallowed time from start of study treatment	5 (2.4)	4 (4.1)	9 (3.0)
Inclusion criteria not met: Patients must have normal organ and bone marrow function measured within 28 days of randomisation	2 (1.0)	0	2 (0.7)
Inclusion criteria not met: Patients must have received treatment with an anthracycline (eg, doxorubicin, epirubicin) and a taxane (eg, paclitaxel, docetaxel) in either a neoadjuvant/adjuvant or metastatic setting	1 (0.5)	0	1 (0.3)
Inclusion criteria not met: Patients who received platinum (cisplatin or carboplatin) for advanced breast cancer are eligible if there was no evidence of disease progression during the platinum chemotherapy	0	1 (1.0)	1 (0.3)
Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment	1 (0.5)	0	1 (0.3)

[a] Important deviations before the start of treatment and during treatment.
Note: The same patient may have had more than 1 important protocol deviation.
bd, twice daily; N, number of patients.

None of the important protocol deviations were considered to have the potential to influence the overall study conclusions in a relevant way. The study conclusions are considered robust and representative of the overall study data.

Baseline data

The demographic and key baseline characteristics of study patients are summarised below.

Table 10: OlympiAD: Summary of selected demographic and patient characteristics at baseline (FAS and Myriad CDx *gBRCAm* subgroup)

	FAS		Myriad CDx *gBRCAm*	
	Olaparib 300 mg bd (n=205)	**Physician's choice[a] (n=97)**	**Olaparib 300 mg bd (n=202)**	**Physician's choice[a] (n=95)**
Demographics				
Age (years)				
Mean (SD)	45.0 (10.9)	45.9 (10.3)	45.2 (10.9)	46.0 (10.4)
Median (range)	44.0 (22 – 76)	45.0 (24 – 68)	44.0 (22 – 76)	45.0 (24 – 68)
Age arm (years), n (%)				
<50	138 (67.3)	63 (64.9)	136 (67.3)	62 (65.3)
≥50 to <65	56 (27.3)	30 (30.9)	55 (27.2)	29 (30.5)
≥65	11 (5.4)	4 (4.1)	11 (5.4)	4 (4.2)
Sex, n (%)				
Female	200 (97.6)	95 (97.9)	197 (97.5)	93 (97.9)
Male	5 (2.4)	2 (2.1)	5 (2.5)	2 (2.1)
Race, n (%)				
White	134 (65.4)	63 (64.9)	132 (65.3)	61 (64.2)
Asian	66 (32.2)	28 (28.9)	65 (32.2)	28 (29.5)
Black/African American	1 (0.5)	4 (4.1)	1 (0.5)	4 (4.2)
Other	4 (2.0)	2 (2.1)	4 (2.0)	2 (2.1)
Ethnicity, n (%)				
Hispanic or Latino	11 (5.4)	6 (6.2)	11 (5.4)	6 (6.3)
Not Hispanic or Latino	194 (94.6)	91 (93.8)	191 (94.6)	89 (93.7)
Disease characteristics				
ECOG performance status, n (%)				
(0) Normal activity	148 (72.2)	62 (63.9)	146 (72.3)	60 (63.2)
(1) Restricted activity	57 (27.8)	35 (36.1)	56 (27.7)	35 (36.8)
Myriad germline *BRCA* status				
BRCA1	114 (55.6)	50 (51.5)	114 (56.4)	50 (52.6)
BRCA2	84 (41.0)	45 (46.4)	84 (41.6)	45 (47.4)
BRCA1 and *BRCA2*	4 (2.0)	0	4 (2.0)	0
Missing[b]	3 (1.5)	2 (2.1)	NA	NA
Tumour characteristics				
Tumour grade at diagnosis				
Well Differentiated (G1)	5 (2.4)	2 (2.1)	5 (2.5)	2 (2.1)
Moderately Differentiated (G2)	52 (25.4)	23 (23.7)	52 (25.7)	22 (23.2)
Poorly Differentiated (G3)	108 (52.7)	55 (56.7)	106 (52.5)	54 (56.8)
Undifferentiated (G4)	4 (2.0)	0	4 (2.0)	0
Unassessable (GX)	27 (13.2)	15 (15.5)	26 (12.9)	15 (15.8)
Missing	9 (4.4)	2 (2.1)	9 (4.5)	2 (2.1)

	FAS		Myriad CDx *gBRCAm*	
	Olaparib 300 mg bd (n=205)	**Physician's choice[a] (n=97)**	**Olaparib 300 mg bd (n=202)**	**Physician's choice[a] (n=95)**
At the time of randomisation, was the patient's breast cancer progressing?				
Yes	159 (77.6)	73 (75.3)	157 (77.7)	71 (74.7)
Overall disease classification				
Locally advanced	0	0	0	0
Metastatic	205 (100)	97 (100)	205 (100)	97 (100)
De Novo Metastatic Disease[c]				
Yes	26 (12.7)	12 (12.4)	NC	NC
Prior endocrine therapy				
For metastatic disease	68 (33.2)	30 (30.9)	NC	NC
For localised disease (adjuvant and/or neoadjuvant)	80 (39.0)	36 (37.1)	NC	NC
Stratification factors (IVRS data)				
Received prior chemotherapy regimens for metastatic breast cancer[d], n (%)				
No	59 (28.8)	28 (28.9)	NC	NC
Yes	146 (71.2)	69 (71.1)	NC	NC
ER and PgR status[e], n (%)				
ER and/or PgR positive	103 (50.2)	49 (50.5)	103 (51.0)	48 (50.5)
ER and PgR negative	102 (49.8)	48 (49.5)	99 (49.0)	47 (49.5)
Prior use of platinum for breast cancer, n (%)[f]				
Yes	60 (29.3)	26 (26.8)	NC	NC

[a] Physician's choice of chemotherapy consisting of either capecitabine, eribulin or vinorelbine.
[b] Patients with Missing status were not confirmed as *gBRCAm* using the Myriad CDx *gBRCA* test. Within the olaparib arm all 3 cases were determined as *BRCA1* by local or CLIA testing and within the physician's choice of chemotherapy arm 1 patient was *BRCA1* and 1 patient was *BRCA2*.
[c] Metastatic disease at time of initial diagnosis of breast cancer.
[d] According to the electronic case report form data, 68 patients in the olaparib arm and 31 patients in the physician's choice of chemotherapy arm had not received prior chemotherapy regimens for metastatic breast cancer.
[e] According to the electronic case report form data, 102 patients in the olaparib arm and 47 patients in the physician's choice of chemotherapy arm were ER and/or PgR positive. Patient E2806008 did not have PgR status assessed but was stratified to the ER negative and PgR negative subgroup for randomisation. The patient was excluded from summaries of eCRF data.
[f] According to the electronic case report form data, 55 patients in the olaparib arm and 21 patients in the physician's choice of chemotherapy arm had prior use of platinum for breast cancer.

bd Twice daily; *BRCA* Breast cancer susceptibility gene; CDx Companion diagnostic; CLIA Clinical laboratory improvement amendments; ECOG Eastern cooperative oncology arm; eCRF electronic case report form; ER Estrogen receptor; FAS Full analysis set; *gBRCA* Germline *BRCA*; IVRS Interactive Voice Response System; NA Not applicable; NC Not calculated; PgR Progesterone receptor; SD Standard deviation.
Source: Table 11.1.4, Table 11.1.4m, Table 11.1.6, Table 11.1.8, Table 11.1.8m, Table 11.1.10.2, Table 11.1.10.4, Table 11.1.10.4m, and Table 11.1.11, OlympiAD CSR, Module 5.3.5.1.

Previous disease-related treatment modalities

Table 11: Previous disease-related treatment modalities (FAS)

	Previous Regimen Number	Previous treatment modalities	Number (%) of patients Olaparib 300 mg bd (N=205)	Chemotherapy (N=97)	Total (N=302)
Metastatic Disease	Any		153 (74.6)	68 (70.1)	221 (73.2)
		Anthracyclines	41 (20.0)	16 (16.5)	57 (18.9)
		Taxanes	107 (52.2)	41 (42.3)	148 (49.0)
		Platinum containing chemotherapy	43 (21.0)	14 (14.4)	57 (18.9)
		Other cytotoxic chemotherapy	94 (45.9)	43 (44.3)	137 (45.4)
		Bevacizumab or everolimus	31 (15.1)	9 (9.3)	40 (13.2)
		Endocrine therapy	68 (33.2)	30 (30.9)	98 (32.5)
		Other systemic therapies	6 (2.9)	6 (6.2)	12 (4.0)
	1st [a]	Anthracyclines	36 (17.6)	15 (15.5)	51 (16.9)
		Taxanes	90 (43.9)	32 (33.0)	122 (40.4)
		Platinum containing chemotherapy	31 (15.1)	11 (11.3)	42 (13.9)
		Other cytotoxic chemotherapy	76 (37.1)	39 (40.2)	115 (38.1)
	2nd [a]	Anthracyclines	7 (3.4)	1 (1.0)	8 (2.6)
		Taxanes	24 (11.7)	11 (11.3)	35 (11.6)
		Platinum containing chemotherapy	16 (7.8)	4 (4.1)	20 (6.6)
		Other cytotoxic chemotherapy	36 (17.6)	13 (13.4)	49 (16.2)
Localized Disease (adjuvant and/or neoadjuvant)	Any		180 (87.8)	80 (82.5)	260 (86.1)
		Anthracyclines	169 (82.4)	76 (78.4)	245 (81.1)
		Taxanes	146 (71.2)	66 (68.0)	212 (70.2)
		Platinum containing chemotherapy	15 (7.3)	7 (7.2)	22 (7.3)
		Other cytotoxic chemotherapy	156 (76.1)	73 (75.3)	229 (75.8)
		Bevacizumab or everolimus	1 (0.5)	2 (2.1)	3 (1.0)
		Endocrine therapy	80 (39.0)	36 (37.1)	116 (38.4)
		Other systemic therapies	3 (1.5)	1 (1.0)	4 (1.3)

Patients may appear under more than one previous treatment modality.
Patients who received disease related previous therapy will be counted at least once under the category of Any and at least once under the relevant regimen number.
[a] Only cytotoxic chemotherapies are summarised under an individual regimen number.
PROGRAM: AZD0819C00003\Trunk\TLF\T11011002.SAS Executed: 15MAR2017: 2:59 Extracted: 10FEB2017.
Data cut-off: 09DEC2016

Patients may appear under more than one previous treatment modality.
Patients who received disease related previous therapy will be counted at least once under the category of Any and at least once under the relevant regimen number.
[a] Only cytotoxic chemotherapies are summarised under an individual regimen number.
PROGRAM: AZD0819C00003\Trunk\TLF\T11011002.SAS Executed: 15MAR2017: 2:59 Extracted: 10FEB2017.
Data cut-off: 09DEC2016

Prior endocrine therapy in patients with HR+ breast cancer

Table 12: OlympiAD: Prior endocrine therapy in patients with HR+ breast cancer (FAS)

	Olaparib 300 mg bd N=205	Physician's choice of chemotherapy N=97
Patients who were HR+, n (%)	**103 (50.2)**	**49 (50.5)**
Patients who received endocrine therapy in the adjuvant setting, n (%)	71 (68.9[a])	36 (73.5[a])
Patients who received endocrine therapy in the metastatic setting, n (%)	66 (64.1[a])	28 (57.1[a])

Percentage value based on the number of patients who were hormone receptor positive.

bd Twice daily; HR+ Hormone receptor positive

Note: Patient numbers are not mutually exclusive, and patient could have received prior endocrine treatment in both the adjuvant and metastatic settings.

Six (5.8%) patients in olaparib arm and 4 (8.2%) in chemotherapy arm did not receive prior endocrine therapy while they were HR+. Among these patients, 4 were mis-stratified as HR+ instead of TNBC, 5 were considered to have a disease inappropriate for endocrine therapy by the investigator (not specified for 1 patient, progressive breast cancer during the neoadjuvant therapy for 1 patient, low HR expression for 2 patients, luminal B for 1 patient), 1 were not justified.

Previous disease-related cytotoxic chemotherapy

The taxanes (docetaxel and paclitaxel) were the most commonly used followed by capecitabine or gemcitabine for metastatic disease. Regarding prior platinum therapy, 43 (21.0%) patients in the olaparib arm and 14 (14.4%) in the physician's choice of chemotherapy arm had received platinum for metastatic disease; 15 (7.3%) patients in the olaparib arm and 7 (7.2%) in the physician's choice of chemotherapy arm had received platinum for localised disease. The median number of regimens of previous disease-related chemotherapy at baseline was 1.0 in both treatment arms. The number of regimens of previous disease-related chemotherapy at baseline (FAS) is summarized Table 13.

Table 13: Number of regimens of previous disease-related chemotherapy at baseline (FAS)

	Number (%) of patients		
Number of regimens*	Olaparib 300 mg bd (N=205)	Physician's choice chemotherapy (N=97)	Total (N=302)
0	68 (33.2)	31 (32.0)	99 (32.8)
1	80 (39.0)	42 (43.3)	122 (40.4)
2	57 (27.8)	24 (24.7)	81 (26.8)
n	205	97	302
Mean	0.9	0.9	0.9
Standard deviation	0.78	0.75	0.77
Median	1.0	1.0	1.0

* Only cytotoxic chemotherapies for metastatic disease are included.
bd, twice daily; N, number of patients in treatment group; n, number of patients.

Table 14: Previous disease-related cytotoxic chemotherapy treatments in localised disease (FAS)

		Number (%) of patients		
Group	Previous treatment	Olaparib 300 mg bd (N=205)	Chemotherapy (N=97)	Total (N=302)
Localized Disease (adjuvant and/or neoadjuvant)	CAPECITABINE	8 (3.9)	0	8 (2.6)
	CARBOPLATIN	7 (3.4)	5 (5.2)	12 (4.0)
	CISPLATIN	8 (3.9)	2 (2.1)	10 (3.3)
	CYCLOPHOSPHAMIDE	154 (75.1)	72 (74.2)	226 (74.8)
	DOCETAXEL	93 (45.4)	38 (39.2)	131 (43.4)
	DOXORUBICIN	92 (44.9)	33 (34.0)	125 (41.4)
	DOXORUBICIN HYDROCHLORIDE	2 (1.0)	2 (2.1)	4 (1.3)
	EPIRUBICIN	64 (31.2)	36 (37.1)	100 (33.1)
	EPIRUBICIN HYDROCHLORIDE	5 (2.4)	4 (4.1)	9 (3.0)
	FLUOROURACIL	59 (28.8)	36 (37.1)	95 (31.5)
	GEMCITABINE	2 (1.0)	2 (2.1)	4 (1.3)
	GIMERACIL+OTERACIL POTASSIUM+TEGAFUR	0	1 (1.0)	1 (0.3)
	LOBAPLATIN	0	1 (1.0)	1 (0.3)
	METHOTREXATE	9 (4.4)	6 (6.2)	15 (5.0)
	MITOXANTRONE	0	1 (1.0)	1 (0.3)
Localized Disease (adjuvant and/or neoadjuvant)	NAB-PACLITAXEL	4 (2.0)	3 (3.1)	7 (2.3)
	PACLITAXEL	65 (31.7)	31 (32.0)	96 (31.8)
	PIRARUBICIN	9 (4.4)	1 (1.0)	10 (3.3)
	TEGAFUR	0	1 (1.0)	1 (0.3)
	VINCRISTINE	3 (1.5)	0	3 (1.0)
	VINORELBINE	1 (0.5)	1 (1.0)	2 (0.7)
	VINORELBINE DITARTRATE	1 (0.5)	0	1 (0.3)

Table 15: Previous disease-related cytotoxic chemotherapy treatments in the metastatic setting according to line of therapy (FAS)

		Number of patients		
Previous regimen number	**Previous treatment**	**Olaparib 300 mg bd (N=205)**	**Chemotherapy (N=97)**	**Total (N=302)**
1	Paclitaxel	56 (27.3)	24 (24.7)	80 (26.5)
	Capecitabine	25 (12.2)	7 (17.5)	42 (13.9)
	Docetaxel	30 (14.6)	9 (9.3)	39 (12.9)
	Cyclophosphamide	23 (11.2)	11 (11.3)	34 (11.3)
	Gemcitabine	23 (11.2)	8 (8.2)	31 (10.3)
	Doxorubicin	18 (8.8)	10 (10.3)	28 (9.3)
	Carboplatin	18 (8.8)	7 (7.2)	25 (8.3)
	Epirubicin	14 (6.8)	3 (3.1)	17 (5.6)
	Cisplatin	10 (4.9)	4 (4.1)	14 (4.6)
	Vinorelbine	5 (2.4)	3 (3.1)	8 (2.6)
	Gemcitabine hydrochloride	6 (2.9)	1 (1.0)	7 (2.3)
	Nab-paclitaxel	5 (2.4)	2 (2.1)	7 (2.3)
	Fluorouracil	4 (2.0)	2 (2.1)	6 (2.0)
	Doxorubicin hydrochloride	3 (1.5)	1 (1.0)	4 (1.3)
	Eribulin	1 (0.5)	3 (3.1)	4 (1.3)

	Lobaplatin	3 (1.5)	1 (1.0)	4 (1.3)
	Investigational drug	3 (1.5)	0	3 (1.0)
	Gimeracil+oteracil potassium+tegafur	0	2 (2.1)	2 (0.7)
	Ixabepilone	2 (1.0)	0	2 (0.7)
	Nedaplatin	2 (1.0)	0	2 (0.7)
	Methotrexate	1 (0.5)	0	1 (0.3)
	Antineoplastic agents	0	1 (1.0)	1 (0.3)
	Daunorubicin	0	1 (1.0)	1 (0.3)
	Pirarubicin	1 (0.5)	0	1 (0.3)
	Lobaplatin	3 (1.5)	1 (1.0)	4 (1.3)
	Investigational drug	3 (1.5)	0	3 (1.0)
	Gimeracil+oteracil potassium+tegafur	0	2 (2.1)	2 (0.7)
2	Paclitaxel	13 (6.3)	7 (7.2)	20 (6.6)
	Capecitabine	12 (5.9)	3 (3.1)	15 (5.0)
	Docetaxel	9 (4.4)	3 (3.1)	12 (4.0)
	Carboplatin	8 (3.9)	2 (2.1)	10 (3.3)
	Gemcitabine	5 (2.4)	4 (4.1)	9 (3.0)
	Cisplatin	7 (3.4)	2 (2.1)	9 (3.0)
	Cyclophosphamide	9 (4.4)	0	9 (3.0)
	Eribulin	4 (2.0)	3 (3.1)	7 (2.3)
	Vinorelbine	4 (2.0)	2 (2.1)	6 (2.0)
	Vinorelbine ditartrate	4 (2.0)	1 (1.0)	5 (1.7)
	Epirubicin	4 (2.0)	0	4 (1.3)
	Doxorubicin	2 (1.0)	1 (1.0)	3 (1.0)
	Fluorouracil	2 (1.0)	1 (1.0)	3 (1.0)
	Nab-paclitaxel	2 (1.0)	1 (1.0)	3 (1.0)
	Methotrexate	2 (1.0)	0	2 (0.7)
	Nedaplatin	2 (1.0)	0	2 (0.7)
	Antineoplastic agents	1 (0.5)	0	1 (0.3)
	Doxorubicin hydrochloride	1 (0.5)	0	1 (0.3)
	Etoposide	1 (0.5)	0	1 (0.3)
	Gemcitabine hydrochloride	1 (0.5)	0	1 (0.3)
	Investigational drug	1 (0.5)	0	1 (0.3)
	Ixabepilone	1 (0.5)	0	1 (0.3)
	Lobaplatin	0	1 (1.0)	1 (0.3)
	Mitomycin	0	1 (1.0)	1 (0.3)
	Vinflunine	1 (0.5)	0	1 (0.3)

bd Twice daily.
Patients can contribute to multiple categories.
Source data: Table 1531.1; Data cut-off: 09 December 2016

Stratification factors

Table 16: Stratification factors (FAS)

Received previous chemotherapy for metastatic breast cancer	Receptor status	Prior platinum for breast cancer	Number (%) of patients		
			Olaparib 300 mg bd (N=205)	Physician's choice chemotherapy (N=97)	Total (N=302)
As randomised (IVRS)					
Yes	ER+ and/or PgR+	Yes	24 (11.7)	10 (10.3)	34 (11.3)
		No	56 (27.3)	27 (27.8)	83 (27.5)
	ER- and PgR-	Yes	32 (15.6)	14 (14.4)	46 (15.2)
		No	34 (16.6)	18 (18.6)	52 (17.2)
No	ER+ and/or PgR+	Yes	0	1 (1.0)	1 (0.3)
		No	23 (11.2)	11 (11.3)	34 (11.3)
	ER- and PgR-	Yes	4 (2.0)	1 (1.0)	5 (1.7)
		No	32 (15.6)	15 (15.5)	47 (15.6)

ER, oestrogen receptor; IVRS, interactive voice response system; PgR, progesterone receptor.
Source: Table 11.1.6.

Numbers analysed

The analysis sets and the number of patients in each analysis set are summarised in Table 17.

Table 17: Analysis sets

	Number (%) of patients		
	Olaparib 300 mg bd	Physician's choice chemotherapy	Total
Patients randomised	205	97	302
Patients included in full analysis set	205	97	302
Patients included in safety analysis set	205	91	296
Patients excluded from safety analysis set[a]	0	6	6
Did not receive treatment	0	6	6
Patients selected for PK assessments	41	NA	41
Patients included in PK analysis set	41	NA	41
Patients excluded from PK analysis set[a]	-	NA	-
Important protocol deviation	-	NA	-
Patients included in the evaluable for response analysis set (BICR)	167	66	233
Patients included in the evaluable for response analysis set (Investigator assessment)	165	72	237

[a] An individual patient could have been excluded for more than 1 reason.
Note: Full analysis set: all randomised patients analysed on an ITT basis. Safety analysis set: all patients who received at least 1 dose of study treatment. PK analysis set: all randomised patients who had PK assessment samples taken at pre-agreed sites, received olaparib as per protocol and did not violate or deviate from the protocol in ways that would significantly affect the PK analyses. Evaluable for response analysis set (BICR): all randomised patients who had measurable disease at baseline as per the RECIST version 1.1 criteria using BICR data. Evaluable for response analysis set (investigator assessment): all randomised patients who had measurable disease at baseline as per the RECIST version 1.1 criteria using investigator assessment data.
bd, twice daily; BICR, blinded independent central review; NA, not applicable; PK, pharmacokinetic; RECIST, Response Evaluation Criteria in Solid Tumors

Outcomes and estimation

Primary variable: PFS by BICR (FAS, DCO 9 December 2016, 77.5% maturity)

Table 18: Progression status at time of PFS analysis (DCO 9 December 2016)

		Number (%) of patients	
Progression status	Type of event	Olaparib 300 mg bd (N=205)	Physician's choice chemotherapy (N=97)
Progression	Total	163 (79.5)	71 (73.2)
	RECIST progression[a]	161 (78.5)	68 (70.1)
	Target lesions[b]	59 (28.8)	23 (23.7)
	Non-target lesions[b]	51 (24.9)	30 (30.9)
	New lesions[b]	77 (37.6)	28 (28.9)
	Death[c]	2 (1.0)	3 (3.1)
No progression	Total	42 (20.5)	26 (26.8)
	Censored RECIST progression[d]	1 (0.5)	1 (1.0)
	Censored death[e]	2 (1.0)	3 (3.1)
	Progression free at time of analysis[f]	36 (17.6)	16 (16.5)
	Lost to follow-up	1 (0.5)	0
	Withdrawn consent	2 (1.0)	6 (6.2)
	Discontinued study[g]	0	0

[a] Only includes progression events that occurred within 2 visits of the last evaluable assessment (excludes censored progressions that occurred after two or more missed visits).
[b] Target lesions, non-target lesions and new lesions are not necessarily mutually exclusive categories.
[c] Death in the absence of RECIST progression. Does not include deaths that occurred after 2 or more missed visits.
[d] RECIST progression event occurred after 2 or more missed visits.
[e] Death occurred after 2 or more missed visits in the absence of RECIST progression.
[f] Patients known to be alive and without RECIST progression, or with no evaluable baseline assessment.
[g] Patients who discontinued the study without consent withdrawal eg, due to site closure.
Note: This analysis was based on independent central review of radiological scans. Modified RECIST version 1.1 was used for independent central review assessments. Although patients were required to enter the study with at least one lesion (measurable and/or non-measurable) based on investigator assessment, independent reviewers may conclude NED at baseline.
bd, twice daily; N, number of patients in treatment group; NED, no evidence of disease; RECIST, Response Evaluation Criteria in Solid Tumors version 1.1.
Source: Table 11.2.1.1.

Table 19: Progression-free survival, stratified log-rank test (DCO 9 December 2016)

			Treatment effect		
			Comparison between groups		
Group	N	Number (%) of patients with events[a]	Hazard ratio	95% CI	2-sided p-value
Olaparib 300 mg bd	205	163 (79.5)	0.58	0.43, 0.80	0.0009
Physician's choice chemotherapy	97	71 (73.2)			

a Progression-free survival was defined as the time from randomisation until date of RECIST progression or death.

Patients who had not progressed or died at the time of analysis, or who progressed or died after 2 or more missed visits, were censored at the latest evaluable RECIST assessment, or Day 1 if the patient had no evaluable visits or no baseline assessment (unless they died within 2 visits of baseline).

Note: A hazard ratio of <1 favours olaparib 300 mg bd. The p-value was determined using log-rank test stratified by received previous chemotherapy regimens for metastatic breast cancer (yes/no), and ER and/or PgR positive versus ER and PgR negative. The hazard ratio and CI were estimated from the stratified log-rank test statistics. This analysis was based on independent central review of radiological scans. Modified RECIST version 1.1 as per Section 5.1. Although patients were required to enter the study with at least one lesion (measurable and/or non-measurable) based on investigator assessment, independent reviewers may conclude NED at baseline.

bd, twice daily; CI, confidence interval; ER estrogen receptor; N, number of patients in treatment group; NED, no evidence of disease; PgR, progesterone receptor; RECIST, Response Evaluation Criteria in Solid Tumors.

Table 20: Median progression-free survival (DCO 9 December 2016)

	Olaparib 300 mg bd (N=205)	Physician's choice chemotherapy (N=97)
Total number of events[a]	163	71
Median progression-free survival (months)[b]	7.03	4.17
95% CI for median progression-free survival	5.68, 8.31	2.79, 4.27
Progression-free at 6 months (%)[b]	54.1	32.9
Progression-free at 12 months (%)[b]	25.9	15.0
Median time from randomisation to censoring (months)[c]	13.62	4.29

[a] Patients who had not progressed or died at the time of analysis, or who progressed or died after 2 or more missed visits, were censored at the latest evaluable RECIST assessment, or Day 1 if the patient had no evaluable visits or no baseline assessment (unless they died within 2 visits of baseline).
[b] Calculated using the Kaplan-Meier technique.
[c] Censored patients only.
Note: Progression included deaths in the absence of RECIST progression. Progression-free included patients who had not progressed or died. This analysis was based on independent central review of radiological scans. RECIST version 1.1. Although patients were required to enter the study with at least one lesion (measurable and/or non-measurable) based on investigator assessment, independent reviewers may conclude NED at baseline.
bd, twice daily; CI, confidence interval; N, number of patients in treatment group; NED, no evidence of disease; RECIST, Response Evaluation Criteria in Solid Tumors.

The Kaplan-Meier plot for the BICR-assessed PFS by modified RECIST version 1.1 is presented in Figure 5 for the FAS.

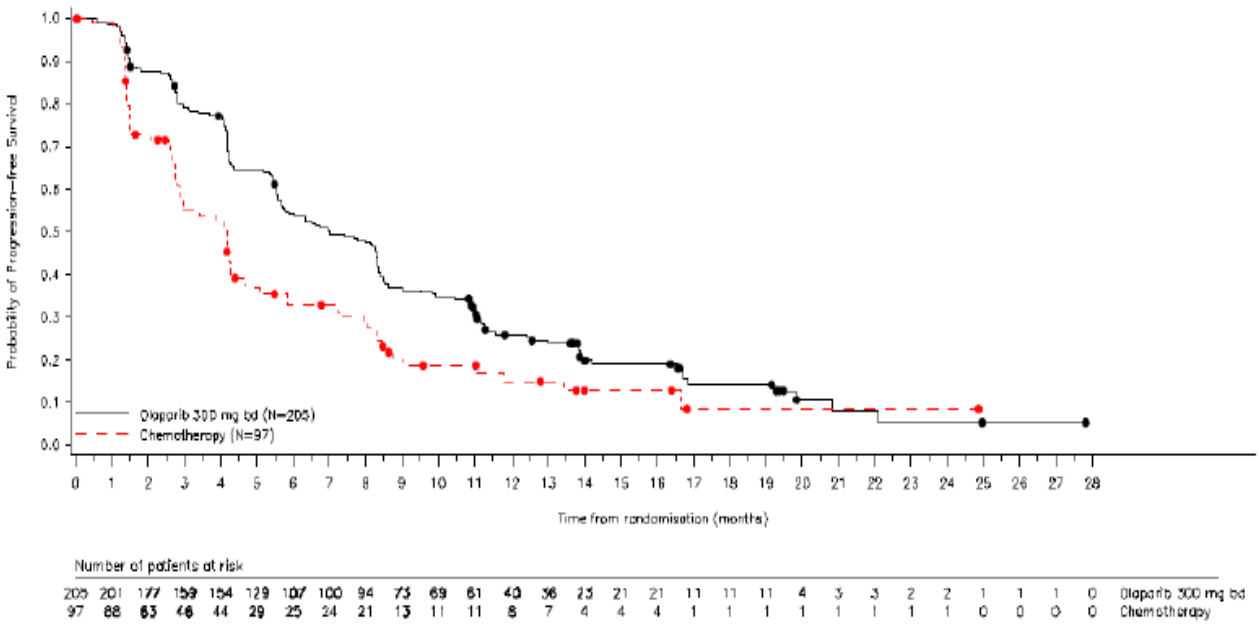


Figure 5: Progression-free survival, Kaplan-Meier plot (FAS) (DCO 9 December 2016)

Supportive and sensitivity analyses of progression-free survival (FAS)

Table 21: Progression-free survival sensitivity analyses (DCO 9 December 2016)

				Treatment effect		
				Comparison between groups		
Analysis	Group	N	Number (%) of patients with events	Hazard ratio	95% CI	2-sided p-value
Removing stratification[a,f]	Olaparib 300 mg bd	205	163 (79.5)	0.59	0.43, 0.80	0.0009
	Physician's choice chemotherapy	97	71 (73.2)			
Ascertainment bias[b,g]	Olaparib 300 mg bd	205	165 (80.5)	0.50	0.36, 0.68	<0.0001
	Physician's choice chemotherapy	97	80 (82.5)			
Evaluation time bias[d,b,f]	Olaparib 300 mg bd	205	163 (79.5)	0.59	0.43, 0.81	0.0012
	Physician's choice chemotherapy	97	71 (73.2)			
Attrition bias[c,b,f]	Olaparib 300 mg bd	205	154 (75.1)	0.53	0.38, 0.74	0.0002
	Physician's choice chemotherapy	97	66 (68.0)			
Adjusted for progressive disease at randomisation[e,f]	Olaparib 300 mg bd	205	163 (79.5)	0.59	0.45, 0.79	0.0004
	Physician's choice chemotherapy	97	71 (73.2)			
Using eCRF data to define stratification factors[h]	Olaparib 300 mg bd	205	163 (79.5)	0.58	0.42, 0.79	0.0007
	Physician's choice chemotherapy	96	71 (74.0)			

[a] The p-value was determined using unstratified log rank test.
[b] The p-value was determined using log-rank test stratified by received previous chemotherapy regimens for metastatic breast cancer (yes/no), ER- and/or PgR-positive versus ER- and PgR-negative and prior platinum for breast cancer (yes/no) based on IVRS stratification data at randomisation.
[c] Patients who progressed or died after 2 or more missed visits were not censored. Patients who took subsequent therapy prior to progression or death were censored at their last evaluable RECIST assessment prior to taking the subsequent therapy.
[d] Progression-free survival was taken as the midpoint between the time of progression and previous evaluable RECIST assessment.
[e] The p-value was determined using a Cox proportional hazards model containing factors for treatment, received previous chemotherapy regimens for metastatic breast cancer (yes/no) and progressive disease at the time of randomisation (yes/no), ER and/or PgR positive versus ER and PgR negative, prior platinum for breast cancer (yes/no). The HR was estimated from the model and CI calculated using a profile likelihood approach.
[f] This analysis is based on independent central review of radiological scans.
[g] This analysis is based on investigator assessment of radiological scans.
[h] The p-value was determined using log-rank test stratified by received previous chemotherapy regimens for metastatic breast cancer (yes/no), and ER and/or PgR positive versus ER and PgR negative, defined according to eCRF data. The HR and CI were estimated from the stratified log-rank test statistics.

Patient E2806008 was ER negative, did not have PgR status assessed and is excluded from analysis

Table 22: Concordance between investigator and central reviews of RECIST progression (DCO 9 December 2016)

Progression	Number (%) of patients		Difference
	Olaparib 300 mg bd (N=205)	Physician's choice chemotherapy (N=97)	Olaparib 300 mg bd - Placebo
RECIST progression[a] declared by			
Investigator and central review	156 (76.1)	70 (72.2)	NA
Progression date agreement (within 2 weeks)	92 (44.9)	40 (41.2)	NA
Progression date ≥2 weeks earlier by central review than by investigator	46 (22.4)	23 (23.7)	NA
Progression date ≥2 weeks earlier by investigator than by central review	18 (8.8)	7 (7.2)	NA
Investigator but not central review	9 (4.4)	10 (10.3)	NA
Central review but not investigator	7 (3.4)	1 (1.0)	NA
No progression by both	33 (16.1)	16 (16.5)	NA
Early discrepancy rate %[b]	16.36	21.25	-4.89
Late discrepancy rate %[c]	66.25	58.54	7.71

[a] Progression events that occur after two or more missed visits, are censored at the latest evaluable RECIST assessment, or Day 1 if the patient has no evaluable visits or no baseline assessment (unless they die within 2 visits of baseline).

[b] Early discrepancy rate is the frequency of investigator review progressions declared before the BICR (≥2 weeks earlier and including progressions declared by investigator but not BICR) as a proportion of all investigator review progressions.

[c] Late discrepancy rate is the frequency of investigator review progressions declared after the BICR (≥2 weeks later and including progressions declared by BICR but not investigator) as a proportion of all discrepancies (including early and late discrepancies).

Modified RECIST version 1.1 was used for independent central review assessments. RECIST version 1.1 for investigator assessment.

bd, twice daily; BICR, blinded independent central review; NA, not applicable; RECIST Response Evaluation Criteria in Solid Tumors.

Secondary variables

Time to second progression or death (PFS2; FAS)

In both treatment arms, of the patients who had a second progression or died, the majority were based on investigator-assessed radiological assessment. At the time of the primary analysis, 32.7% of olaparib-treated patients and 24.7% of comparator-treated patients had no second progression or death event.

Table 23: Time to second progression or death (PFS2), stratified log-rank test (DCO: 09 December 2016)

Group	N	Treatment effect			
		Comparison between groups			
		Number (%) of patients with events[a]	Hazard ratio	95% CI	2-sided p-value
Olaparib 300 mg bd	205	104 (50.7)	0.57	0.40, 0.83	0.0033
Physician's choice chemotherapy	97	53 (54.6)			

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.

A hazard ratio <1 favours Olaparib 300 mg bd.

The p-value was determined using log-rank test stratified by received previous chemotherapy regimens for metastatic breast cancer (yes/no), and ER and/or PgR positive versus ER and PgR negative. The hazard ratio (HR) and confidence

interval (CI) were estimated from the stratified log-rank test statistics.
The analysis is based on the investigator assessment of second progression.
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Data cut-off: 09DEC2016

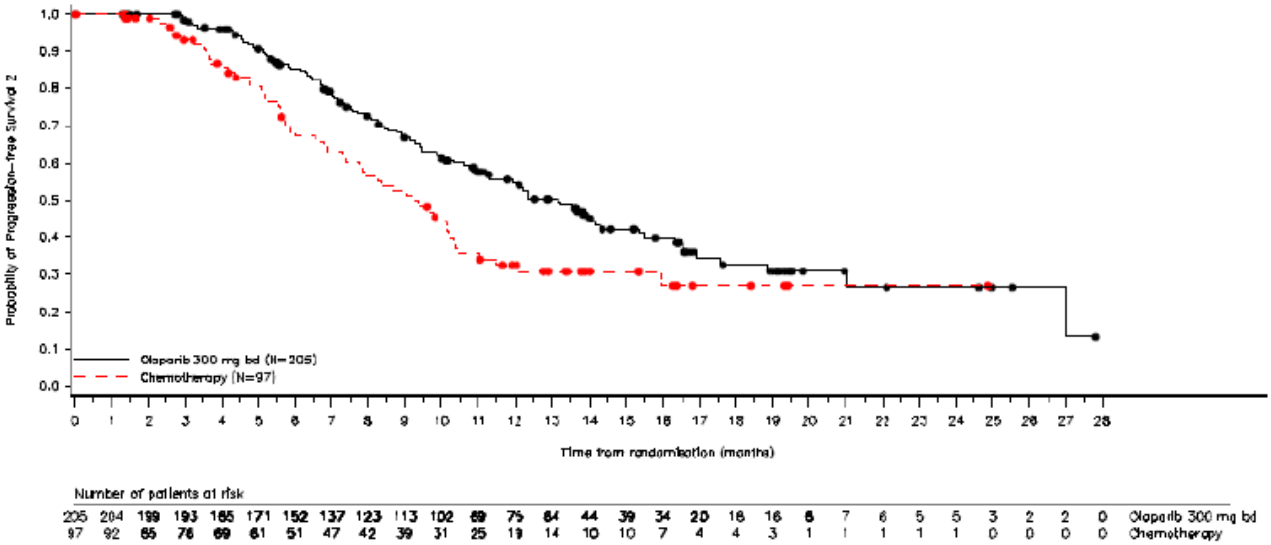


Figure 6: Time to second progression or death (PFS2), Kaplan-Meier plot (DCO: 09 December 2016)

Table 24: Median time to second progression or death (PFS2) (DCO: 09 December 2016)

Analysis	Olaparib 300 mg bd (N=205)	Physician's choice chemotherapy (N=97)
Total number of events[a]	104	53
Median second progression-free survival (months)[b]	13.17	9.26
95% CI for median second progression-free survival	10.94, 15.34	7.29, 10.35
Second progression free at 6 months (%)[b]	85.3	68.4
Second progression free at 12 months (%)[b]	54.7	32.6
Median follow-up for second progression-free survival (months)[c]	11.79	9.71

[a] Patients who had not had a second disease progression or died at the time of analysis, or who had second progression or died after 2 or more missed visits, were censored at the latest evaluable assessment where they were known to be alive and without a second disease progression.
[b] Calculated using the Kaplan-Meier technique.
[c] Censored patients only.
Note: This analysis is based on investigator assessment of second progression.
bd, twice daily; CI, confidence interval; N, number of patients in treatment group.

Table 25: Summary of PFS2 at 25 September 2017 DCO (Full Analysis Set)

	Olaparib 300 mg bd (N=205)	Physician's choice of chemotherapy[a] (N=97)
Number of events (%)	130 (63.4)	66 (67.0)
Median PFS2 (months)	12.8	9.4
Hazard ratio (95% CI)[b]	0.55 (0.39, 0.77)	
Nominal p-value (2-sided)	0.0005	

[a] Physician's choice of chemotherapy consisting of either capecitabine, eribulin or vinorelbine

[b] A hazard ratio <1 favours olaparib

CI Confidence interval; DCO Data cut-off date; PFS2 Time to second progression or death

Data cut-off date: 25 September 2017

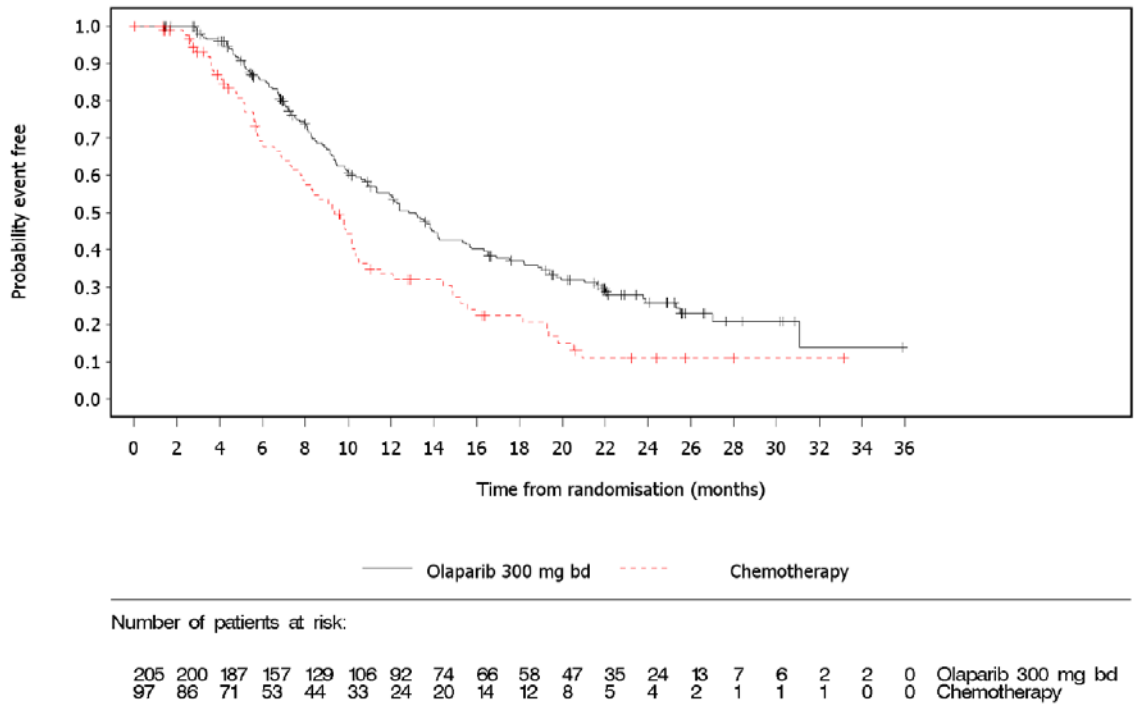


Figure 7: Time to second progression or death (PFS2), Kaplan-Meier plot (DCO 25 September 2017)

Overall survival (OS; FAS)

Table 26: OS, stratified log-rank test (FAS, DCO 9 December 2016, 46% maturity)

			Treatment effect		
			Comparison between groups		
Group	N	Number (%) of patients with events[a]	Hazard ratio	95% CI	2-sided p-value
Olaparib 300 mg bd	205	94 (45.9)	0.90	0.63, 1.29	0.5665
Physician's choice chemotherapy	97	46 (47.4)			

[a] Overall survival was defined as the time from the date of randomisation until death due to any cause. Patients not known to have died at the time of analysis were censored at the last recorded date on which the patient was known to be alive.

Note: A HR <1 favours olaparib 300 mg bd. The p-value was determined using log-rank test stratified by received previous chemotherapy regimens for metastatic breast cancer (yes/no), ER and/or PgR positive versus ER and PgR negative. The HR and CI were estimated from the stratified log-rank test statistics.

bd, twice daily; CI, confidence interval; ER, oestrogen receptor; HR, hazard ratio; N, number of patients in treatment group; PgR, progesterone receptor.

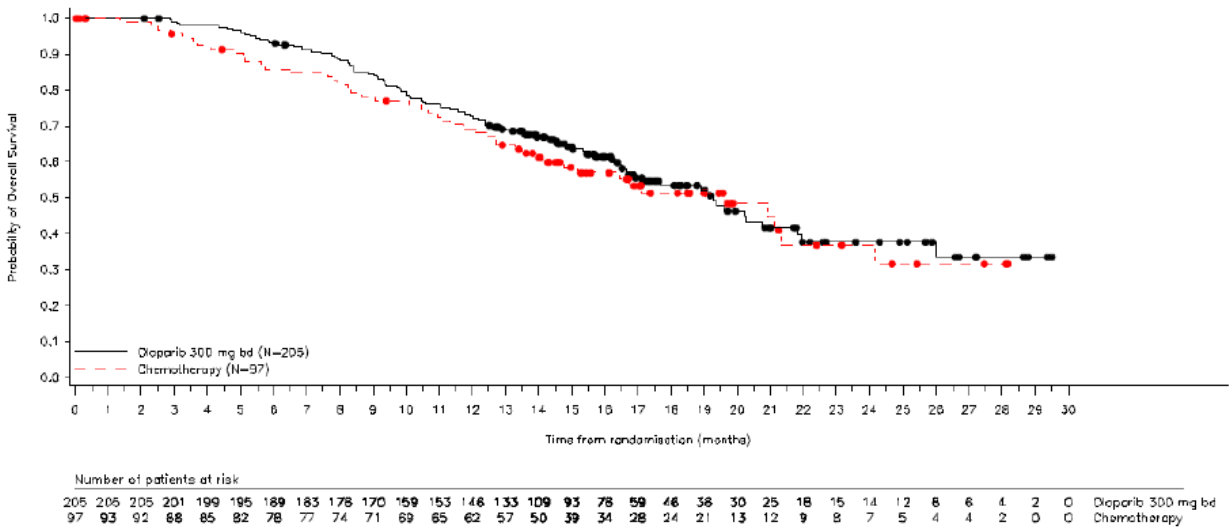


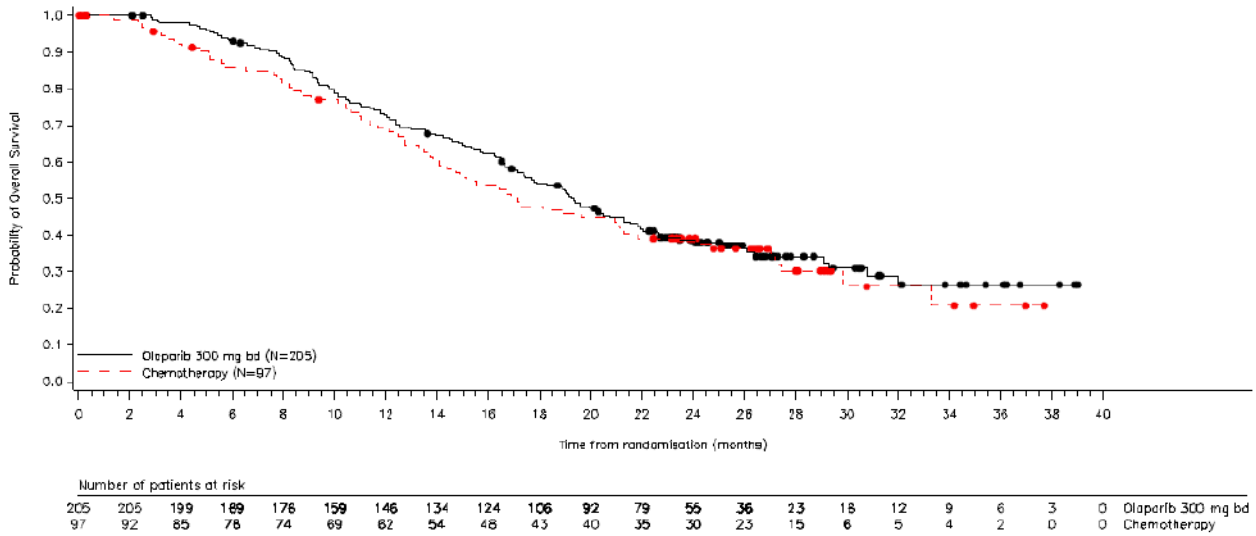
Figure 8: OS, Kaplan-Meier plot (FAS, 1st DCO 9 December 2016)

A final analysis of OS was performed when the OS data were approximately 60% mature (approximately 190 events) and thus based on a DCO of 25 September 2017. At this time, 26 patients were still receiving study treatment (all 26 were in the olaparib arm), and an additional 67 patients were ongoing in the study, off treatment (39 in the olaparib arm, and 28 in the physician's choice of chemotherapy arm).

Table 27: Overall survival, stratified log-rank test, secondary analysis (FAS) (DCO: 25 September 2017)

Treatment arm	N	Number (%) of patients with events[a]	Treatment effect Comparison between groups		
			Hazard ratio	95% CI	2-sided p-value
Olaparib 300 mg bd	205	130 (63.4)	0.90	(0.66, 1.23)	0.5131
Physician's choice chemotherapy	97	62 (63.9)			

a Overall survival was defined as the time from the date of randomisation until death due to any cause. Patients not known to have died at the time of analysis were censored at the last recorded date on which the patient was known to be alive.
The p-value was determined using log-rank test stratified by received previous chemotherapy regimens for metastatic breast cancer (yes/no), ER and/or PgR positive versus ER and PgR negative. The HR and CI were estimated from the stratified log-rank test statistics.
bd, twice daily; CI, confidence interval; ER, oestrogen receptor; HR, hazard ratio; N, number of patients in treatment group; PgR, progesterone receptor.



Patients not known to have died at the time of analysis were censored at the latest recorded date on which the patient was known to be alive.
Data cut-off date: 25 September 2017.
bd, twice daily; N, number of patients in treatment group.

Figure 9: Overall survival, Kaplan-Meier plot (FAS) (DCO: 25 September 2017)

Table 28: Median overall survival (FAS) (DCO: 25 September 2017)

Analysis	Olaparib 300 mg bd (N=205)	Physician's choice chemotherapy (N=97)
Total number of deaths	130	62
Median overall survival (months)[a]	19.25	17.12
95% CI for median overall survival	17.15, 21.55	13.86, 21.85
Survival at 6 months (%)[a]	93.1	85.8
Survival at 12 months (%)[a]	72.7	69.2
Survival at 18 months (%)[a]	54.1	48.0
Median follow-up for overall survival (months) in all patients[b]	18.92	15.54
Median follow-up for overall survival (months) in censored patients[c]	25.30	26.25

[a] Calculated using the Kaplan-Meier technique.
[b] Time from randomisation to date of death or to date of censoring for censored patients.
[c] Time from randomisation to date of censoring (date last known to be alive) for patients who had not died at the time of analysis.

The results of the sensitivity analyses (unstratified log rank test and stratified log-rank test in confirmed Myriad gBRCAm subset) were consistent with the main OS analysis.

The final OS outcome in the confirmed Myriad gBRCAm patients (HR 0.87; 95% CI: 0.63, 1.18; p=0.3658) was consistent with the overall population (FAS).

Time to first subsequent cancer therapy (TFST; FAS)

Table 29: Summary analysis of TFST (DCO 9 December 2016)

			Treatment effect		
Group	N	Number (%) of events[a]	Hazard ratio	95% CI	2-sided p-value
Olaparib 300 mg bd	205	154 (75.1)	0.34	0.24, 0.47	<0.0001
Physician's choice chemotherapy	97	85 (87.6)			

[a] Time to first subsequent cancer therapy was the time from randomisation to the earlier of the second subsequent therapy start date following study treatment discontinuation, or death. Any patient not known to have died at the time of the analysis and not known to have had a further intervention of this type was censored at the last known time to have not received second subsequent therapy, ie, the last follow-up visit where this was confirmed.

Note: A HR <1 favours olaparib 300 mg bd. The p-value was determined using log-rank test stratified by received previous chemotherapy regimens for metastatic breast cancer (yes/no) and ER and/or PgR positive versus ER and PgR negative. The HR and CI were estimated from the stratified log-rank test statistics.

bd, twice daily; CI, confidence interval; ER, oestrogen receptor; HR, hazard ratio; N, number of patients in treatment group; PgR, progesterone receptor.

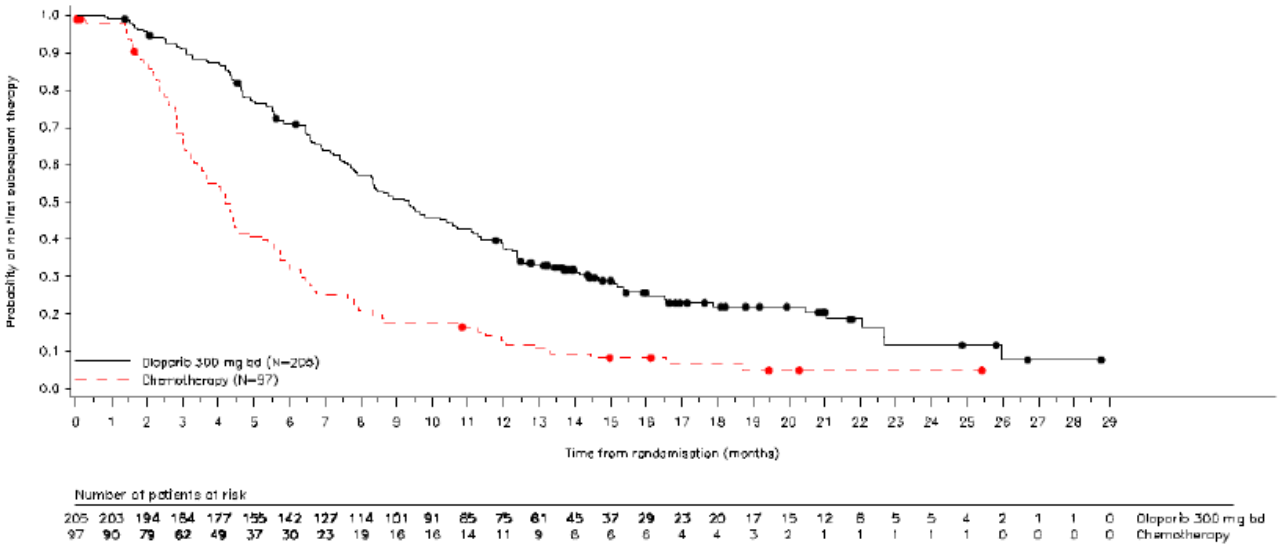


Figure 10: TFST, Kaplan-Meier plot (DCO 9 December 2016)

Time to second subsequent cancer therapy (TSST; FAS)

Table 30: Summary of analysis of TSST (DCO 9 December 2016)

			Treatment effect		
Group	**N**	**Number (%) of events[a]**	**Hazard ratio**	**95% CI**	**2-sided p-value**
Olaparib 300 mg bd	205	122 (59.5)	0.53	0.38, 0.74	0.0002
Physician's choice chemotherapy	97	69 (71.1)			

[a] Time to second subsequent cancer therapy is the time from randomisation to the earlier of the second subsequent therapy start date following study treatment discontinuation, or death. Any patient not known to have died at the time of the analysis and not known to have had a further intervention of this type was censored at the last known time to have not received second subsequent therapy, ie, the last follow-up visit where this was confirmed.

Note: A HR <1 favours olaparib 300 mg bd. The p-value was determined using log-rank test stratified by received previous chemotherapy regimens for metastatic breast cancer (yes/no) and ER and/or PgR positive versus ER and PgR negative. The HR and CI were estimated from the stratified log-rank test statistics.

bd, twice daily; CI, confidence interval; ER, oestrogen receptor; HR, hazard ratio; N, number of patients in treatment group; PgR, progesterone receptor.

Source: Table 11.2.6.1.

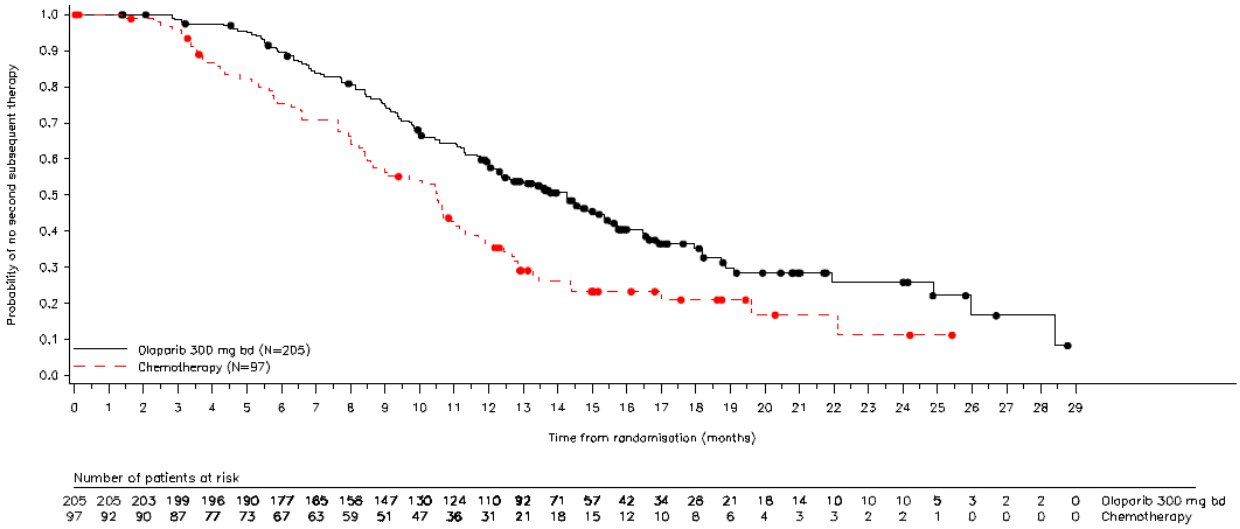


Figure 11: TSST, Kaplan-Meier plot (DCO 9 December 2016)

Objective response rate (ORR = complete or partial response)

Table 31: Non-confirmed ORR based on independent central review (in patients with measurable disease) (DCO 9 December 2016)

	N	Number (%) of patients with response[a]	95% CI[b]
Olaparib 300 mg bd	167	100 (59.9)	52.03, 67.38
Chemotherapy	66	19 (28.8)	18.30, 41.25

[a] Response does not require confirmation.
[b] The CIs for response rate were calculated using the Clopper-Pearson exact method for binomial proportions.
Modified RECIST version 1.1 was used for independent central review assessments. Although patients were required to enter the study with at least one lesion (measurable and/or non-measurable) based on investigator assessment, independent reviewers may conclude NED at baseline.
bd, twice daily; CI, confidence interval; N, number of patients in treatment group; NED, no evidence of disease; RECIST: Response Evaluation Criteria in Solid Tumors.

Table 32: Confirmed ORR (DCO 9 December 2016)

Confirmed ORR – DCO 09 December 2016		
	Olaparib 300 mg bd	Chemotherapy
Number of objective responders: Total number of patients with measurable disease (%)	87: 167 (52)[d]	15:66 (23)
95% CI	44.2-59.9	13.3-34.7

Note: Confirmed responses (by BICR) were defined as a recorded response of either CR/PR, confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed. In the olaparib arm 8% with measurable disease had a complete response versus 1.5% of patients in the comparator arm; 74/167 (44%) of patients in the olaparib arm had a partial response versus 14/66 (21%) of patients in the chemotherapy arm. In the TNBC patient subgroup the confirmed ORR was 48% (41/86) in the olaparib arm and 12% (4/33) in the comparator arm. In the HR+ patient subgroup the confirmed ORR was 57% (46/81) in the olaparib arm and 33% (11/33) in the comparator arm.

Table 33: Onset and duration of objective response in patients with objective response (patients with objective response) (DCO 9 December 2016)

	Olaparib 300 mg bd (N=102)	Physician's choice chemotherapy (N=21)
Number of responders who subsequently progressed or died	78	15
Duration of response form onset of response (days)[a b]		
25th percentile	86.0	98.0
Median (95% CI)	196.0 (151.0, 218.0)	216.0 (98.0, 372.0)
75th percentile	296.0	372.0
Time to onset of response from randomisation (days)		
25th percentile	42.0	39.0
Median (95% CI)	47.0	45.0
75th percentile	86.0	85.0

[a] Duration of response was the time from the first documentation of CR/PR until the date of progression, or the last evaluable RECIST assessment for patients that did not progress or progressed after two or more missed visits.
[b] Calculated using Kaplan-Meier technique.
Note: This analysis was based on independent central review of radiological scans. RECIST version 1.1. Although patients were required to enter the study with at least one lesion (measurable and/or non-measurable) based on investigator assessment, independent reviewers may conclude NED at baseline.
bd, twice daily; CI, confidence interval; CR, complete response; N, number of patients in treatment group; NED, no evidence of disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

Patient reported outcomes/health-related quality of life (FAS)

The EORTC QLQ-C30 questionnaires were completed at baseline (prior to randomisation) and every 6 weeks until disease progression. Baseline compliance rate (99.0% for olaparib; 95.9% for physician's choice of chemotherapy) and overall compliance rate (93.2% for olaparib; 77.3% for physician's choice of chemotherapy) of the EORTC QLQ-C30 questionnaire were >75%.

Change from baseline global health status/QoL score (average across all visits) was nominally statistically significant in favour of olaparib treated patients compared to the physician's choice of chemotherapy patients. The differences in changes from baseline were observed across all visits with the maximum difference at Visit 12 of 12.7 (95% CI 5.45, 19.95). The overall estimated mean difference in change from baseline global health status/QoL score was 7.5 measured on a 100-point scale (95% CI 2.48, 12.44; p=0.0035).

Table 34: Global HRQoL score - best overall QoL response (DCO 9 December 2016)

Best QOL Response		Number (%) of patients: Olaparib 300 mg bd (N=205)	Chemotherapy (N=97)
Improved [a]		69 (33.7)	13 (13.4)
No change [b]		85 (41.5)	25 (25.8)
Deterioration [c]		24 (11.7)	19 (19.6)
Non-evaluable	Cannot demonstrate improvement/deterioration/no change	10 (4.9)	17 (17.5)
Missing	Total	13 (6.3)	19 (19.6)
	No follow up data	13 (6.3)	19 (19.6)

The denominator is the full analysis set; however best overall QoL response is only determined for patients who have a baseline global HRQoL score ≥10.

[a] Two visit responses of 'improved' a minimum of 21 days apart without an intervening visit response of 'deterioration'.

[b] Does not qualify for overall score response of 'improved'. Two visit response of either 'no change' or 'improved' and 'no change' a minimum of 21 days apart without an intervening visit response of 'deterioration'.

[c] Does not qualify for overall score response of 'improved'. A visit response of 'deterioration' without a response of 'improved' or 'no change' within 21 days. Non-evaluable category contains those patients who do not meet criteria for Improved, No change or Deterioration.

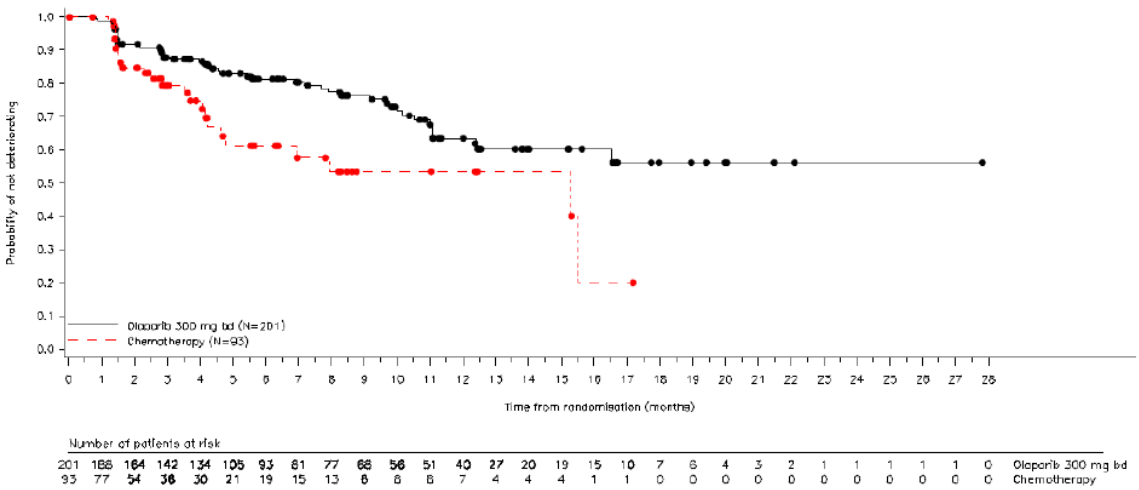
There was a nominally statistically significant difference in the time to global health status/QoL deterioration in the olaparib arm compared with the physician's choice of chemotherapy arm (HR 0.44; 95%CI: 0.25, 0.77; p=0.0043).

Table 35: Analysis of time to HRQoL deterioration in patients whose baseline Global HRQoL score ≥10 (DCO 9 December 2016)

		Treatment effect: Comparison between groups			
Group	N	Number (%) of patients with events[a]	Hazard ratio	95% CI	2-sided p-value
Olaparib 300 mg bd	201	49 (24.4)	0.44	0.25, 0.77	0.0043
Physician's choice chemotherapy	93	25 (26.9)			

[a] Time to deterioration of HRQoL was defined as the time from date of randomisation to the date of a clinically important deterioration (decrease in 10 points or more in global HRQoL score or reason for not completing form was "Subject too heavily affected by symptoms of disease under investigation") sustained at the next scheduled visit. Patients whose global HRQoL score had not shown a clinically important deterioration and who were alive at the time of analysis, or who experienced HRQoL deterioration or death after 2 or more missed assessments, were censored at the latest evaluable EORTC QLQ-C30 assessment.

Figure 12: Time to HRQoL deterioration, Kaplan Meier plot (DCO 9 December 2016)



Cancer therapy satisfaction questionnaire

The primary objective of the CTSQ-16 was to assess satisfaction with the therapy and the questionnaire was administered every 6 weeks from baseline and at treatment discontinuation. The compliance rates were relatively high throughout the study and never fell below 50%.

The CTSQ-16 is scored on 0-100 scale and higher scores are associated with better therapy expectations, feeling less impact of side effects, and greater satisfaction with therapy. Across the majority of visits, satisfaction with therapy mean scores were higher in the olaparib arm (range 71.6 to 89.3) compared with the physician's choice of chemotherapy arm (range 62.5 to 77.8). Similar patterns of higher mean scores for therapy expectations and feeling less impact of side effects were observed for olaparib patients compared with physician's choice of chemotherapy patients.

Ancillary analyses

Subgroup analyses of progression-free survival

Results of the subgroup analyses of PFS are presented in Figure 13 as a forest plot. The global interaction test of PFS showed no evidence of treatment effect being different across all pre-specified subgroups (p=0.1933).

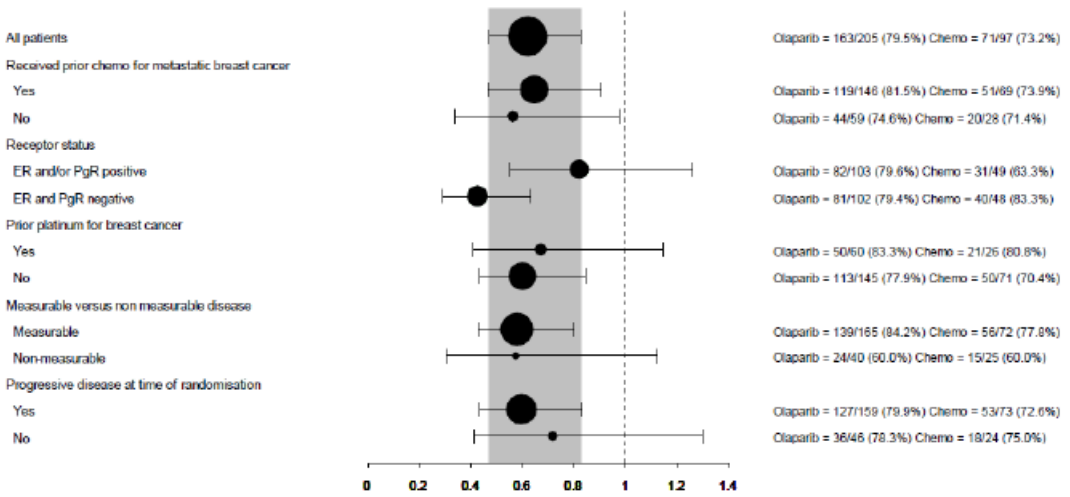


Figure 13: PFS, forest plot, by subgroup (FAS, DCO 09 December 2016)

Subgroup analyses of overall survival

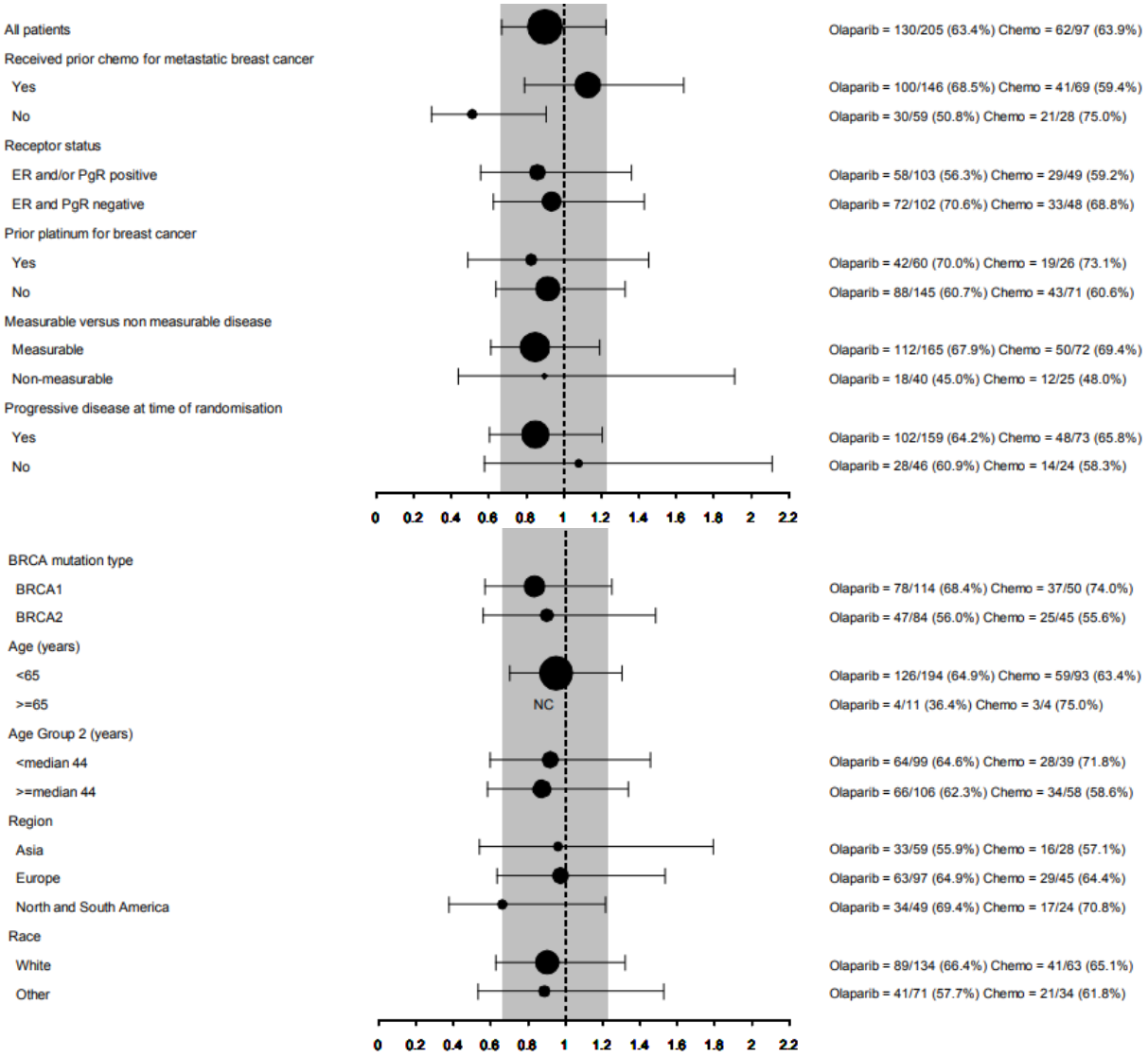


Figure 14: Overall survival, Forest plot by subgroup (FAS) (DCO 09 December 2016)

Size of circle is proportional to the number of events. Estimated from a Cox proportional hazards model including treatment, subgroup and treatment by subgroup interaction. Grey band represents the 95% CI for the overall (all patients) HR. HRs and 95% CIs are not presented for subgroups with <20 events. bd, twice daily; CI, confidence interval; ER, oestrogen receptor; HR, hazard ratio; NC, not calculated; PgR, progesterone receptor. Source: Figure 11.2.5.

Subsequent cancer therapies (FAS)

Switch over to olaparib was not permitted within the study design. Patients could, however, receive a PARP inhibitor as a subsequent therapy outside of the study.

Table 36: Subsequent cancer therapies (FAS) (DCO 25 September 2017)

	Number (%) of patients	
	Olaparib 300 mg bd (N=205)	**Physician's choice chemotherapy (N=97)**
Continuing study treatment at data cut-off	26 (12.7)	0
No subsequent therapy	32 (15.6)	18 (18.6)
PARP inhibitors	2 (1.0)	8 (8.2)
Platinum chemotherapy	77 (37.6)	44 (45.4)
Other cytotoxic chemotherapy	125 (61.0)	70 (72.2)
Hormonal therapy	33 (16.1)	24 (24.7)
Targeted/Biologics	30 (14.6)	19 (19.6)
Other	8 (3.9)	2 (2.1)

Data cut-off date: 25 September 2017.
bd, twice daily; PARP, polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerase.

Efficacy of olaparib in Myriad CDx gBRCAm patients

Table 37: Summary of key efficacy outcome variables for confirmed Myriad gBRCAm patients (FAS) (DCO 09 December 2016)

	Olaparib 300 mg bd (N=202)	Physician's choice chemotherapy (N=95)
Progression-free survival[a,b]		
Number (%) of patients with events	160 (79.2)	71 (74.7)
HR (95% CI)	0.57 (0.41, 0.78)	
2-sided p-value	p=0.0005	
Median PFS[c] (months)	7.39	4.17
Sensitivity analyses of PFS:		
Evaluation time bias[a,b,d]		
Number (%) of patients with events	160 (79.2)	71 (74.7)
HR (95% CI)	0.58 (0.42, 0.80)	
2-sided p-value	p=0.0008	
Attrition bias[a,e]		
Number (%) of patients with events	151 (74.8)	66 (69.5)
2-sided p-value	p=0.0001	
Ascertainment bias[b,f]		
Number (%) of patients with events	162 (80.2)	80 (84.2)
HR (95% CI)	0.48 (0.35, 0.66)	
2-sided p-value	p<0.0001	
Time to second progression or death (PFS2)[h,i]		
Number (%) of patients with events	102 (50.5)	53 (55.8)
HR (95% CI)	0.56 (0.39, 0.82)	
2-sided p-value	p=0.0024	
Median second progression-free survival (months)[b]	13.24	9.24
Overall survival[g]		
Number (%) of patients with events	91 (45.0)	46 (48.4)
HR (95% CI)	0.86 (0.60, 1.25)	
2-sided p-value	p=0.4348	
Median OS (months)[c]	19.38	19.61
Time to first subsequent cancer therapy or death[j]		
Number (%) of patients with events	151 (74.8)	85 (89.5)
HR (95% CI)	0.33 (0.23, 0.45)	
2-sided p-value	p<0.0001	
Median time to first subsequent therapy from randomisation (months)	9.40	4.21
Time to second subsequent therapy or death[k]		
Number (%) of patients with events	119 (58.9)	69 (72.6)
HR (95% CI)	0.52 (0.37, 0.72)	
2-sided p-value	p=0.0001	
Median time to second subsequent therapy from randomisation (months)	14.26	10.51

[a] This analysis was based on independent central review of radiological scans.
[b] PFS defined as the time from randomisation until date of RECIST progression or death. Patients who had not progressed or died at the time of analysis, or who progressed or died after 2 or more missed visits, were censored at the latest evaluable RECIST assessment, or Day 1 if the patient had no evaluable visits or no baseline assessment (unless they died within 2 visits of baseline).
[c] Calculated using the Kaplan-Meier technique.
[d] PFS was taken as the midpoint between the time of progression and previous evaluable RECIST assessment.

[e] PFS defined as the time from randomisation until date of RECIST progression or death. Patients who had not progressed or died at the time of analysis were censored at the latest evaluable RECIST assessment or Day 1 if the patient had no evaluable visits or no baseline assessment (unless they died within 2 visits of baseline). Patients who took subsequent therapy prior to progression or death were censored at their last evaluable RECIST assessment prior to taking the subsequent therapy, or Day 1 if there were no evaluable visits. Patients who progressed or died after 2 or more missed visits were not censored.

[f] This analysis was based on investigator assessment of radiological scans.

[g] OS was defined as the time from the date of randomisation until death due to any cause. Patients not known to have died at the time of analysis were censored at the last recorded date on which the patient was known to be alive.

[h] Patients who had not had a second disease progression or died at the time of analysis, or who had second progression or died after 2 or more missed visits, were censored at the latest evaluable assessment where they were known to be alive and without a second disease progression.

[i] This analysis was based on investigator assessment of second progression.

[j] Time to first subsequent cancer therapy was the time from randomisation to the earlier of first to subsequent therapy start date following study treatment discontinuation, or death. Any patient not known to have died at the time of the analysis and not known to have had a further intervention of this type was censored at the last known time to have received subsequent therapy, ie, the last follow-up visit where this was confirmed.

[k] Time to second subsequent cancer therapy was the time from randomisation to the earlier of the second subsequent therapy start date following study treatment discontinuation, or death. Any patient not known to have died at the time of the analysis and not known to have had a further intervention of this type was censored at the last known time to have not received second subsequent therapy, ie, the last follow-up visit where this was confirmed.

bd, twice daily; CI, confidence interval; ER, oestrogen receptor; *gBRCAm*, germline breast cancer susceptibility gene mutated; HR, hazard ratio; N, number of patients in treatment group; OS, overall survival; PFS, progression-free survival; PgR, progesterone receptor; RECIST, Response Evaluation Criteria in Solid Tumors.

Additional efficacy results by line of therapy

Exploratory subgroup analyses were conducted to evaluate PFS by prior lines of chemotherapy, results are summarised below.

Table 38: Summary statistics of PFS by BICR for olaparib vs. physician's choice of chemotherapy by line of therapy (Full analysis set) (DCO 09 December 2016)

	Olaparib 300 mg bd (N=205)	Physician's choice of chemotherapy[a] (N=97)
Number of patients with no prior lines of chemotherapy for mBC (n) (olaparib as 1st line treatment)	68	31
Number of events (%)	51 (75)	22 (71)
Median PFS (months) (95% CI)[b]	7.4 (5.6, 8.5)	3.0 (1.5, 5.8)
Hazard Ratio (95% CI)[c]	0.50 (0.30, 0.84)	
Number of patients with one prior line of chemotherapy for mBC (n) (olaparib as 2nd line treatment)	80	42
Number of events (%)	62 (77.5)	35 (83.3)
Median PFS (months) (95% CI)[b]	8.3 (5.8, 11.0)	4.1 (2.6, 4.6)
Hazard Ratio (95% CI)[c]	0.50 (0.33, 0.76)	
Number of patients with two prior lines of chemotherapy for mBC (n) (olaparib as 3rd line treatment)	57	24
Number of events (%)	50 (87.7)	14 (58.3)
Median PFS (months) (95% CI)[b]	5.7 (4.2, 8.2)	5.1 (2.9, 9.0)
Hazard Ratio (95% CI)[c]	1.21 (0.69, 2.27)	
Number of patients with any prior chemotherapy for mBC (n) (olaparib as 2nd/3rd line treatment)	137	66
Number of events (%)	112 (81.8)	49 (74.2)
Median PFS (months) (95% CI)[b]	7.0 (5.6, 8.3)	4.2 (2.9 ,4.7)
Hazard Ratio (95% CI)[c]	0.69 (0.49, 0.97)	

[a] Physician's choice of chemotherapy consisting of either capecitabine, eribulin or vinorelbine [b] Calculated using the Kaplan-Meier technique.

[c] Each subgroup analysis was performed using a single Cox proportional hazards model containing the treatment term, subgroup and the treatment by subgroup interaction. A hazard ratio of <1 favours olaparib. CI: confidence interval; mBC Metastatic breast cancer; PFS Progression free survival Data derived from Table 895.1; Table 901.4.

Table 39: Summary statistics of OS for olaparib vs. physician's choice of chemotherapy by line of therapy (Full analysis set) (Data cut-off 25 September 2017)

	Olaparib 300 mg bd (N=205)	Physician's choice of chemotherapy[a] (N=97)
Number of patients with no prior lines of chemotherapy for mBC (n) (olaparib as 1st line treatment)	68	31
Number of events (%)	35 (51.5)	24 (77.4)
Median OS (months) (95% CI)[b]	22.60 (19.1, NC)	13.86 (10.4, 18.2)
Hazard Ratio (95% CI)[c]	0.45 (0.27, 0.77)	
Number of patients with one prior line of chemotherapy for mBC (n) (olaparib as 2nd line treatment)	80	42
Number of events (%)	49 (61.3)	24 (57.1)
Median OS (months) (95% CI)[b]	18.92 (14.9, 26.0)	24.74 (13.3, NC)
Hazard Ratio (95% CI)[c]	1.17 (0.72, 1.93)	
Number of patients with two prior lines of chemotherapy for mBC (n) (olaparib as 3rd line treatment)	57	24
Number of events (%)	46 (80.7)	14 (58.3)
Median OS (months) (95% CI)[b]	17.02 (12.4, 20.4)	16.76 (10.9, 27.2)
Hazard Ratio (95% CI)[c]	1.24 (0.70, 2.35)	
Number of patients with any prior chemotherapy for mBC (n) (olaparib as 2nd/3rd line treatment)	137	66
Number of events (%)	95 (69.3)	38 (57.6)
Median OS (months) (95% CI)[b]	17.71 (15.3, 20.4)	21.13 (15.2, 27.4)
Hazard Ratio (95% CI)[c]	1.25 (0.86, 1.84)	

[a] Physician's choice of chemotherapy consisting of either capecitabine, eribulin or vinorelbine [b] Calculated using the Kaplan-Meier technique.

[c] Each subgroup analysis was performed using a single Cox proportional hazards model containing the treatment term, subgroup and the treatment by subgroup interaction. A hazard ratio of <1 favours olaparib.

CI: confidence interval; mBC Metastatic breast cancer; PFS Progression free survival Data derived from Table 1144.1.
Data cut-off 25 September 2017.

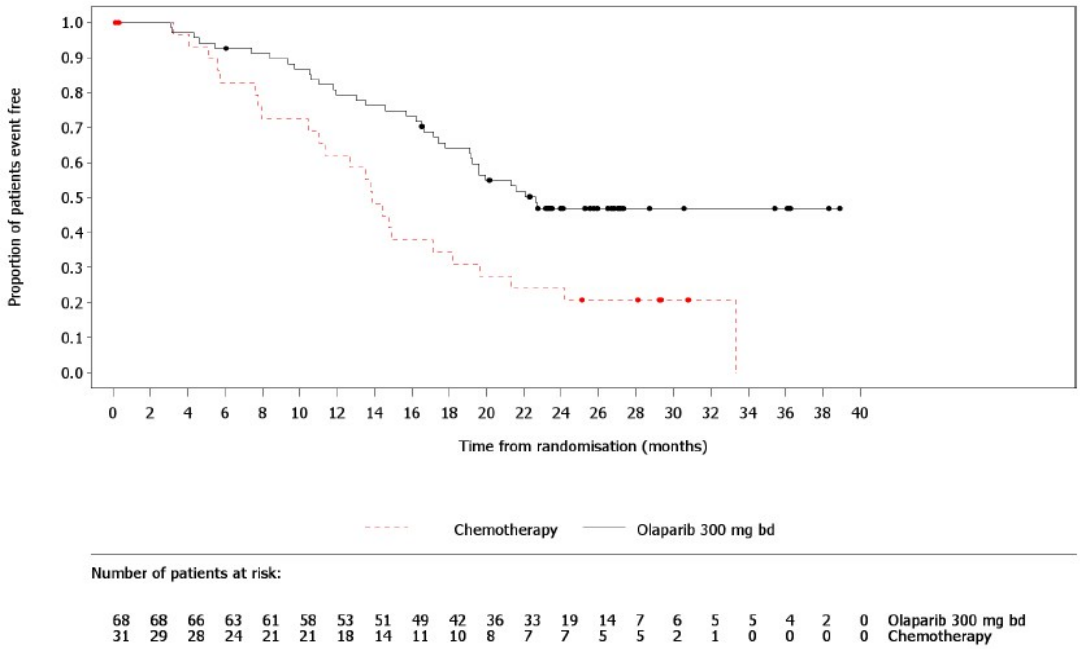


Figure 15: Overall survival, Kaplan-Meier plot comparing olaparib to physician's choice of chemotherapy in patients with no prior chemotherapy (i.e. olaparib as 1st line treatment) in metastatic setting (Full analysis set) (Data cut-off date: 25 September 2017)

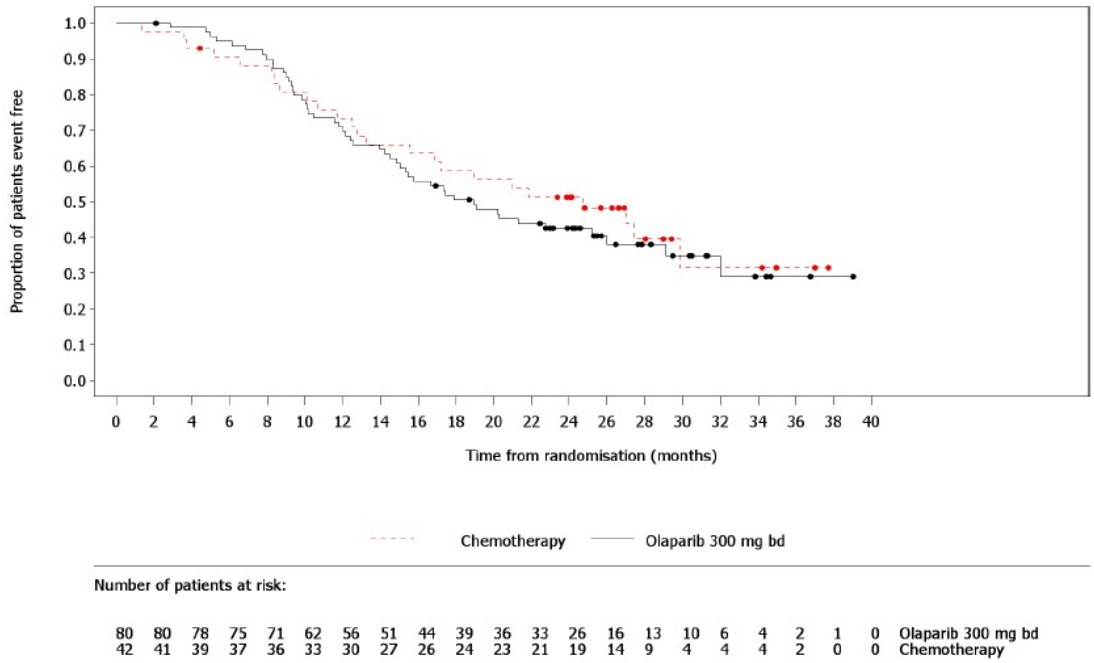


Figure 16: Overall survival, Kaplan-Meier plot comparing olaparib to physician's choice of chemotherapy in patients with one prior chemotherapy (i.e. olaparib as 2nd line treatment) in metastatic setting (Full analysis set) (Data cut-off date: 25 September 2017)

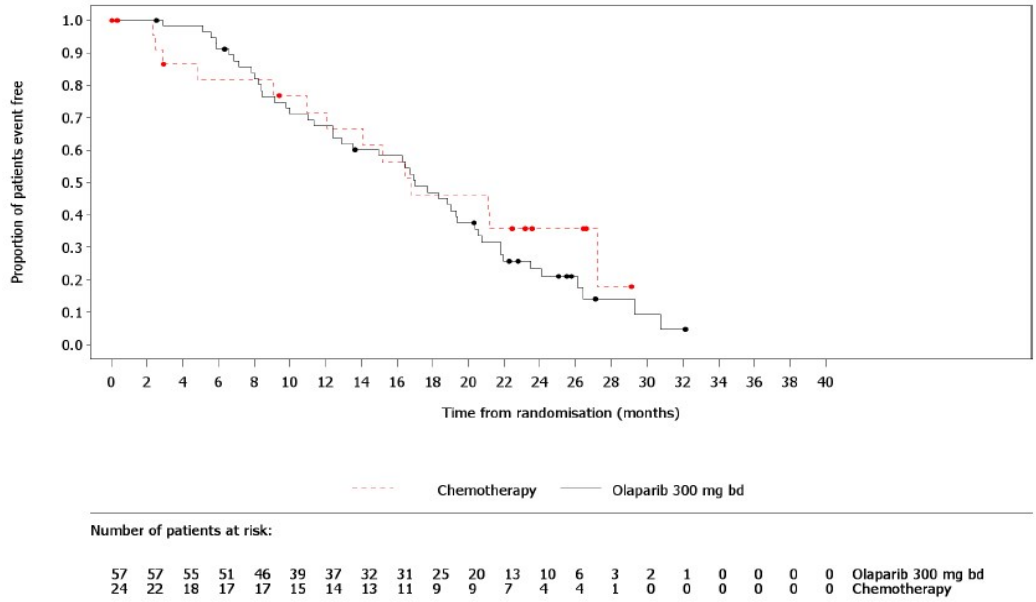


Figure 17: Overall survival, Kaplan-Meier plot comparing olaparib to physician's choice of chemotherapy in patients with two prior chemotherapy (i.e. olaparib as 3rd line treatment) in metastatic setting (Full analysis set) (Data cut-off date: 25 September 2017)

Additional efficacy results for ER and/or PgR positive and ER and PgR negative breast cancer subgroups

Table 40: Summary of exploratory efficacy results in the ER and/or PgR positive and ER and PgR negative breast cancer subgroups (DCO 9 December 2016)

Efficacy endpoints	ER and/or PgR positive N=152	ER and PgR negative N=150	FAS N=302
PFS by BICR (DCO 09 December 2016)			
HR (95% CI)	0.82 (0.55, 1.26)	0.43 (0.29, 0.63)	0.58 (0.43, 0.80)
Median PFS (months) with olaparib vs physician's choice of chemotherapy (difference in median)	8.3 vs 5.1 (Δ3.2)	5.6 vs 2.9 (Δ2.7)	7.0 vs 4.2 (Δ2.8)
PFS by investigator (DCO 09 December 2016)			
HR (95% CI)	0.57 (0.39, 0.84)	0.49 (0.34, 0.72)	0.50 (0.36, 0.68)
Median PFS (months) with olaparib vs physician's choice of chemotherapy	9.9 vs 4.2	5.6 vs 2.9	7.8 vs 3.8
PFS2 (DCO 09 December 2016)			
HR (95% CI)	0.54 (0.33, 0.89)	0.69 (0.44, 1.10)	0.57 (0.40, 0.83)
Median PFS2 (months) with olaparib vs physician's choice of chemotherapy	15.3 vs 9.6	9.9 vs 8.3	13.2 vs 9.3
OS (DCO 25 September 2017)			
HR (95% CI)	0.86 (0.55, 1.36)	0.93 (0.62, 1.43)	0.90 (0.66, 1.23)
Median OS (months) with olaparib vs physician's choice of chemotherapy	21.8 vs 21.3	17.4 vs 14.9	19.3 vs 17.1
TFST (DCO 09 December 2016)			
HR (95% CI)	0.44 (0.30, 0.65)	0.37 (0.26, 0.55)	0.34 (0.24, 0.47)
Median time (months) with olaparib vs physician's choice of chemotherapy	10.7 vs 4.9	7.8 vs 4.2	9.4 vs 4.2
TSST (DCO 09 December 2016)			
HR (95% CI)	0.56 (0.37, 0.87)	0.59 (0.39, 0.89)	0.53 (0.38, 0.74)
Median time (months) with olaparib vs physician's choice of chemotherapy	15.3 vs 10.5	12.0 vs 10.5	14.3 vs 10.5
ORR by BICR (DCO 09 December 2016) (%) olaparib vs physician's choice of chemotherapy (Evaluable for response analysis set)	65.4 vs 36.4	54.7 vs 21.2	59.9 vs 28.8

Table 41: OlympiAD: Confirmed response rate according to hormone receptor status (by BICR): Evaluable for response set (DCO 9 December 2016)

Hormone receptor status	Treatment group	N	Number (%) of patients with response[a]	95% CI
ER and/or PgR positive	Olaparib 300 mg bd	81	46 (56.8)	45.3, 67.8
	Physician's choice of chemotherapy	33	11 (33.3)	18.0, 51.8
ER and PgR negative	Olaparib 300 mg bd	86	41 (47.7)	36.8, 58.7
	Physician's choice of chemotherapy	33	4 (12.1)	3.4, 28.2

[c] A confirmed response of CR/PR means that a response of CR/PR is recorded at 1 visit and confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit. Both visits contributing to a response must be prior to subsequent anti-cancer therapy for the patient to be considered as a responder.

bd Twice daily; BICR Blinded independent central review; CI confidence interval; CR Complete response; ER Oestrogen receptor; PgR Progesterone receptor; PR Partial response; NC Not calculable.

Source data: Table 1138.3. Data cut-off date: 09 December 2016..

Additional efficacy results in patients with prior platinum therapy

Table 42: OlympiAD: PFS by prior platinum therapy (Data cut-off 09 December 2016)

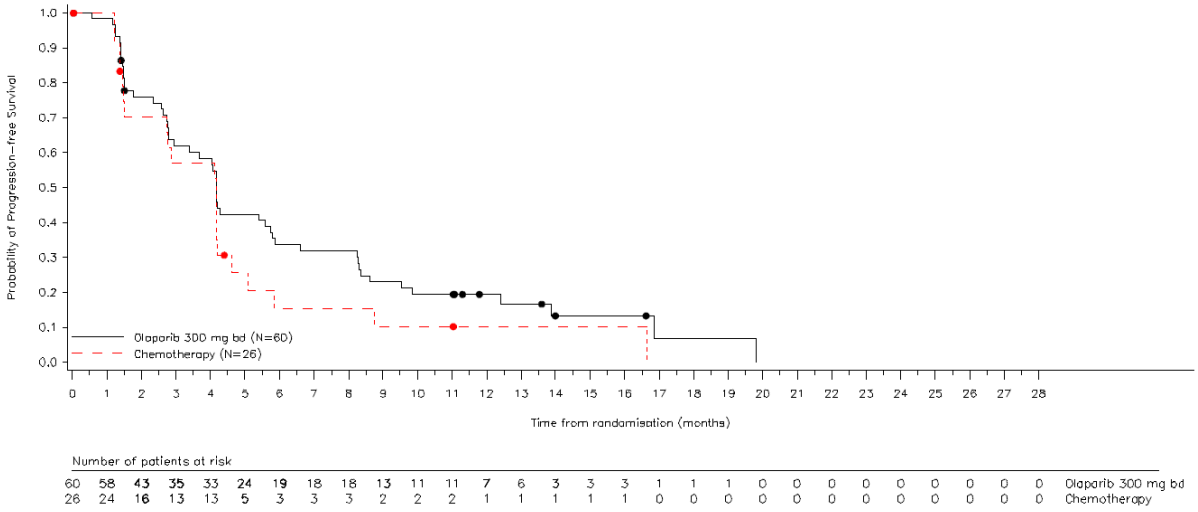
Prior platinum therapy	Treatment Group	Total number of events	Median (95%CI) PFS (months)	Hazard ratio (95%CI)[a]	Total number of censored patients	Median time to censoring (months)
Yes	Olaparib 300 mg bd (N=60)	50	4.17 (2.79, 5.75)	0.67 (0.41, 1.14)	10	11.19
	Physician's choice of chemotherapy[b] (N=26)	21	4.17 (1.51, 4.21)		5	1.38
No	Olaparib 300 mg bd (N=145)	113	8.31 (6.93, 9.00)	0.60 (0.43, 0.84)	32	13.75
	Physician's choice of chemotherapy[b] (N=71)	50	4.17 (2.76, 7.20)		21	5.49

[d] Cox proportional hazards model; a hazard ratio <1 favours olaparib

[e] Physician's choice of chemotherapy consisting of either: capecitabine, eribulin or vinorelbine.

bd Twice daily; *BRCA* breast cancer susceptibility gene; CI Confidence interval; PFS Progression free survival.

Source: Table 11.2.1.6 and Table 11.2.1.7. OlympiAD CSR, Module 5.3.5.1 (Data cut-off 09 December 2016).



Source data: Figure 11.2.1.3.5, OlympiAD CSR, Module 5.3.5.1. Data cut-off 09 December 2016

Figure 18: OlympiAD: Progression-free survival; Kaplan-Meier plot of subset of patients who received prior platinum (Data cut-off 09 December 2016)

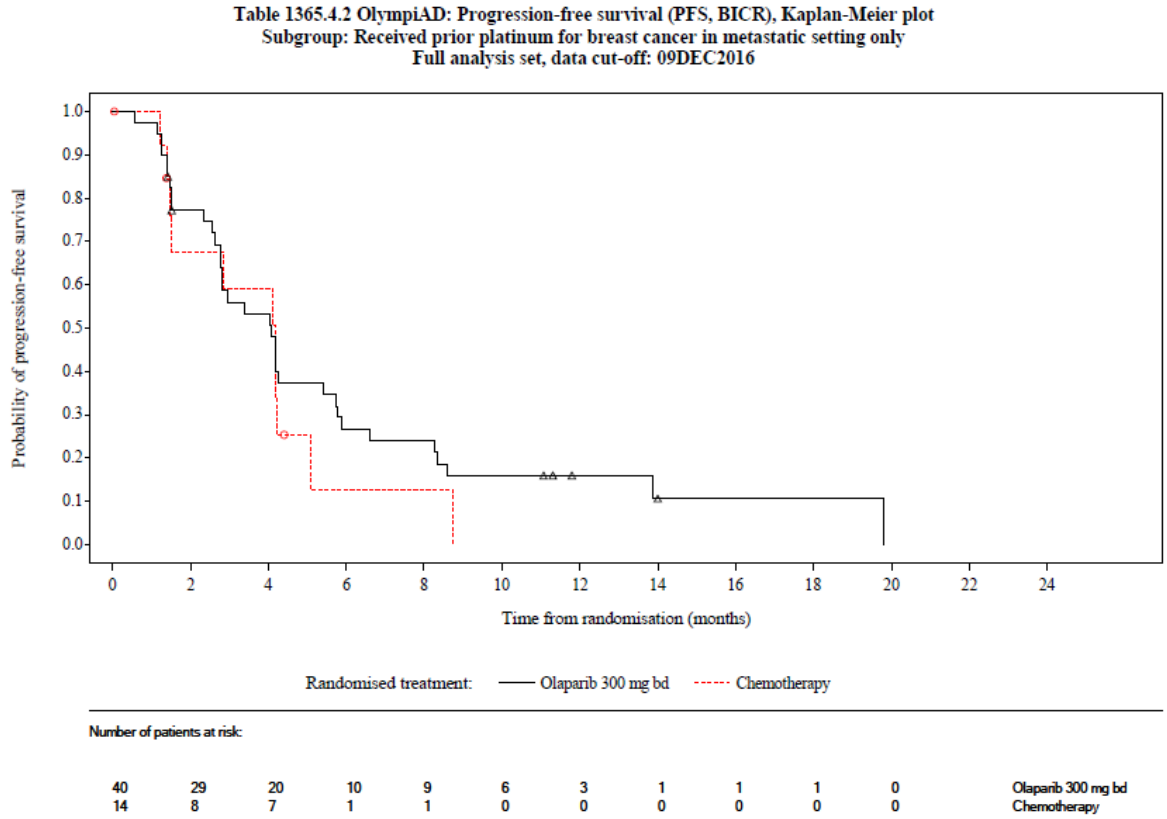
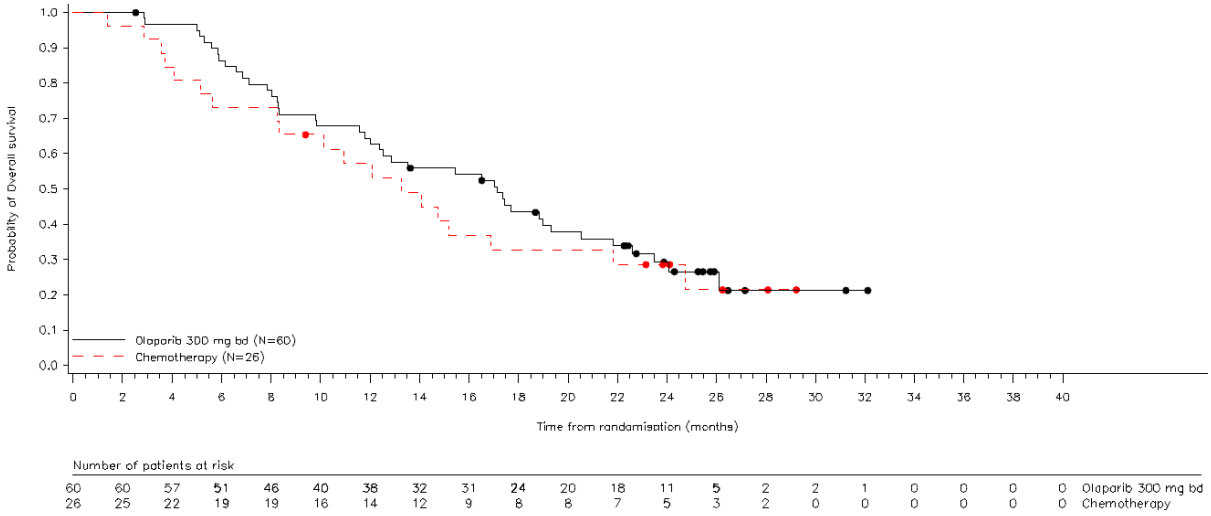


Figure 19: Kaplan-Meier plot for PFS in patients who received prior platinum in the metastatic setting (DCO 9 December 2016)



Source data: Figure 11.2.4.3.5, OlympiAD CSR Addendum, Module 5.3.5.1. Data cut-off 25 September 2017.

Figure 20: OlympiAD: Overall survival; Kaplan-Meier plot of subset patients of who received prior platinum (DCO 25 September 2017)

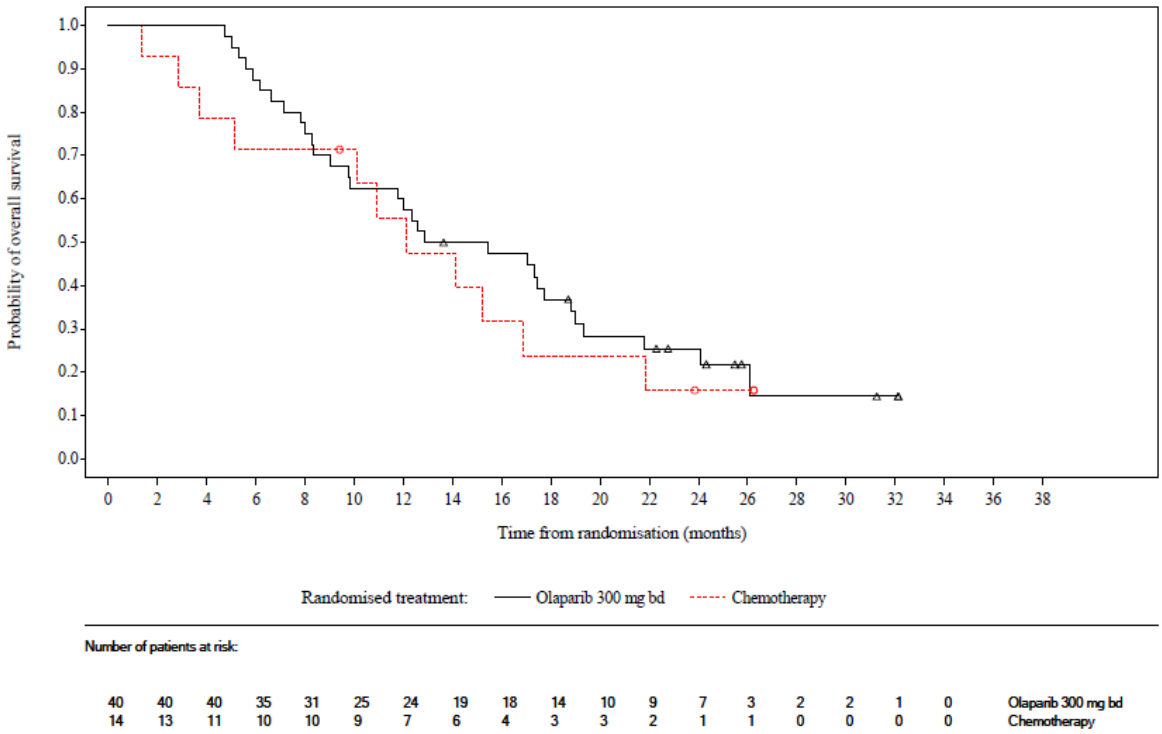


Figure 21: Kaplan-Meier plot for OS in patients who received prior platinum in the metastatic setting (FAS) (DCO 25 September 2017)

Additional efficacy results in patients with non-progressive disease

There were 70 (46 olaparib, 24 chemotherapy) patients enrolled in OlympiAD with non-progressive disease at randomisation of which, 38 patients received chemotherapy other than platinum. In the 32 patients (24 olaparib, 8 chemotherapy) with non-progressive disease at randomisation who had received a prior platinum, 20 of the 24 olaparib-treated patients had received a prior platinum in the metastatic setting and were a subset of the patients that were heavily pre-treated.

Table 43: OlympiAD: Response rate and duration of response (by BICR) by prior therapy: Evaluable for response analysis set (patients with non-progressive disease at randomisation)(DCO 09 December 2016)

Patients with non-progressive disease at randomisation	Treatment group	N	Number (%) of patients with response[a]	95% CI	Median (95% CI) duration of response from onset of response (months)	Median time to onset of response from randomisation (days)
All patients	Olaparib 300 mg bd	38	17 (44.7)	28.62, 61.70	6.9 (5.6, 12.6)	1.6
	Physician's choice of chemotherapy	15	6 (40.0)	16.34, 67.71	5.0 (1.4, NC)	2.1
Patients who received prior chemotherapy (except platinum)	Olaparib 300 mg bd	17	7 (41.2)	18.44, 67.08	10.4 (6.7, NC)	1.3
	Physician's choice of chemotherapy	11	3 (27.3)	6.02, 60.97	7.1 (1.4, NC)	2.8

[f] Response does not require confirmation.
bd Twice daily; BICR Blinded Independent Central Review; *BRCA* Breast cancer susceptibility gene; CI Confidence interval; NC Not calculable.
Source data: Table 1427.1 and Table 1427.2. Data cut-off date: 09 December 2016.

Table 44: OlympiAD: Summary of exploratory efficacy results in patients with non-progressive disease (DCO 09 December 2016)

Efficacy endpoints	Patients with non-progressive disease at randomisation		Full Analysis Set (N=302)
	All patients (N=70)	Patients who received prior chemotherapy (except platinum) (N=38)	
PFS by BICR (DCO 9 December 2016)			
Hazard Ratio[a] (95% CI)	0.72 (0.39, 1.33)	0.54 (0.24, 1.23)	0.58 (0.43, 0.80)
Median PFS (months) with olaparib vs physician's choice of chemotherapy[b]	5.4 vs 4.1	8.3 vs 2.8	7.0 vs 4.2
PFS2 (DCO 9 December 2016)			
Hazard Ratio[a] (95% CI)	0.79 (0.40, 1.54)	0.69 (0.28, 1.69)	0.57 (0.40, 0.83)
Median PFS2 (months) with olaparib vs physician's choice of chemotherapy[b]	12.2 vs 7.4	18.2 vs 7.4	13.2 vs 9.3
OS (DCO 25 September 2017)			
Hazard Ratio[a] (95% CI)	1.08 (0.57, 2.03)	0.76 (0.31, 1.87)	0.90 (0.66, 1.23)
Median OS (months) with olaparib vs physician's choice of chemotherapy[b]	19.4 vs 16.9	26.4 vs 19.0	19.3 vs 17.1

[g] Cox proportional hazards model; a hazard ratio <1 favours olaparib
Physician's choice of chemotherapy consisting of either: capecitabine, eribulin or vinorelbine.

Post-hoc analysis in patients with history of treated CNS metastases

Table 45: Progression-free survival, Cox proportional hazards model, additional subgroup analysis (DCO 09 December 2016)

Subgroup		Olaparib 300 mg bd	Physician's choice of chemotherapy
Brain/CNS	n	18	8
	Total number of events, (%)	14 (77.8)	5 (62.5)
	Median follow-up for PFS, (months)	15.2	0
	Median PFS (95% CI), (months)	8.3 (4.2, 11.3)	2.8 (1.4, 8.0)
	Hazard ratio (95% CI)	**0.51 (0.19, 1.58)**	

bd twice daily; CI Confidence interval; CNS Central nervous system; PFS Progression free survival.

Table 46: Objective response rate, Cox proportional hazards model, additional subgroup analysis (EFR set) (DCO 09 December 2016)

Subgroup		Olaparib 300 mg bd	Physician's choice of chemotherapy
Brain/CNS	N	17	5
	Patients with a response, n (%)	11 (64.7)	1 (20.0)
	95% CI	38.33, 85.79	0.51, 71.64
Other[a]	N	150	61
	Patients with a response, n (%)	89 (59.3)	18 (29.5)
	95% CI	51.02, 67.27	18.52, 42.57

[h] Other group includes patients without brain/CNS metastases: Visceral , bone/locomotor, non-classified sites (not bone, not visceral).

bd twice daily; CI Confidence interval; CNS Central nervous system; EFR Evaluable for response.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 47: Summary of Efficacy for trial D0819C00003

Title: A Phase III, Open Label, Randomised, Controlled, Multi-centre Study to Assess the Efficacy and Safety of Olaparib Monotherapy Versus Physician's Choice Chemotherapy in the Treatment of Metastatic Breast Cancer Patients with Germline BRCA1/2 Mutations.			
Study identifier	D0819C00003		
Design	a Phase III, open-label, randomised, controlled, multi-centre study		
	Duration of main phase:		Treatment until progression of the underlying disease, discontinuation of study drug, death, loss to follow up or withdrawal of consent to all study related procedures and follow up.
	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 continuous N=205
	Physician's choice of chemotherapy		-Oral capecitabine 2500 mg/m^2 to be taken daily (divided in 2 doses) for 14 days, repeated every 21 days or, -Intravenous (IV) vinorelbine 30 mg/m^2 on Day 1 and Day 8, repeated every 21 days or, -Intravenous eribulin mesylate 1.4 mg/m^2 eribulin (active substance) 1.23 mg/m^2 on Day 1 and Day 8, repeated every 21 days N=97
Endpoints and definitions	Primary endpoint	PFS (Progression Free Survival)	PFS: the time from randomisation until the date of objective radiological disease progression according to RECIST version 1.1, or to death (by any cause in the absence of disease progression), regardless of whether the patient withdraws from randomised therapy or receives another cancer therapy prior to disease progression. This was supported by time to first subsequent therapy (TFST)
	Secondary endpoint	OS (Overall Survival)	OS: the time from the date of randomisation until death due to any cause.
	Secondary endpoint	PFS2	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. This was supported by time to second subsequent therapy (TSST).
	Secondary endpoint	ORR (Objective Response Rate)	ORR: the number of responders (CR or PR) divided by the number of patients in the treatment group in the EFR analysis set (ITT population with measurable disease at baseline)
Database lock	09 December 2016 (33 months after the first patient enrolled)		

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	Physician's choice of chemotherapy
	Number of subject	205	97
	Median PFS (months)	7.03	4.17
	95% CI	5.68-8.31	2.79-4.27
	Median TFST (months)	9.36	4.21
	95% CI	8.28-10.64	3.32- 5.19
	Median PFS2 (months)	13.17	9.26
	95% CI	10.94-15.34	7.29-10.35
	Median TSST (months)	14.26	10.51
	95% CI	12.16-15.47	8.41-11.3
	Median OS (months)	19.25	19.61
	95% CI	16.66-21.82	14.09-24.18
	ORR (%)	59.9	28.8
	95% CI	52.03-67.38	18.3-41.25
Effect estimate per comparison	Primary endpoint **PFS**	Comparison groups	Olaparib versus physician's choice of chemotherapy
		Hazard ratio	0.58
		95% CI	0.43-0.80
		2 sided P-value	0.0009
	Secondary endpoint **TFST**	Comparison groups	Olaparib versus physician's choice of chemotherapy
		Hazard ratio	0.34
		95% CI	0.24-0.47
		2 sided P-value	<0.0001
	Secondary endpoint **PFS2 (DCO 25 Sept 2017)**	Comparison groups	Olaparib versus physician's choice of chemotherapy
		Hazard ratio	0.55
		95% CI	0.39-0.77
		2 sided P-value	0.0005
	Secondary endpoint **TSST**	Comparison groups	Olaparib versus physician's choice of chemotherapy
		Hazard ratio	0.53
		95% CI	0.38-0.74
		2 sided P-value	0.0002
	Secondary endpoint **OS (final, DCO 25 Sept 2017)**	Comparison groups	Olaparib versus physician's choice of chemotherapy
		Hazard ratio	0.90
		95% CI	0.66-1.23
		2 sided P-value	0.5131

Supportive studies

Supportive data were provided from three Phase II studies (Studies 20, 42 and D0810C00008) and two Phase I studies (Studies 24 and 02) in advanced cancer (one Phase II study only included patients with gBRCAm advanced breast cancer [Study D0810C00008], and the other 4 studies included patients with breast cancer as well as other solid tumours) (see Table 2). Some of the supportive studies investigated different doses and formulations of olaparib and none included comparators. The majority of patients in the supportive studies were more heavily pre-treated compared with those in OlympiAD.

PFS

PFS was a secondary or exploratory efficacy outcome in Study D0810C00008, Study 24, Study 20, Study 42 and time to progression (TTP) was a secondary efficacy outcome in Study 02. In Study D0810C00008, in patients with gBRCAm breast cancer, median PFS was 6.5 months with the 400 mg bd capsule dose (Table 9), which compared favourably to the results in the literature for an unselected population. In Study 42, in the subgroup of patients with gBRCAm breast cancer, the median PFS was 3.7 months. In Study 20 and Study 02, median PFS and median TTP, respectively were longer with olaparib in patients with gBRCAm breast cancer compared with unselected breast cancer. In Study 24, approximately one third of patients had gBRCAm breast cancer and median PFS was between 5 and 7 months. Thus, accounting for the different degrees of pre-treatment and considering the limitations of cross-study comparisons in general, the PFS on olaparib, as observed in the Phase II studies, supports the results observed in OlympiAD.

OS

OS was a secondary endpoint in Study 42. Median OS in Study 42 was 11.01 months (Table 9) on olaparib, which is shorter than the median OS observed in OlympiAD. Subsequent therapy use was documented for 38/62 (61.3%) of patients with gBRCAm breast cancer in Study 42 and 179/298 (60.1%) overall.

Other efficacy endpoints – ORR and DoR

Results for ORR for olaparib appeared generally consistent between the Phase II studies and OlympiAD when accounting for differences in study populations, such as different degrees of pre-treatment. As shown in Table 48, the majority of these studies showed that olaparib had activity in patients with gBRCAm breast cancer and other solid tumours. In Study D0810C00008, in patients with gBRCAm breast cancer, the ORR was 42.3% with the 400 mg bd capsule dose. Although no breast cancer patients in Study 20 had an objective response, a decrease in target lesion size was observed in 6/8 patients with gBRCAm breast cancer and only 1/14 patients with non-gBRCAm breast cancer.

Table 48: Summary of efficacy across olaparib studies: other supportive studies

	Study 20	Study 42	Study D0810C00008		Study 24			Study 02
	Phase II relapsed ovarian and breast cancer study (evaluable for RECIST response)	Phase II advanced *gBRCAm* tumours (Full analysis set)	Phase II advanced *gBRCAm* breast cancer (Per-protocol population)		Phase I formulation comparison study in patients with advanced solid tumours (Full analysis set)			Phase I FTIM study in advanced tumours (Intent-to-treat Population)
	400 mg bd capsule	400 mg bd capsule	400 mg bd capsule	100 mg bd capsule[a]	Group 1 – 400 mg bd capsule	Group 6 – 400 mg bd capsule	Group 6 – 300 mg bd tablet	All olaparib doses combined capsule
Number of patients								
Overall population if study not just breast cancer	86	298	NA	NA	11	18	18	98 (*gBRCAm* n=60)
Breast cancer population	23	62	26	24	4	5	5	13 (*gBRCAm* n=7)
Median PFS, months								
Overall population if study not just breast cancer	NA	NA	NA	NA	5.5[b]	5.7	7.1	2.8 (TTP) (3.8 for *gBRCAm*)
Breast cancer population	1.8 (3.6 for *gBRCAm* [n=10])	3.7 (n=62)	6.5	4.1	NR	NR	NR	5.4 (TTP) for *gBRCAm* (n=7)
Median OS, months								
Breast cancer population	NA	11.01 (8.44, 15.38) (n=62)	NA	NA	NA	NA	NA	NA
ORR % (95% CI)								
Overall population if study not just breast cancer	NA	29.3 (23.92, 35.19) (FAS measureable disease n=266)	NA	NA	18.2[c]	38.9	33.3	14.3 (8.7, 22.6) (21.7 [13.3, 33.6] for *gBRCAm*)
Breast cancer population	0 (0, 14.31) (0 [0, 32.44] for *gBRCAm* [n=8[c]])	13.8 (6.15, 25.38) (FAS measureable disease n=58)	42.3 (25.5, 61.1)	25.0 (12.0, 44.9)	NR	NR	NR	14.3 (2.6, 51.3) for *gBRCAm* (n=7)
Median DoR (range), days								
Overall population if study not just breast	NA	208	NA	NA	NR	NR	NR	252 (170 for *gBRCAm* [n=13])
Breast cancer population	NA	204	144 (92-393)	141 (55-175)	NR	NR	NR	NE

[a] A total of 23 patients in the 100 mg bd arm dose escalated to 400 mg bd following protocol amendment 3.
[b] 10/11 (90.9%) patients had a *gBRCA* mutation (see Section 6.5.4, Study 24 CSR).
[c] Two patients in the *BRCA* cohort had metastatic ovarian cancer in addition to breast cancer and were deemed not evaluable for breast cancer response; however the breast cancer cohort response rate is not affected by this.

2.4.3. Discussion on clinical efficacy

This application for an extension of indication for the treatment of adult patients with BRCA1/2-mutated HER2-negative metastatic breast cancer is based on the results of the pivotal Phase III, randomised, controlled, open-label, multicentre study OlympiAD.

Design and conduct of clinical studies

The 300 mg bd tablet dose was chosen as the recommended Phase III monotherapy dose based on tolerability and tumour shrinkage data from Study 24 in an advanced gBRCA mutated ovarian cancer population. Study 24 explored the safety data and tumour shrinkage data across a number of different doses and schedules of olaparib tablet or capsule in an advanced gBRCA mutated ovarian cancer population. This exploration resulted in the recommendation of 300 mg bd tablet dose for Phase III studies. This dosing regimen is expected to maintain plasma concentrations above the estimated mouse 90% inhibitory concentration ([IC90]; and its upper 95% CI) for tumour PARP inhibition across the full dosing interval, i.e., 12 hours. The recommended dose is acceptable. The exposure to olaparib following

administration of 300mg bd tablet formulation observed in the Phase III study OlympiAD (Olaparib-MS-05, N=36) was comparable to that in SOLO2 (Olaparib-MS-03, N=94) and was within the range previously predicted for the capsule formulation at 400mg bd (Olaparib-MS-01). In addition, in the pivotal phase 3 study supporting the breast cancer indication, only the currently approved tablet formulation was used.

This pivotal study OlympiAD is a 2:1 randomised, open-label, controlled, multi-centre phase III study evaluating olaparib monotherapy versus Physician's Choice Chemotherapy. The selection of appropriate therapy for metastatic breast cancer is complex because of the many treatments options, biologic heterogeneity of the disease and prior treatments received in the neo/adjuvant, locally advanced or metastatic settings. In addition, solid evidence is lacking as regards the most appropriate regimens for the treatment of germline BRCA 1/2 mutation positive breast cancer. The appropriateness of a comparison with Physician's Choice Chemotherapy is therefore endorsed.

Physician's Choice Chemotherapy included capecitabine, vinorelbine or eribulin as single-agent regimen used according to their marketing authorisation conditions. In patients who have received a taxane/anthracycline-based regimen, either neo/adjuvant or as first-line treatment for metastatic disease, it is accepted from a regulatory perspective that a single-agent regimen is used as reference mainly because of the absence of relevant data comparing sequential versus combination therapy.

Patients with platinum resistant tumours were excluded from the study due to expected cross-resistance to PARP inhibitors. The absence of a platinum therapy as a treatment option is questioned as previously discussed during the scientific advice procedure. Although carboplatin is mentioned in the ESMO recommendations for the treatment of BRCA mutation positive and negative mTNBC after taxane/anthracycline, the applicant considered that there were insufficient data to recommend platinum agents over standard chemotherapy in advanced breast cancer (Byrski et al 2012). However the TNT study (Tutt et al 2014) has shown a superiority of carboplatin compared to 'standard' docetaxel in the subgroup of patients with gBRCA mutated TNBC with a significantly better toxicity profile making it a treatment option recommended in clinical practice guidelines in this population (3rd ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer). It is also acknowledged that the results of TNT study were not available at the start of the study. Although the absence of platinum agent as a comparator option in OlympiAD study is considered a deficiency in the design of the study, it could be considered as acceptable considering the timing of the study. It is noted that it is not possible to conclude for the time being whether platinum would be more effective in first instance or after PARPi in this setting.

The study population is heterogeneous as patients could have received between 0 and 2 prior lines of cytotoxic chemotherapy for metastatic disease. Patients with HER2-positive breast cancer were excluded from the study because of the existing therapeutic options in this population.

Patients with ER and/or PgR positive disease were required to have received and progressed on at least 1 endocrine therapy (adjuvant or metastatic), or had disease that the treating physician believed to be inappropriate for endocrine therapy. This inclusion criterion is not aligned with the current clinical practice and recommendations since it does not specify if patients could have received targeted anticancer therapies such as mTOR inhibitors or CDK4/6 inhibitors. It is acknowledged that CDK4/6 inhibitors were not available at the time of study initiation. However, this would have been important to understand the place of olaparib therapy in the treatment sequence of patients with gBRCA HR+ metastatic breast cancer.

Patients with ECOG status ≥2 were excluded from the study. This is a standard selection criterion for all olaparib studies to safeguard patients who are in poor health, as the need to attend repeated clinic appointments and undergo additional testing associated with study participation may be detrimental to

their health. Low numbers of breast cancer patients with ECOG PS2 scores have received olaparib treatment in earlier clinical studies. This is adequately reflected in the section 5.1 of the SmPC.

To be enrolled into the OlympiAD study, subjects were required to have documented evidence of a deleterious or suspected deleterious gBRCA1 or gBRCA2 mutation. The presence of germline BRCA1 or BRCA2 mutations was assumed to result in homologous recombination deficiency (HRD) and sensitivity to olaparib in all the subgroups (independent on histology, hormone receptor status or line of therapy).Evidence of a qualifying BRCA mutation could be from either an existing BRCA mutation result generated by local testing or from prospective testing performed by BGI (Chinese patients) or by Myriad using either the Integrated BRACAnalysis (Myriad CLIA gBRCA test) or BRACAnalysis CDx test (non-Chinese patients).

Although germline BRCA1/2 mutations are neither necessary not sufficient for conferring HR-deficiency in breast cancer patients, for the time being there is no validated biomarker for determining patients with homologous-recombination deficient tumours and the development of tumours in BRCA1/2 carriers is thought to be due to alterations of the second allele in BRCA1 or 2 locus and consequently a functional deficiency of BRCA1 or BRCA2 proteins leading to homologous recombination deficiency and genomic instability. From this mechanistic point of view, the determining factor for selection of patients is a particular genotype, namely a presence of germline BRCA mutations.

At the time of study initiation, the inclusion of patients with a somatic mutation was not possible because an appropriate diagnostic test based on tissue analysis was not available. Thus, patients with a somatic mutation were excluded from this study and there is currently no clinical data available on the responsiveness of breast tumours with somatic BRCA mutation to PARPi. The difficulty to conduct a clinical trial only in patient with somatic BRCA mutated breast cancer is acknowledged due to low prevalence. Several ongoing clinical trials including TAPUR, VIOLETTE and LUCY studies in patients with either germline or somatic BRCA1/2 mutations might provide relevant data in this regard. The extrapolation of results from patients with germline BRCA mutations that developed breast cancer to patients with sporadic breast cancers that harbour somatic BRCA mutations in their tumours is not justified for the time being in the absence of any clinical data and other data supporting the proposed mechanistic rationale (see also SAG consultation below in this regard). Considering the CHMP assessment, the MAH has withdrawn its request for an indication in somatic breast cancer susceptibility genes mutated HER2-negative metastatic breast cancer. Data in patients with somatic BRCA mutations and deficiencies in other homologous recombination related genes are expected to be collected in MAH sponsored and other studies (TAPUR, LUCY and VIOLETTE and new planned study to be conducted in patients with only somatic BRCAm). The MAH is recommended to provide the results of these studies.

It is agreed that double-blind design is not an option due to obvious differences in tolerability and treatment schedules between the therapeutic options in the study. Measures included independent review and conduct of sensitivity analyses (for ascertainment bias, for deviation bias and evaluation time bias if scans are not performed at the protocol scheduled time points) to limit potential bias related to the open-label nature of the trial.

The primary efficacy endpoint was PFS (supported by TFST). Progression was assessed by the blinded independent central review (BICR) using RECIST 1.1. The primary efficacy endpoint was supported by OS, PFS2 (investigator assessment), TFST, TSST and ORR (by BICR) as secondary efficacy endpoints.

Primary and efficacy endpoints were in line with recommendations from EMA 'Guideline on the evaluation of anticancer medicinal products in man' (EMA/CHMP/205/95/Rev.5) since when PFS is the selected primary endpoint, OS should be reported as a secondary endpoint.

PFS as primary efficacy endpoint instead of OS was discussed during scientific advice and is considered acceptable. The study was intended to be performed in the 1st, 2nd and 3rd line in metastatic setting

meaning that time from progression on study therapy to death will vary. Also, next-line therapies may influence OS. In this context, result on PFS2 (supported by TSST) will be useful.

The study was adequately powered to observe a 2.3 months improvement in median PFS assuming 4-month median PFS for the control arm taking into account that median PFS for the selected comparators (eribulin, vinorelbine and capecitabine) varied depending on agents, line of therapy and previous treatments received.

Analysis of primary and secondary endpoints were based on the ITT population [= all randomised patients defined as the time from randomisation to the earliest date of assessment of objective progression (per RECIST criteria) or death by any cause (in the absence of disease progression)] and included the stratified 2-sided log-rank test for PFS, PFS2 and OS analysis, the Kaplan-Meier method to estimate median survival and the extended Cox regression model for the estimation of HR. In order to strongly control the type I error at 2.5% 1-sided, a multiple testing procedure was also employed across the primary endpoint and secondary endpoints intended for key label claims (i.e. PFS2 and OS).

The proposed analysis methods for the primary and secondary endpoints are standard methods in this fields in line with recommendations from EMA 'Guideline on the evaluation of anticancer medicinal products in man' (EMA/CHMP/205/95/Rev.5) and are therefore considered acceptable.

Cross-over was not allowed in this study as not considered appropriate since there were a number of active compounds available for most patients and it could have a confounding effect on OS and PFS2. However, it is acknowledged that patients were able to access PARPi outside of the study. As subsequent therapy, 0.5% and 8% of patients have received a subsequent PARP inhibitor in the treatment and comparator arm respectively, whereas 29% and 42% of patients received subsequent platinum therapy, respectively.

Of the 302 patients included in the FAS, the majority were female (97.7%), white (65.2%) with a median age 44 years (range 22 to 76), ECOG PS 0 (69.5%). A slightly higher percentage of patients with an ECOG PS 1 in the physician's choice of chemotherapy arm (36.1%) compared with the olaparib arm (27.8%) was observed.

All patients had metastatic disease as per protocol requirement with at least 2 metastatic sites in approximately ¾ of patients. A majority had a poorly differentiated tumour grade (54%).

167 patients (55.3%) had a known locally confirmed gBRCA mutation: 99 BRCA1 mutations (32.8%), 67 BRCA2 (22.2%), 1 BRCA1/2 (0.3%) and not reported for 135 patients (44.7%).

Approximately half of patients (50.3%) were HR+/HER2- and half of patients (49.7%) were TNBC at baseline.

The mean time from original diagnosis to randomisation in the study was approximately 5 years and 38 days from the most recent disease progression.

Twenty four (24) patients (11.7%) in the olaparib arm and 6 (6.2%) in the physician's choice of chemotherapy received disallowed concomitant medication, mainly for treatment of bone diseases [19 (9.3%) in the olaparib arm and 5 (5.2%) in the physician's choice of chemotherapy]. The use of disallowed concomitant medication did not raise concerns about the conduct of the study.

The patients randomised in the study were representative of the intended target population of gBRCAm patients with HER2-negative metastatic breast cancer. The demographic and disease characteristics in the FAS population were generally well balanced between the two treatment arms. Stratification factors by receipt of prior chemotherapy, hormone receptor status, and receipt of prior platinum therapy were also well balanced between the treatment arms.

At DCO for the primary analysis (9 December 2016), there was ~15% reduction risk of discontinuations in olaparib arm. Discontinuations were mainly due to the disease progression, including deaths. These discontinuations were rather well balanced between both arms (72.7% vs 74.7% for PD and 45.9% vs 47.4% for deaths). In the contrary, there were 66% and 26% reduction risk of discontinuation due to patients decision and AEs respectively in olaparib arm.

Since ethnic/physical characteristics were reported in the trial, it was noticed that very few Black or African-American included in the trial (1.7%). The mutations rates in this population seem to be similar to other populations included in the study. The low recruitment rate was partly explained by a lack of recommendation to undergo BRCA1/2 testing in the US. The SmPC mentions in section 4.2 that there are limited data available in non-Caucasian patients.

Overall, the proportion of patients with at least 1 important protocol deviation was 4.0%, and balanced between the treatment arms: 3.9% on olaparib and 4.1% on physician's choice of chemotherapy.

Efficacy data and additional analyses

OlympiAD met its primary endpoint demonstrating a statistically significant and clinically relevant 3-months improvement in PFS based on BICR in the FAS population treated with olaparib compared to physician's choice of chemotherapy (HR 0.58; 95% CI: 0.43, 0.80; p<0.0001; median 7.03 vs 4.17 months) which was supported by sensitivity analysis by investigator assessment (HR 0.50; 95% CI: 0.36, 0.68; p=0.0009; median 7.8 vs 3.8 months).

The improvement in PFS in the olaparib arm compared with the physician's choice of chemotherapy arm was statistically significant and clinically relevant, as evidenced by the magnitude of effect: a 42% reduction in risk of progression or death. There was clear separation of curves in favour of olaparib. This separation appeared to start with the first radiologic assessment scheduled at 6 weeks.

The robustness of the primary analysis is supported by sensitivities analysis (eg, ascertainment bias, evaluation time bias, attrition bias) demonstrating a consistent and favourable treatment benefit for olaparib. Discordance between BICR and investigator review for progression assessment was relatively low, 9% and not suggestive for major bias. Only 1 patient (0.5%) in the olaparib arm and 2 patients (2.1%) in the comparator arm missed ≥ 2 RECIST assessment with no impact of differential censoring between the 2 treatment groups.

Following the subgroup analyses of PFS, no subgroups derived a differential benefit compared with the overall population. Regarding subgroup analyses of PFS, consistent results were observed across all the pre-specified subgroup.

The design of the OlympiAD study does not allow making definitive conclusions in terms of comparison of efficacy of olaparib in HR+ BC vs TNBC but allows making conclusions in terms of consistency of results. PFS subgroup analysis results in TNBC and HR+ patients have been included in section 5.1 of the SmPC. Consistent benefit was seen in both ER and/or PgR positive and ER and PgR negative patients in all efficacy outcomes, including PFS2 and ORR.

gBRCA mutations are found in 10% of male breast cancer patients. Male breast cancer patients generally have gBRCA2 mutation. In study OlympiAD, 7 male patients were randomised (5 olaparib and 2 comparator). At the time of the PFS analysis, 1 patient had a confirmed partial response with a duration of response of 9.7 months in the olaparib arm. There were no confirmed responses in the comparator arm. Three of the male subjects on the olaparib arm had stable disease at the DCO for the primary analysis and 1 male on the olaparib arm had progressive disease. While the proportion of men in the study program is very low, it is still considered possible to extrapolate results to men, based on the common biological and pharmacological rationale.

At the time of DCO for primary analysis (DCO 9 December 2016), a statistical significance on PFS2 improvement in the olaparib arm (HR: 0.57, 95% CI 0.40 – 0.87; p=0.0033) with a median second PFS 13.17 months in the olaparib arm and 9.26 months in the comparator arm.

Post-hoc analysis with the DCO 25 September 2017 of PFS2 (65% maturity, DCO 25 September 2017) was consistent (HR 0.55, 95% CI 0.39-0.77) with the results for PFS2 at the primary analysis. PFS2 event rate was 63% (130/205) with a median time of 12.8 months in the olaparib arm and 67% (65/97) with a median time of 9.4 months in the comparator arm. The nominal p value was 0.0005, this test was not pre-specified under the multiplicity testing procedure.

Final OS analysis was conducted at 64% maturity of the FAS population (DCO 25 September 2017). There was no suggestion of an OS detriment, with the HR numerically favouring olaparib. The results of the final OS analysis were consistent the interim analysis (46% maturity of FAS population). Even if switch to olaparib was not permitted within the study design OlympiAD, it is acknowledged that patients were able to access PARPi outside of the study. This has the potential to confound interpretation of OS data. However, the number of patient who received PARPi as subsequent therapy is relatively low (2 patient (1%) in the olaparib arm and 8 (8.2%) in the comparator arm). Thus, the impact on OS analysis from subsequent PARPi therapy would be minor and did not favour olaparib. Subsequent platinum therapy was reported in 29% of patients in the olaparib arm and in 42% of patients in the chemotherapy arm. There is no evidence of a differential subgroup effect on OS.

A statistically and clinically longer TSFT and TSST in the olaparib arm than the comparator arm have been observed. ORR in the olaparib arm (59.9%) was doubled compared with the comparator arm (28.8%).

Efficacy outcomes in the Myriad CDx gBRCAm subgroup (297 patients overall; 202 in the olaparib arm and 97 in the comparator arm) were consistent with the FAS.

The statistically significant improvement of HRQoL (mean difference in change from baseline = 7.5 out of 100 points scale 95%CI 2.5, 12.4; p=0.0035) and difference in time to HRQoL deterioration (HR 0.44; 95% CI 0.5, 0.77; p=0.0043) in favour of olaparib were supported by sensitive analyses. However, the data from this open label are not considered robust enough to be included in the SmPC based on the review of the pre-planned analyses and hypotheses for PROs including the handling of missing data.

Only 32.5% of patients received endocrine therapy in metastatic disease and 38.4% in adjuvant/neoadjuvant setting while 152 patients (50.3%) were HR+ in OlympiAD study. Among the HR+ patients, 103 (50.2%) were treated with olaparib and 49 (50.5%) with physician's choice of chemotherapy. Six (5.8%) patients in olaparib arm and 4 (8.2%) in chemotherapy arm did not receive prior endocrine therapy while they were HR+.

Treatment options for patients with hormone receptor positive (HR+) breast cancer have changed over the last few years, with the introduction of new endocrine therapies (new first line treatment options and combination therapies with CDK4/6 inhibitors) after the start of OlympiAD study. Even if eCRF in the OlympiAD study, did not capture how many patients had progressed on, or after, being treated with hormonal therapy, it is expected that all HR+ patients have a progressive disease at the time of olaparib initiation and HR+ patients with non-progressive disease should be excluded from the indication. Overall, it is considered that the indication should reflect that patients with hormone receptor (HR)-positive breast cancer should also have progressed on or after prior endocrine therapy or be considered unsuitable for endocrine therapy in line with the studied population.

The median of previous chemotherapy received for metastatic disease was 1 for each treatment arm.

As required for eligibility in the study, nearly all patients had received prior treatment with anthracycline (unless contraindicated) and a taxane in either the neoadjuvant, adjuvant or metastatic setting. Patients had received prior treatment with anthracycline (unless contraindicated) in the localised (81%) or

metastatic (19%) setting and a taxane in the localised (70%) or metastatic setting (49%). Prior therapy with platinum was allowed in the (neo)adjuvant setting provided the last dose was received at least 12 months prior to randomisation and in metastatic setting if there had been no evidence of disease progression during platinum treatment. Patients have received platinum either for localised disease (7% of patients in the olaparib arm and 7% in the chemotherapy arm) or for metastatic disease (21% of patients in the olaparib arm and 14% in the chemotherapy arm) with the exception of 3 patients (2 olaparib and 1 comparator) who had received platinum in both settings.

According to eligibility criteria, patients must have completed previous courses of cytotoxic chemotherapy more than 21 days of randomisation. Absence of progressive disease at the time of randomisation was reported for 46 patients in olaparib arm and 24 patients in chemotherapy arm.

It is expected that median PFS varied depending on line of therapy and the nature of physician's choice chemotherapy. The results for each of the individual chemotherapy regimens are considered as exploratory and showed that the treatment effects observed in individual chemotherapies were similar to that observed in the ITT set, with slight variations.

Additional analyses of PFS were provided in patients who received 0 line, 1 line and 2 lines of previous CT in metastatic setting. HR greatly varied between subgroups of patient who received <2 prior lines of chemotherapy [no prior line: HR 0.50 (0.30, 0.84); one prior line: HR 0.50 (0.33, 0.76)] and subgroup of patients who received 2 prior lines of chemotherapy: HR 1.21 (0.69, 2.27).

Patients who received 2 prior lines of chemotherapy for mBC treated with olaparib (57 patients) experienced more progression or death (87.7%) than in chemotherapy arm (24 patients; number of events: 58.3%) with no numerical difference in median PFS (5.7 months versus 5.1 months). Resistant mechanisms of PARP inhibitors should have been further investigated to better determine the optimal sequence of use for PARP inhibitors and chemotherapy for breast cancer and to elaborate on more effective therapeutic strategies in metastatic BRCAm breast cancer. Given the data indicating a lower response to olaparib treatment after several lines of cytotoxic chemotherapy, the efficacy outcomes in subgroups of patient who received no prior line vs one or 2 prior lines of chemotherapy have been reflected in the SmpC section 5.1.

It is considered that anthracycline and taxane should be specified prior regimens in the indication, based on the proven OS benefit in the breast cancer setting for these drugs and the risk of loss of chance if not included. The study was performed under these conditions and no data have been produced to justify the extrapolation. Therefore, the indication reflects patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments (see SmPC sections 4.1 and 5.1).

Absence of progressive disease at the time of randomisation was reported for 46 patients in olaparib arm and 24 patients in chemotherapy arm. Of the 70 patients with non-progressive disease at randomisation, 38 patients received chemotherapy other than platinum. In the provided post-hoc analysis of the subgroup of patients that had not progressed on chemotherapy other than platinum, the median PFS in the olaparib arm (n=22) was 8.3 months (95% CI 3.1-16.7) and 2.8 months (95% CI 1.4-4.2) in the chemotherapy arm (n=16) with a HR of 0.54 (95% CI 0.24-1.23). However, the number of patients is too limited to make meaningful conclusions on the efficacy in this subgroup (see SmPC section 5.1).

The currently available data do not provide sufficient level of evidence whether platinum would be more effective in first instance or after PARPi. Data in patients with prior platinum exposure are limited and it is not known whether olaparib would have activity in platinum-resistant breast cancers since these patients have not been enrolled in the OlympiAD trial. Information on prior and subsequent platinum therapy is considered relevant for the prescribers and has been included in the SmPC section 5.1.

Other chemotherapeutic options than platinum are suggested to have activity in HRD tumours. In particular, 'anthracycline-sensitive' tumours might be responsive to PARP inhibitors and/or induce cross-resistance diminishing further responsiveness to PARPi. The MAH provided data on type of response to anthracycline in localised disease for patients enrolled in OlympiAD trials in order to estimate the initial responsiveness of tumours to anthracyclines that have a similar mechanism of action as platinum agents and might be considered, similarly to platinum, as potential treatment option to target tumours with HRD (data not shown).

Response rate for patients who received prior anthracycline in localised setting was 13.2% in the population of patients enrolled and well balanced between arm (13.7% in the olaparib arm and 12.4% in the physician's choice of chemotherapy arm. However, 3 patients (1.5%) on the olaparib arm reported a complete response to prior anthracycline. The response rate and duration of response for patients with a response to prior anthracycline by platinum treatment was also presented (data not shown). Patients who received both prior anthracycline and platinum appear to have numerically worse outcomes than patients without prior exposure to platinum, indicating plausible resistance mechanisms.

Overall, except prior platinum therapy that is known to share a similar mechanism of action supported by clinical data, it is not known whether other type of prior chemotherapy could have an impact on the response to PARP inhibitors in progressive BRCAm metastatic breast cancer. Anthracyclines are suggested to have similar mechanism of action but supporting data are still limited and OlympiAD trial results do not allow making conclusions on the role of anthracyclines in predicting HRD in tumours or in inducing cross-resistance when used prior to olaparib.

The Applicant is recommended to investigate tumour heterogeneity and mechanisms of resistance to DNA-damaging agents that could impact the efficacy of Lynparza in different lines of therapy in patients with BRCA1- and BRCA2-mutated tumours and breast tumours of particular histological and molecular subtypes. The investigation of efficacy in platinum-resistant tumours and comparative efficacy to platinum agents is recommended.

Patients with locally advanced disease with a generally better prognosis have not been included in the pivotal trial, but the extrapolation to this patient population was considered acceptable by the CHMP given a similar clinical management for locally advanced and metastatic disease and based on a biological and pharmacological rationale.

Despite the relatively small sample size and the more advanced stage of disease of the patients included in the supportive studies, the data collected in patients with *gBRCAm* breast cancer from these studies is considered supportive.

Results reported in early phase trials with capsule formulation of olaparib appear to be inconsistent in terms of ORR reported in patients with germline BRCA mutations (varying from no response to 42.3% of ORR).

Additional expert consultation

The SAG Oncology was consulted on the following aspects.

1. **Can the efficacy of olaparib, demonstrated by selecting patients through gBRCA mutations in blood samples, be extrapolated to patients with tumors exhibiting only sBRCA mutations?**

   The majority of the SAG agreed that the validity of extrapolating the efficacy associated with PARP inhibitors observed in patients with germline BRCA mutations to patients with tumours with somatic BRCA mutations is only a hypothesis. Clinical data are lacking and extrapolating from the experience

in ovarian cancer mainly based on the mechanism of action may not be appropriate in view of potential different tumour biology in terms of tumour microenvironment, immune system involvement, etc., between gBRCA- and sBRCA-associated breast cancers, and also considering that previous exposure to platinum differs in ovarian and breast cancer. Even if the BRCA-mutation is likely to be of great biological importance, the BRCA mutations per se may not be a sufficient "driver" for tumorigenesis in sBRCA-associated breast cancer. Other factors are probably involved, such as the extent of tumour heterogeneity and if somatic BRCA loss is an early or late event, TP53 abnormalities, etc. Thus, the effect of olaparib in tumours harbouring only a somatic mutation, although an effect is biologically plausible, might be qualitatively or quantitatively different from the effect in gBRCA-associated breast cancer. In conclusion, there is uncertainty about both the treatment effect and a potentially differential side effect profile for sBRCA-associated breast cancer in comparison with gBRCA-associated disease.

According to a minority of SAG members, however, although acknowledging the challenges expressed above, given that the effect of somatic mutation is in terms of phenotype is similar to what is seen with a germline mutation, it seems counter-intuitive that the response would be different for somatic v. germline BRCA mutated breast cancer. Safety advantages might also be hypothesized as the drug would act more specifically on cancer cells (albeit not observed in ovarian cancer).

The SAG agreed that further clinical studies, even just looking at response rate and duration in patients with tumours harbouring somatic mutations, are needed in order to support the hypothesis of sBRCA as a treatment predictive factor in patients with breast cancer. Observational studies (registries) might also be useful to explore this hypothesis. Studies should also investigate the incidence of MDS and AML.

The SAG further noted that the control group of the pivotal clinical study excluded the use of a platinum-containing regimen, which is considered more efficacious than the physician's choice monotherapies used in the pivotal trial. Thus, a smaller effect of PARP-inhibition would be expected compared to current standard treatments (although the toxicity profile is likely improved compared to platinum-containing regimen). Furthermore, the compliance in the physician's choice arm indicated problems. Whether a PARP-inhibitor is more efficacious than platinum-containing regimens in the population of gBRCA-associated metastatic breast cancer has not been established.

2. **Can efficacy be extrapolated from patients with gBRCA mutations to those with tumours displaying germline/somatic mutations in other genes potentially impacting HRD status?**

Given the challenges expressed above regarding extrapolation to tumours harbouring somatic mutations and the less clear role for other mutations and other mechanisms causing HRD, further extrapolation is not considered justified.

3. **What methods for establishing the HRD status of breast cancers are appropriate and available?**

Currently, multiple different HRD assays have been explored. No studies of the effect of PARP-inhibitors using HRD as a treatment predictive marker has been presented. Thus, no HRD assay can be considered having clinical validity and utility for predicting PARP inhibitor sensitivity.

4. **What methods for establishing the BRCA1/2 locus-specific loss of heterozygosity (LOH) are appropriate and available? Is there an established relationship between the extent of LOH and the degree HRD in BRCA1/2 germline mutation-associated and sporadic breast tumours?**

There are methods available in a research setting, to test for BRCA1/2 locus-specific loss of heterozygosity; however, the SAG could not confirm to what extent any particular test is well-established. Furthermore, the relationship between LOH and HRD in germline mutation-associated and sporadic breast tumours is unclear, and mechanisms apart from LOH do operate in gBRCA-associated breast cancer as a mechanism for biallelic inactivation of BRCA1 and BRCA2, so the clinical utility of such tests over BRCA testing is not likely to be important in the context of treatment effect with PARP inhibition.

5. **What is the likelihood of non-HRD tumours in patients with gBRCA mutations and HER2-/hormone-receptor positive disease? Does this possibility give rise to further diagnostic considerations?**

There are no data to quantify the rate of "sporadic" cancer in germline mutation carriers, i.e. non-hereditary breast cancers occurring as a consequence of other mechanisms apart from the BCRA mutation in a germ line mutation carrier. Such cancers certainly exist, but in general, this is not considered to be of such clinical importance as to warrant further diagnostic considerations.

6. **Could other genotype/phenotype features of breast tumours (e.g. molecular subtype, tumour grade, concomitant mutations, platinum/other chemotherapy sensitivity) indicate HRD, similarly to ovarian cancers?**

The SAG was not aware of any patient, tumour, or treatment characteristics that could be used as a present valid indication of HRD; further clinical data are required.

2.4.4. Conclusions on the clinical efficacy

The results of the different efficacy outcomes in the pivotal OlympiAD study support efficacy of olaparib for the treatment of adult patients with germline *BRCA1/2*-mutations who have HER2 negative metastatic breast cancer. There was a statistically significant improvement in PFS, with supportive data for PFS2, TFST and TSST in favour of olaparib at the time of primary analysis. There was no indication on a detrimental effect on OS at interim and final analysis at 64% maturity, with HR numerically favouring olaparib.

For the time being, there is no clinical data available on the responsiveness of breast tumours with somatic BRCA mutation to PARPi and the extrapolation is not supported in the context of different types of breast cancer.

2.5. Clinical safety

Patient exposure

Across the entire clinical programme, as of 15 December 2017, 8319 patients are estimated to have received treatment with olaparib.

The OlympiAD study provides the main safety data for the use of olaparib 300 mg bd therapy in patients with HER2-negative metastatic gBRCAm breast cancer. The OlympiAD data are supported by safety data from patients receiving olaparib monotherapy at 300 mg bd (as a continuous dose) in an additional 10 studies, corresponding to a total of 759 patients with advanced solid tumours.

The majority of patients in the 300 mg bd pool had either ovarian, fallopian tube or primary peritoneal cancer (335/759 [44.1%] patients) or breast cancer (268/759 [35.3%] patients). Patients with other advanced solid tumours, including colon/colorectal (n=23), pancreas (n=12) or prostate (n=11) cancers

were also treated in these studies. Patients were also being treated for different stages of their disease. Data are summarised regardless of BRCA mutation status.

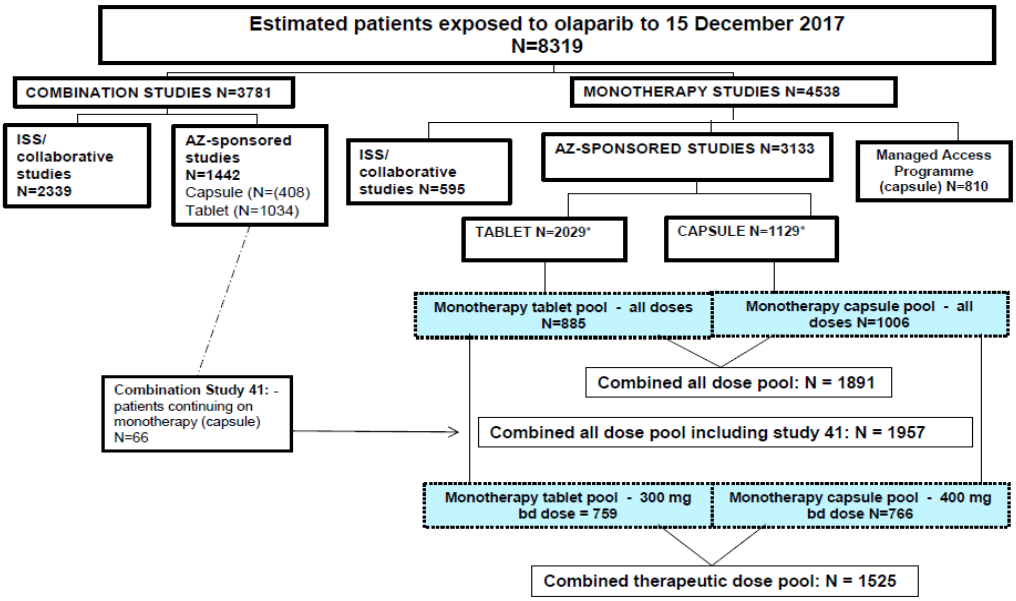


Figure 22: Overview of the olaparib clinical programme as of 15 December 2017

Table 49: Number of patients exposed to olaparib tablet monotherapy (as of DCO: 25 September 2017)

Study/pooled dataset	Number of patients receiving olaparib 300 mg bd (all tumour types)
OlympiAD: Phase III HER2-negative breast cancer patients with *gBRCA1/2* mutation	205
300 mg bd pool	759
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
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ADME: Absorption, distribution, metabolism and elimination; bd: Twice daily; CYP: Cytochrome P450; *gBRCA*: Germline breast cancer susceptibility gene; HER2: Human epidermal growth factor receptor-2; PK: Pharmacokinetic(s); SAE: Serious adverse event;

Overall extent of exposure: OlympiAD

A total of 302 patients were randomised in OlympiAD, 205 were randomised to the olaparib arm and 97 to the physician's choice of chemotherapy arm. All of the 205 patients randomised to olaparib received study treatment. Of the 91 patients who received treatment in the physician's choice of chemotherapy arm, 41 (42.3%) patients received capecitabine, 34 (35.1%) patients received eribulin and 16 (16.5%) patients received vinorelbine. Six patients randomised to the physician's choice of chemotherapy arm did not receive any treatment and were therefore excluded from the SAS.

Table 50: Overall extent of exposure in OlympiAD (SAS)

Month (approximate)	Number (%) of patients: Olaparib 300 mg bd N=205	Number (%) of patients: Physician's choice[a] N=91
Day 1	205 (100)	91 (100)
≥1 month (30.4 days)	201 (98.0)	87 (95.6)
≥3 months (91.3 days)	176 (85.9)	48 (52.7)
≥6 months (182.6 days)	123 (60.0)	25 (27.5)
≥9 months (273.9 days)	86 (42.0)	15 (16.5)
≥12 months (365.3 days)	57 (27.8)	9 (9.9)
≥18 months (547.9 days)	39 (19.0)	2 (2.2)
≥24 months (730.5 days)	18 (8.8)	1 (1.1)
≥30 months (913.1 days)	5 (2.4)	0
≥36 months (1095.8 days)	2 (1.0)	0

[a] Physician's choice of chemotherapy consisting of either capecitabine, eribulin or vinorelbine

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. Exposure includes treatment interruptions for olaparib and treatment delays for physican's choice of chemotherapy.

bd: Twice daily; CSR: Clinical study report; DCO: Data cut-off; SAS: Safety analysis set.

Data derived from Table 11.3.1.6.1, OlympiAD CSR Addendum, Module 5.3.5.1 (DCO: 25 September 2017).

Duration of treatment

Table 51: Duration of treatment in OlympiAD (SAS)

Treatment duration (days)		Olaparib 300 mg bd N=205	Physician's choice[a] N=91
Total treatment duration (days)	Mean (sd)	315.8 (249.04)	156.3 (150.83)
	Median (range)	251.0 (14 - 1165)	105.0 (21 - 759)
	Total treatment days	64744	14226
Actual treatment duration (days)	Mean (sd)	305.0 (245.48)	NA[b]
	Median (range)	230.0 (14 - 1158)	
	Total treatment days	62517	
Actual treatment duration at the assigned dose (days)	Mean (sd)	243.9 (229.25)	NA[b]
	Median (range)	162.0 (3 - 1061)	
	Total treatment days	49502	

[a] Physician's choice of chemotherapy consisting of either capecitabine, eribulin or vinorelbine.
[b] Actual treatment duration (which excludes treatment interruptions) is not applicable to the physician's choice of chemotherapy arm in OlympiAD due to the complexity of defining the duration of an interruption).

bd: twice daily; CSR: Clinical study report; DCO: Data cut-off; NA: not applicable; SAS: Safety analysis set; sd: standard deviation.

Data derived from Table 11.3.1.1, OlympiAD CSR Addendum, Module 5.3.5.1 (DCO: 25 September 2017).

Dose intensity

Table 52: Relative and percentage intended doses of study treatment in OlympiAD (SAS)

Treatment duration (days)		Olaparib 300 mg bd N=205	Physician's choice[a] N=91
Relative dose intensity (RDI) (days)	N	205	90[b]
	Mean (sd)	92.2 (12.81)	89.2 (20.88)
	Median (range)	99.4 (42 – 100)	92.4 (49 – 201)
Percentage intended dose (PID) (days)	N	205	90[b]
	Mean (sd)	90.4 (15.30)	82.5 (25.31)
	Median (range)	99.4 (28 – 100)	84.9 (12 – 186)

[a] Physician's choice of chemotherapy consisting of either capecitabine, eribulin or vinorelbine
[b] One patient had no height measurement recorded at baseline. As planned dose for physician's choice of chemotherapy was based on body mass index at baseline, it was not possible to calculate a planned dose, and therefore not possible to calculate RDI and PID.

The RDI is the percentage of the actual dose delivered relative to the intended dose through to treatment discontinuation. The PID is the percentage of the actual dose delivered relative to the intended dose through to progression.

bd: twice daily; CSR: Clinical study report; DCO: Data cut-off; NA: not applicable; PDI percentage intended dose; RDI relative dose intensity; SAS: Safety analysis set; sd: standard deviation.

Data derived from Table 11.3.1.4 OlympiAD CSR Addendum, Module 5.3.5.1 (DCO: 25 September 2017).

Table 53: Mean daily dose of olaparib by time period in OlympiAD (SAS)

Olaparib daily dose (mg)	Number (%) of patients by time period				
	Up to 3 months (N=205)	>3 to ≤6 months (N=176)	>6 to ≤9 months (N=123)	>9 to ≤12 months (N=86)	>12 months (N=56)
>600	1 (0.5)[a]	0	0	0	0
>500 to ≤600	171 (83.4)	132 (75.0)	88 (71.5)	61 (70.9)	36 (64.3)
>400 to ≤500	22 (10.7)	18 (10.2)	11 (8.9)	10 (11.6)	10 (17.9)
≤400	11 (5.4)	26 (14.8)	24 (19.5)	15 (17.4)	10 (17.9)

[a] This was Patient who took daily dose 900 mg olaparib (3 x 300 mg) for 1 day only, due to accidentally taking an extra dose.

bd: twice daily; CSR: Clinical study report; DCO: Date cut-off; SAS: Safety analysis set.

Data derived from Table 11.3.1.7 and Appendix 12.2.10.3, OlympiAD CSR, Module 5.3.5.1 (DCO: 09 December 2016).

Dose modification

Table 54: Dose interruptions or delays and reductions in OlympiAD (SAS)

Treatment duration (days)		Number (%) of patients: Olaparib 300 mg bd N=205	Number (%) of patients: Physician's choice[a] N=91
Number of patients with no interruptions/delays		101 (49.3)	56 (61.5)
Number of patients with an interruption/delay	Any	104 (50.7)	35 (38.5)
	1	42 (20.5)	21 (23.1)
	2	32 (15.6)	7 (7.7)
	3	12 (5.9)	2 (2.2)
	4	8 (3.9)	2 (2.2)
	>4	10 (4.9)	3 (3.3)
Reason for interruption/delay	Adverse event	72 (35.1)	24 (26.4)
	Other[b]	66 (32.2)	22 (24.2)
Number of patients with no reductions		150 (73.2)	63 (69.2)
Number of patients with a reduction	Any	55 (26.8)	28 (30.8)
	1	37 (18.0)	24 (26.4)
	2	17 (8.3)	4 (4.4)
	3	1 (0.5)	0
Reason for reduction	Adverse event	52 (25.4)	28 (30.8)
	Laboratory abnormality not reported as an adverse event	1 (0.5)	0
	Other	5 (2.4)	0
Number of patients with both an interruption/delay and a reduction		51 (24.9)	15 (16.5)

Note: Dose interruptions were used to manage toxicity in the olaparib arm, dose delays were used to manage toxicity in the physician's choice of chemotherapy arm.

[a] Physician's choice of chemotherapy consisting of either capecitabine, eribulin or vinorelbine

[b] Reasons for interruptions are not mutually exclusive for patients with multiple interruptions, although reasons were counted only once per category.

bd: twice daily; CSR: Clinical study report; DCO: Data cut-off; SAS: Safety analysis set.

Data derived from Table 11.3.1.2.1 and Table 11.3.1.3 OlympiAD CSR Addendum, Module 5.3.5.1 (DCO: 25 September 2017).

Overall extent of exposure: 300 mg bd pool

Table 55: Overall extent of exposure in the 300 mg bd pool

Month (days)	Number (%) of patients Olaparib 300 mg bd N=759
0	759 (100.0)
≥1 month (30.4 days)	698 (92.0)
≥3 months (91.3 days)	526 (69.3)
≥6 months (182.6 days)	378 (49.8)
≥9 months (273.9 days)	214 (28.2)
≥12 months (365.3 days)	144 (19.0)
≥24 months (730.5 days)	80 (10.5)
≥30 months (913.1 days)	20 (2.6)
≥36 months (1095.8 days)	2 (0.3)

Duration of treatment was collected in days. An approximation of treatment duration in months was made by dividing the time points in days by 30.4375 (based on 365.25 days/12 months) and selecting the one that was closest to (but not longer than) the treatment month.
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.
Data derived from Table 2.7.4.1.9.2, 300 mg bd pool, Module 5.3.5.3 (DCO: 25 September 2017).

Demographics and other characteristics of patients in OlympiAD study are presented in Table 10 in the section on clinical efficacy.

Adverse events

Table 56: Number (%) of patients who had at least 1 AE in any category in OlympiAD (SAS)

AE category[a]	Number (%) of patients	
	Olaparib 300 mg bd N=205	Physician's choice[b] N=91
Any AE	200 (97.6)	87 (95.6)
Any AE causally related to study drug[c]	178 (86.8)	74 (81.3)
Any AE of CTCAE Grade 3 or higher	78 (38.0)	45 (49.5)
Any AE with outcome = Death	1 (0.5)	0
Any SAE (including events with outcome = death)	34 (16.6)	15 (16.5)
Any AE leading to discontinuation of study treatment	10 (4.9)	7 (7.7)
Any AE leading to dose reduction of study treatment	52 (25.4)	28 (30.8)
Any AE leading to interruption/delay of study treatment	74 (36.1)	26 (28.6)

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

[b] Physician's choice of chemotherapy consisting of either capecitabine, eribulin or vinorelbine

[c] As assessed by the investigator.

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.

Data derived from Table 11.3.2.1.1, Table 11.3.2.9.1 and Table 11.3.2.9.2 OlympiAD CSR Addendum, Module 5.3.5.1 (DCO: 25 September 2017).

Table 57: Number (%) of patients who had at least 1 AE in any category (olaparib treatment groups) in OlympiAD and the 300 mg bd pool

	Number (%) of patients	
	Olaparib 300 mg bd	
AE category[a]	OlympiAD SAS N=205	300 mg bd pool N=759
Any AE	200 (97.6)	741 (97.6)
Any AE causally related to study drug[b]	178 (86.8)	654 (86.2)
Any AE of CTCAE Grade 3 or higher	78 (38.0)	278 (36.6)
Any AE with outcome = Death	1 (0.5)	3 (0.4)
Any SAE (including events with outcome = death)	34 (16.6)	143 (18.8)
Any AE leading to discontinuation of study treatment	10 (4.9)	50 (6.6)
Any AE leading to dose reduction of study treatment	52 (25.4)	134 (17.7)
Any AE leading to interruption/delay of study treatment	74 (36.1)	239 (31.5)

[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

[b] As assessed by the investigator.

300 mg bd pool includes data from OlympiAD

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.

Data derived from Table 11.3.2.1.1, Table 11.3.2.9.1 and Table 11.3.2.9.2 OlympiAD CSR Addendum, Module 5.3.5.1 (DCO: 25 September 2017); Table 2.7.4.1.1.1, 300 mg bd pool, Module 5.3.5.3 (DCO: 25 September 2017).

Common adverse events: OlympiAD

Table 58: Most common AEs (reported by ≥10% patients in either arm) and adjusted by patient years' exposure in OlympiAD (SAS)

	Olaparib 300 mg bd N=205		Physician's choice[a] N=91	
Preferred term	Number (%) of patients with events	Event rate (per 1000 patient years)	Number (%) of patients with events	Event rate (per 1000 patient years)
Any AE	200 (97.6)	12722.05	87 (95.6)	23451.48
Nausea	119 (58.0)	1367.12	32 (35.2)	980.04
Anaemia	81 (39.5)	575.83	23 (25.3)	674.38
Vomiting	66 (32.2)	441.23	14 (15.4)	341.40
Neutropenia	37 (18.0)	234.14	28 (30.8)	862.97
Fatigue	61 (29.8)	406.96	22 (24.2)	597.97
Diarrhoea	42 (20.5)	261.52	20 (22.0)	602.72
PPE syndrome	1 (0.5)	5.21	19 (20.9)	593.85
WBC count decreased	33 (16.1)	192.02	19 (20.9)	504.82
Headache	42 (20.5)	250.20	14 (15.4)	349.45
Neutrophil count decreased	23 (11.2)	128.04	17 (18.7)	467.25
Pyrexia	30 (14.6)	172.90	16 (17.6)	440.43
ALT increased	24 (11.7)	136.31	16 (17.6)	426.23
Decreased appetite	35 (17.1)	208.31	11 (12.1)	265.76
Cough	35 (17.1)	209.97	6 (6.6)	143.54
AST increased	20 (9.8)	111.26	15 (16.5)	385.23
Back pain	30 (14.6)	169.94	8 (8.8)	202.85
Upper respiratory tract infection	27 (13.2)	155.87	9 (9.9)	228.87
Constipation	26 (12.7)	147.35	12 (13.2)	297.72
Asthenia	19 (9.3)	109.25	12 (13.2)	318.53
Alopecia	7 (3.4)	37.26	12 (13.2)	300.60
Arthralgia	23 (11.2)	131.09	9 (9.9)	215.42
Leukopenia	23 (11.2)	134.70	9 (9.9)	233.11
Stomatitis	16 (7.8)	89.47	10 (11.0)	244.48

[a] Physician's choice of chemotherapy consisting of either capecitabine, eribulin or vinorelbine. Table ordered by decreasing incidence in either treatment arm.

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; PPE Palmar-plantar erythrodysaesthesia; SAE: serious adverse event; SAS: safety analysis set.

Data derived from Table 11.3.2.2, OlympiAD CSR Addendum, Module 5.3.5.1 (DCO: 25 September 2017).

In OlympiAD, the AE preferred terms (PTs) that were reported at a 5% greater frequency in the olaparib 300 mg tablet bd group compared with the physician's choice of chemotherapy group were: nausea (58.0% of patients on olaparib vs. 35.2% on the physician's choice of chemotherapy), anaemia (39.5% vs. 25.3%), vomiting (32.2% vs. 15.4%), fatigue (29.8% vs. 24.2%), headache (20.5% vs. 15.4%), cough (17.1% vs. 6.6%), decreased appetite (17.1% vs. 12.1%) and back pain (14.6% vs. 8.8%).

Whereas, the AE preferred terms (PTs) that were reported at a 5% greater frequency in the physician's choice of chemotherapy group compared with the olaparib 300 mg tablet bd group were: neutropenia (30.8% on the physician's choice of chemotherapy vs. 18.0% on olaparib), PPE syndrome (20.9% vs. 0.5%), WBC count decreased (20.9% vs. 16.1%), neutrophil count decreased (18.7% vs. 11.2%), ALT increased (17.6% vs. 11.7%), AST increased (16.5% vs. 9.8%) and alopecia (13.2% vs. 3.4%).

Common adverse events: tablet pool

Table 59: Most common AEs (reported in ≥10%) in the olaparib treatment arm of OlympiAD or the 300 mg bd pool

	Number (%) of patients	
	Olaparib 300 mg bd	
Preferred term	OlympiAD SAS N=205	300 mg bd pool N=759
Any AE	200 (97.6)	741 (97.6)
Nausea	119 (58.0)	455 (59.9)
Anaemia	81 (39.5)	277 (36.5)
Vomiting	66 (32.2)	260 (34.3)
Fatigue	61 (29.8)	297 (39.1)
Diarrhoea	42 (20.5)	187 (24.6)
Headache	42 (20.5)	129 (17.0)
Neutropenia	37 (18.0)	94 (12.4)
Cough	35 (17.1)	110 (14.5)
Decreased appetite	35 (17.1)	178 (23.5)
WBC count decreased	33 (16.1)	56 (7.4)
Pyrexia	30 (14.6)	89 (11.7)
Back pain	30 (14.6)	86 (11.3)
Upper respiratory tract infection	27 (13.2)	61 (8.0)
Constipation	26 (12.7)	121 (15.9)
ALT increased	24 (11.7)	51 (6.7)
Neutrophil count decreased	23 (11.2)	47 (6.2)
Arthralgia	23 (11.2)	83 (10.9)
Leukopenia	23 (11.2)	61 (8.0)
Dysgeusia	19 (9.3)	116 (15.3)

Asthenia	19 (9.3)	105 (13.8)
Dyspnoea	18 (8.8)	100 (13.2)
Dizziness	18 (8.8)	77 (10.1)
Abdominal pain	14 (6.8)	107 (14.1)

300 mg bd pool includes data from OlympiAD
Table ordered by incidence of events in the OlympiAD study
Includes AEs with an onset date between the date of first dose and 30 days following the date of last dose of study treatment.
AE: Adverse event; ALT: Alanine aminotransferase; bd: Twice daily; CSR: Clinical study report; DCO: Data cut-off.; N: Total number of patients; SAS: Safety analysis set; WBC: White blood cell.
Data derived from Table 11.3.2.5, OlympiAD CSR Addendum, Module 5.3.5.1 (DCO: 25 September 2017); Table 2.7.4.1.1.2 and Table 11.3.2.1.1, 300 mg bd pool, Module 5.3.5.3 (DCO: 25 September 2017).

Adverse events by treatment period: OlympiAD

Table 60: Onset of AE in the first 3 months and 3-6 months of treatment for the most common AEs (reported in ≥10% of patients in either arm) in OlympiAD (SAS)

	Number (%) of patients			
	Onset in 0-3 months		Onset in 3-6 months	
System organ class Preferred term	Olaparib 300 mg bd N=205	Physician's choice[a] N=91	Olaparib 300 mg bd N=185	Physician's choice[a] N=61
Nausea	105 (51.2)	27 (29.7)	15 (8.1)	1 (1.6)
Anaemia	55 (26.8)	19 (20.9)	27 (14.6)	6 (9.8)
Neutropenia	23 (11.2)	25 (27.5)	13 (7.0)	4 (6.6)
Vomiting	43 (21.0)	14 (15.4)	13 (7.0)	1 (1.6)
Fatigue	45 (22.0)	20 (22.0)	10 (5.4)	0
Diarrhoea	32 (15.6)	20 (22.0)	7 (3.8)	4 (6.6)
PPE syndrome	0	17 (18.7)	1 (0.5)	1 (1.6)
WBC count decreased	24 (11.7)	16 (17.6)	10 (5.4)	5 (8.2)
Headache	35 (17.1)	12 (13.2)	4 (2.2)	2 (3.3)
Neutrophil count decreased	17 (8.3)	16 (17.6)	9 (4.9)	6 (9.8)
Pyrexia	17 (8.3)	14 (15.4)	6 (3.2)	3 (4.9)
ALT increased	19 (9.3)	15 (16.5)	7 (3.8)	3 (4.9)
Cough	16 (7.8)	5 (5.5)	14 (7.6)	0
AST increased	14 (6.8)	12 (13.2)	5 (2.7)	2 (3.3)
Decreased appetite	30 (14.6)	10 (11.0)	3 (1.6)	0
Constipation	16 (7.8)	11 (12.1)	3 (1.6)	1 (1.6)
Asthenia	13 (6.3)	11 (12.1)	5 (2.7)	2 (3.3)
Alopecia	3 (1.5)	10 (11.0)	1 (0.5)	0
Upper respiratory tract infection	12 (5.9)	7 (7.7)	6 (3.2)	3 (4.9)
Back pain	7 (3.4)	8 (8.8)	7 (3.8)	0
Dyspnoea	6 (2.9)	8 (8.8)	7 (3.8)	1 (1.6)
Stomatitis	6 (2.9)	9 (9.9)	5 (2.7)	1 (1.6)
Arthralgia	10 (4.9)	8 (8.8)	4 (2.2)	0
Leukopenia	11 (5.4)	8 (8.8)	10 (5.4)	2 (3.3)

[a] Physician's choice of chemotherapy consisting of either capecitabine, eribulin or vinorelbine

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; 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; PPE: Palmar-plantar erythrodysaesthesia; SAE: serious adverse event; SAS: safety analysis set; WBC: White blood cell.

Data derived from Table 2.7.4.1.7.3, Module 5.3.5.3 (DCO: 25 September 2017).

Causally-related adverse events: OlympiAD

Table 61: Most common AEs of CTCAE Grade 3 or higher (reported in ≥2% patients in either arm) in OlympiAD (SAS)

System organ class Preferred term	Number (%) of patients Olaparib 300 mg bd N=205	Number (%) of patients Physician's choice[a] N=91
Any Grade ≥3 AE	**78 (38.0)**	**45 (49.5)**
Blood and lymphatic system disorders	**38 (18.5)**	**18 (19.8)**
Anaemia	32 (15.6)	4 (4.4)
Neutropenia	11 (5.4)	12 (13.2)
Leukopenia	5 (2.4)	3 (3.3)
Febrile neutropenia	0	3 (3.3)
Investigations	**23 (11.2)**	**19 (20.9)**
Neutrophil count decreased	10 (4.9)	12 (13.2)
WBC count decreased	7 (3.4)	9 (9.9)
Platelet count decreased	5 (2.4)	1 (1.1)
AST increased	5 (2.4)	0
GGT increased	4 (2.0)	1 (1.1)
Musculoskeletal and connective tissue disorders	**9 (4.4)**	**4 (4.4)**
Back pain	4 (2.0)	1 (1.1)
General disorders and administration site conditions	**10 (4.9)**	**2 (2.2)**
Fatigue	7 (3.4)	1 (1.1)
Respiratory, thoracic and mediastinal disorders	**6 (2.9)**	**3 (3.3)**
Dyspnoea	2 (1.0)	2 (2.2)
Nervous system disorders	**6 (2.9)**	**3 (3.3)**
Headache	2 (1.0)	2 (2.2)
Skin and subcutaneous tissue disorders	**1 (0.5)**	**3 (3.3)**
PPE syndrome	0	2 (2.2)

[a] Physician's choice of chemotherapy consisting of either capecitabine, eribulin or vinorelbine

Includes AEs with an onset date between the date of first dose and 30 days following the date of last dose of study treatment. Table ordered by decreasing incidence in either treatment arm by System Organ Class and Preferred Term.

AE: Adverse event; AST Aspartate aminotransferase; bd: Twice daily; CSR: Clinical study report; CTCAE: Common Terminology Criteria for Adverse Events; DCO: Data cut-off; GGT: Gamma-glutamyltransferase; N: Total number of patients; PPE Palmar-plantar erythrodysaesthesia; SAE: serious adverse event; SAS: safety analysis set; WBC White blood cell count.

Data derived from Table 11.3.2.7, OlympiAD CSR Addendum, Module 5.3.5.1 (DCO: 25 September 2017).

Table 62: Most common AEs of CTCAE Grade 3 or higher (reported in ≥2% patients in olaparib treatment arm of OlympiAD and the 300 mg bd pool

	Number (%) of patients	
	Olaparib 300 mg bd	
System organ class Preferred term	OlympiAD SAS N=205	300 mg bd pool N=759
Any Grade ≥3 AE	**78 (38.0)**	**278 (36.6)**
Blood and lymphatic system disorders	**38 (18.5)**	**132 (17.4)**
Anaemia	32 (15.6)	111 (14.6)
Neutropenia	11 (5.4)	29 (3.8)
Leukopenia	5 (2.4)	12 (1.6)
Investigations	**23 (11.2)**	**49 (6.5)**
Neutrophil count decreased	10 (4.9)	21 (2.8)
WBC count decreased	7 (3.4)	13 (1.7)
AST increased	5 (2.4)	7 (0.9)
Platelet count decreased	5 (2.4)	10 (1.3)
GGT increased	4 (2.0)	6 (0.8)
General disorders and administration site conditions	**10 (4.9)**	**46 (6.1)**
Fatigue	7 (3.4)	24 (3.2)
Musculoskeletal and connective tissue disorders	**9 (4.4)**	18 (2.4)
Back pain	4 (2.0)	7 (0.9)

300 mg bd pool includes data from OlympiAD
Table ordered by incidence of events in the OlympiAD study
Includes AEs with an onset date between the date of first dose and 30 days following the date of last dose of study treatment.
AE: Adverse event; bd: Twice daily; CSR: Clinical study report; CTCAE: Common Terminology Criteria for Adverse Events; DCO: Data cut-off.; N: Total number of patients; SAS: Safety analysis set.
Data derived from Table 11.3.2.7, OlympiAD CSR Addendum, Module 5.3.5.1 (DCO: 25 September 2017); Table 2.7.4.1.1.5, 300 mg bd pool, Module 5.3.5.3 (DCO: 25 September 2017).

Serious adverse event / deaths / other significant events

Table 63: Patients who died in OlympiAD (FAS)

Category	Number (%) of patients	
	Olaparib 300 mg bd N=205	Physician's choice[a] N=97
Total number of deaths	130 (63.4)	62 (63.9)
Death related to disease under investigation only (death <30 days after last treatment dose)	3 (1.5)	4 (4.1)
Death related to disease under investigation only (death >30 days after last treatment dose)	117 (57.1)	57 (58.8)
AE with outcome = death only	1 (0.5)	0
Death related to disease and an AE with outcome = death	0	0
Deaths >30 days after last treatment dose, unrelated to AE or disease under investigation[b]	9 (4.4)	1 (1.0)

[a] Physician's choice of chemotherapy consisting of either capecitabine, eribulin or vinorelbine

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

AE: Adverse event; bd: Twice daily; CSR: Clinical study report; DCO: Data cut-off; FAS: full analysis set; N: Total number of patients.

Data derived from Table 11.3.3.1.1 and Table 11.3.3.2.1, OlympiAD CSR Addendum, Module 5.3.5.1 (DCO: 25 September 2017).

Table 64: Patients who died in the olaparib treatment arm of OlympiAD and the 300 mg bd pool

	Number (%) of patients	
	Olaparib 300 mg bd	
AE category[a]	OlympiAD SAS N=205	300 mg bd pool N=759
Total number of deaths	130 (63.4)	205 (27.0)
Death related to disease under investigation only	120 (58.5)	190 (25.0)
AE with outcome = death only	1 (0.5)	1 (0.1)
Death related to disease and an AE with outcome = death	0	2 (0.3)
Deaths >30 days after last treatment dose, unrelated to AE or disease under investigation	9 (4.4)[b]	12 (1.6)[c]

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

Serious adverse events: OlympiAD

Table 65: Most common SAEs (≥2 patients in either treatment arm) in OlympiAD (SAS)

	Number (%) of patients	
System organ class Preferred term	Olaparib 300 mg bd N=205	Physician's choicea N=91
Patients with any SAE	**34 (16.6)**	**15 (16.5)**
Blood and lymphatic system disorders	**6 (2.9)**	**6 (6.6)**
Anaemia	5 (2.4)	2 (2.2)
Febrile neutropenia	0	2 (2.2)
Respiratory, thoracic and mediastinal disorders	**5 (2.4)**	**2 (2.2)**
Dyspnoea	3 (1.5)	0
General disorders and administration site conditions	**3 (1.5)**	**1 (1.1)**
Pyrexia	3 (1.5)	0
Investigations	**3 (1.5)**	**0**
Neutrophil count decreased	2 (1.0)	0
Platelet count decreased	2 (1.0)	0

The majority of SAEs had resolved with either no action taken or following a temporary dose interruption or delay/dose change, or were recovering. Sixteen patients (9 in the olaparib arm and 7 in the physician's choice of chemotherapy arm) had SAEs that were 'not recovered/not resolved' or 'resolving' at the DCO date for this analysis.

At an event level, the 34 olaparib-treated patients had a total of 46 SAEs and the 15 physician's choice of chemotherapy-treated patients had a total of 23 SAEs.

Table 66: Most common SAEs (reported by ≥2 patients in the olaparib treatment arm of OlympiAD and/or reported by ≥5 patients in the 300 mg bd pool)

	Number (%) of patients	
	Olaparib 300 mg bd	
System organ class Preferred term	OlympiAD SAS N=205	300 mg bd pool N=759
Patients with any SAE	**34 (16.6)**	**143 (18.8)**
Blood and lymphatic system disorders	**6 (2.9)**	**39 (5.1)**
Anaemia	5 (2.4)	31 (4.1)
Infections and infestations	**6 (2.9)**	**32 (4.2)**
Pneumonia	1 (0.5)	7 (0.9)
Urinary tract infection	0	6 (0.8)
Gastrointestinal disorders	**0**	**22 (2.9)**
Abdominal pain	0	5 (0.7)
General disorders and administration site conditions	**3 (1.5)**	**14 (1.8)**
Pyrexia	3 (1.5)	5 (0.7)
Respiratory, thoracic and mediastinal disorders	**5 (2.4)**	**10 (1.3)**
Dyspnoea	3 (1.5)	4 (0.5)
Investigations	**3 (1.5)**	**6 (0.8)**
Neutrophil count decreased	2 (1.0)	3 (0.4)
Platelet count decreased	2 (1.0)	2 (0.3)

300 mg bd pool includes data from OlympiAD
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, OlympiAD CSR Addendum, Module 5.3.5.1 (DCO: 25 September 2017); Table 2.7.4.1.3.1, 300 mg bd pool, Module 5.3.5.3 (DCO: 25 September 2017).

Other significant events

Important potential risks

MDS/AML, pneumonitis and new primary malignancies are important potential risks (see RMP).Reports for events of MDS/AML and new primary malignancies continue to be collected beyond 30 days after the last dose of olaparib, by use of targeted safety questionnaire, and can be reported at any point in OS follow-up.Since MDS/AML, pneumonitis and new primary malignancies occur at low frequency, to improve the sensitivity and precision of estimates to characterise these important potential risks, information has been drawn from larger pools of olaparib studies:

Olaparib monotherapy combined therapeutic dose pool (n=1525 patients) consists of all patients who have received olaparib as a monotherapy treatment (tablet or capsule formulation) at the therapeutic dose (ie, 300 mg bd tablet formulation or 400 mg bd capsule formulation as a continuous dose). All patients from the 300 mg bd pool are included in the olaparib monotherapy combined therapeutic dose pool.

Olaparib monotherapy all doses pool (n=1957 patients) consists of all patients who have received at least 1 dose of olaparib as a monotherapy treatment (tablet or capsule formulation) at any dose. In addition, 66 patients from Study 41 are included. All patients from the olaparib monotherapy combined therapeutic dose pool are included in the olaparib monotherapy all doses pool.

Entire clinical programme as of 15 December 2017 (n=8319 patients): This pool includes all the studies shown in Table 1, any studies where olaparib is given in combination with other anticancer treatments, investigator-sponsored studies (ISSs) and data from the managed access programme (MAP).

Myelodysplastic syndrome/acute myeloid leukaemia

The table below shows the AEs of MDS/AML in the olaparib all doses monotherapy pool and across the entire olaparib clinical programme, and provides incidence rates.

Table 67: Summary of AEs of MDS/AML occurring across the olaparib programme

	TEAEs[a] + AEs after 30 day follow-up			
	Olaparib		Physician's choice[b]	
Data source	Number of cases	Incidence	Number of cases	Incidence
OlympiAD N=205 olaparib N=91 physician's choice	0	0	0	0
Olaparib monotherapy, all doses pool N=1957 olaparib	23	1.18%	NA	NA
Entire clinical programme pool N=8319 olaparib	50	0.60%	NA	NA

[a] TEAEs are events occurring on-study or during 30-day follow-up.
[b] Physician's choice of chemotherapy consisting of either capecitabine, eribulin or vinorelbine
AE: Adverse event; AML: Acute myeloid leukaemia; MDS: Myelodysplastic syndrome; N: Total number of patients; NA: Not applicable; TEAE: Treatment emergent adverse event.
Data derived from Table 11.3.2.2 and Table 11.3.2.4, OlympiAD CSR Addendum, Module 5.3.5.1 (DCO: 25 September 2017)

New primary malignancies

In the OlympiAD study, there was 1 event of new primary malignancy reported in the olaparib arm (0.5% of patients) compared with no event in physician's choice of chemotherapy arm. The olaparib-treated patient had an AE of malignant melanoma in situ of CTCAE Grade 1; this was a non-serious event in a patient who had a medical history of melanoma and which was reported as resolved after a duration of one day.

Table 68 shows the AEs of new primary malignancies in OlympiAD compared with other studies in the clinical programme, and provides incidence rates.

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

	TEAEs[a] + AEs after 30 day follow-up			
	Olaparib		Physician's choice[b]	
Data source	Number of cases	Incidence	Number of cases	Incidence
OlympiAD N=205 olaparib N=91 physician's choice	1	0.5%	0	0
Olaparib monotherapy, all doses pool N=1957 olaparib	24	1.23%	NA	NA
Entire clinical programme pool N=8319 olaparib	59	0.71%	NA	NA

[a] TEAEs are events occurring on-study or during 30-day follow-up.
[b] Physician's choice of chemotherapy consisting of either capecitabine, eribulin or vinorelbine.
Note that events of tumour pain, and benign malignancies are excluded from this analysis.
AE: Adverse event; N: Total number of patients; NA: Not applicable; TEAE: Treatment emergent adverse event.
Data derived from Table 11.3.2.2, OlympiAD CSR, Module 5.3.5.1 (DCO: 25 September 2017).

Pneumonitis

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

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

	TEAEs[a]			
	Olaparib		Physician's choice[b]	
Data source	Number of cases	Incidence	Number of cases	Incidence
OlympiAD N=205 olaparib N=91 physician's choice	0	0	0	0
Olaparib monotherapy combined therapeutic dose pool N=1525 olaparib	8	0.52%	NA	NA
Entire clinical programme pool N=8319 olaparib	53	0.64%	NA	NA

[a] TEAEs are events occurring on-study or during 30-day follow-up.
[b] Physician's choice of chemotherapy consisting of either capecitabine, eribulin or vinorelbine
AE: Adverse event; N: Total number of patients; NA: Not applicable; TEAE: Treatment emergent adverse event.
Data derived from Table 11.3.2.2, OlympiAD CSR Addendum, Module 5.3.5.1 (DCO: 25 September 2017) and on follow-up of patients post the DCO date.

Analysis of other adverse drug reactions (OlympiAD SAS)

Hematologic toxicities

Anaemia

AEs of anaemia were reported for a higher percentage of patients in the olaparib arm (40.0%) compared with the physician's choice of chemotherapy arm (26.4%). These events were predominantly Grade 1 or 2 in severity, rarely led to permanent discontinuation of treatment (2.0%), were manageable by standard supportive therapies, and generally resolved whilst on treatment.

CTCAE Grade ≥ 3 anaemia was reported in 33 (16.1%) patients in olaparib arm vs. 4 (4.4%) patients in the physician's choice of chemotherapy arm.

Onset of anaemia was early, generally in the first 3 months of starting olaparib (median time to onset was 1.45 months), although the risk of developing anaemia remained fairly constant throughout exposure with no evidence of cumulative effect; the majority (64 of 82 patients) of first events with olaparib resolved (median duration of resolution 1.36 months).

In total, 37 (18.0%) patients in the olaparib arm, and 5 (5.5%) patients in the physician's choice of chemotherapy arm had blood transfusions.

Approximately half of the patients in the olaparib arm with anaemia (38 [46.3%] of 82 patients) were treated for the AE compared with approximately one third of patients in the physician's choice of chemotherapy arm (7 [29.2%] of 24 patients).

Gastrointestinal toxicity

Nausea and vomiting

AEs of nausea and vomiting were reported for a higher percentage of patients in the olaparib arm (58.0% and 32.2% respectively) compared with the physician's choice of chemotherapy arm (35.2% and 15.4% respectively) in OlympiAD. These events were predominantly Grade 1 or 2 in severity and none led to permanent discontinuation of treatment in the olaparib arm.

A total of 54 (26.3%) olaparib-treated patients reported both nausea and vomiting. Approximately half of the olaparib-treated patients with nausea (63 [52.9%] of 119 patients) were treated for the AE and one third (22 [33.3%] of 66 patients) with vomiting received treatment.

Events of nausea and vomiting were generally reported early in the treatment period (median time to onset was 0.16 months and 0.87 months, respectively) and the majority (109 of 119 AEs of nausea and 63 of 66 AEs of vomiting) of first events with olaparib resolved (median duration of 1.12 months and 0.07 months, respectively).

Cough

AEs of cough (grouped term consisting of cough and productive cough) were reported for a higher percentage of patients in the olaparib arm (18.0%) than the physician's choice of chemotherapy arm (7.7%). There was no association between the reporting of AEs of cough and the length of time on olaparib treatment. In the OlympiAD study, AEs of cough in the olaparib-treated arm were reported throughout the study period (median time to first onset was 3.12 months [range 0.20 to 19.45 months]); the majority (28 of 37 patients) of first events with olaparib resolved (median duration of 1.02 months).

Adverse drug reactions

The safety profile is based on pooled data from 1,525 patients with solid tumours treated with Lynparza monotherapy in clinical trials at the recommended dose.

Table 70: Frequency of AEs in tablet pool and overall events identified as ADRs associated with olaparib treatment

	Tablet monotherapy pool N=759		Overall (tablet and capsule) N=1525			
System organ class/ PT	All CTCAE grades n (%)	CTCAE grades ≥3 n (%)	All CTCAE grades n (%)	Frequency descriptor	CTCAE grades ≥3 n (%)	Frequency descriptor
Blood and lymphatic system disorders						
Anaemia[a]	284 (37.4)	113 (14.9)	502 (32.9)	Very common	217 (14.2)	Very common
Neutropenia[a]	137 (18.1)	48 (6.3)	188 (12.3)	Very common	74 (4.9)	Common
Thrombocytopenia[a]	85 (11.2)	21 (2.8)	138 (9.0)	Common	39 (2.6)	Common
Lymphopenia[a]	36 (4.7)	8 (1.1)	41 (2.7)	Common	10 (0.7)	Uncommon
Leukopenia[a]	113 (14.9)	24 (3.2)	157 (10.3)	Very Common	45 (3.0)	Common
Gastrointestinal disorders						
Nausea	455 (59.9)	8 (1.1)	932 (61.1)	Very common	29 (1.9)	Common
Vomiting	260 (34.3)	11 (1.4)	540 (35.4)	Very common	36 (2.4)	Common
Diarrhoea	187 (24.6)	6 (0.8)	372 (24.4)	Very common	19 (1.2)	Common
Dyspepsia	69 (9.1)	0	196 (12.9)	Very common	0	-
Upper abdominal pain	65 (8.6)	1 (0.1)	140 (9.2)	Common	3 (0.2)	Uncommon
Stomatitis	47 (6.2)	3 (0.4)	83 (5.4)	Common	6 (0.4)	Uncommon
General disorders and administration site conditions						
Fatigue (including asthenia)	388 (51.1)	37 (4.9)	859 (56.3)	Very common	94 (6.2)	Common
Investigations						
Increase in creatinine	34 (4.5)	0	77 (5.0)	Common	2 (0.1)	Uncommon
Mean corpuscular volume elevation	2 (0.3)	0	2 (0.1)	Uncommon	0	-
Metabolism and nutrition disorders						
Decreased appetite	178 (23.5)	6 (0.8)	349 (22.9)	Very common	11 (0.7)	Uncommon
Nervous system disorders						
Headache	129 (17.0)	3 (0.4)	263 (17.2)	Very common	5 (0.3)	Uncommon
Dysgeusia	116 (15.3)	0	223 (14.6)	Very common	0	-
Dizziness	77 (10.1)	1 (0.1)	180 (11.8)	Very common	4 (0.3)	Uncommon
Immune system disorders						
Hypersensitivity[a]	2 (0.3)	0	9 (0.6)	Uncommon	0	-
Rash[a]	46 (6.1)	0	129 (8.5)	Common	0	-
Dermatitis[a]	4 (0.5)	0	8 (0.5)	Uncommon	0	-
Respiratory, thoracic and mediastinal disorders						
Cough[a]	121 (15.9)	2 (0.3)	246 (16.1)	Very common	3 (0.2)	Uncommon

Frequencies of occurrence of adverse reactions are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); and very rare (<1/10,000) including isolated reports

[a] Anaemia includes PTs of anaemia, erythropenia, haemoglobin decreased, red blood cell count decreased, and haematocrit decreased; Neutropenia includes PTs of neutropenia, granulocytopenia, granulocyte count decreased, neutrophil count decreased, febrile neutropenia, neutropenic infection, and neutropenic sepsis; Thrombocytopenia includes PTs of thrombocytopenia, platelet count decreased and platelet production decreased; Lymphopenia includes PTs of lymphocyte count decreased, lymphocyte percentage decreased, lymphopenia; Leukopenia includes PTs of leukopenia and white blood cell count decreased; Hypersensitivity includes PTs of drug hypersensitivity and hypersensitivity; Rash includes PTs of exfoliative rash, generalised erythema, rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular, and rash pruritic; Dermatitis includes PTs of dermatitis, dermatitis allergic, and dermatitis exfoliative; Cough includes cough and productive cough.

ADRs Adverse drug reactions; AEs Adverse events; CTCAE Common Terminology Criteria for Adverse Events; PTs Preferred terms.

Laboratory findings

In OlympiAD, the changes in haematological laboratory parameters reported were generally mild or moderate in severity.

No patients in OlympiAD had CTCAE Grade 4 haemoglobin values during the study in both arms; 16.6% of olaparib-treated patients had decreases to CTCAE Grade 3 haemoglobin values compared with 3.3% of patients in the physician's choice of chemotherapy arm.

A low proportion of olaparib-treated patients (9 patients [4.4%]) had CTCAE Grade ≥3 reductions in platelet count during the study; no patients in the physician's choice of chemotherapy arm had a CTCAE Grade ≥3 reduction in platelet count.

The majority of patients in both treatment arms in OlympiAD had a maximum CTCAE Grade of ≤ 2 reported for leukocyte laboratory values thoughout treatment.

The majority of olaparib-treated patients in OlympiAD had a maximum grade of ≤2 reported for neutrophil laboratory values. Moreover, 9.9% of olaparib-treated patients had decreases to CTCAE Grade≥3 neutrophil values whereas approximately one-third of patients in the physician's choice of chemotherapy arm had CTCAE Grade 3 or 4 absolute neutrophil count (ANC) during the OlympiAD study.

The majority of patients in OlympiAD had a maximum CTCAE Grade of ≤2 reported for lymphocyte laboratory values throughout treatment. The proportion of patients with CTCAE Grade 3 or 4 reductions in lymphocyte count during the study was higher for the olaparib arm (36 of 165 patients [21.8%]) than for the physician's choice of chemotherapy arm (2 patients [2.8%]).

Potential for drug-induced liver injury (DILI)

There were no confirmed or suspected Hy's Law cases.

In the OlympiAD study, the majority of patients in the olaparib arm and the physician's choice of chemotherapy arm had AST (188/205 [91.7%] and 84/91 [92.3%] patients, respectively) and ALT (191/205 [93.2%] and 79/91 [86.8%] patients, respectively) below 3 × ULN. The majority of patients with AST or ALT values above 3 × ULN in OlympiAD had values ≥3 × ULN to <5 × ULN, both for the olaparib arm and the physician's choice of chemotherapy arm. ALT and AST values in the range of ≥10 × ULN to <20 × ULN were each reported for 1 olaparib-treated patient; no patients in the physician's choice of chemotherapy arm had values outside the range of ≥5 × ULN to <10 × ULN. No patient in either treatment arm had an AST or ALT value of ≥20 × ULN.

There were 6 (3.0%) patients in the olaparib arm who had a laboratory value of AST elevation of CTCAE Grade 3 (worst grade), and 4 (2.0%) patients with CTCAE Grade 3 elevated ALT (worst grade) during treatment. In general, AST and ALT elevations in all 6 patients were transient in nature and resolved on continued treatment.

An assessment of ALT, AST maximal elevations during treatment by maximal total bilirubin elevations showed that 1 (0.5%) patient in the olaparib arm and 2 (2.2%) physician's choice of chemotherapy arm had concurrent elevation of bilirubin and either ALT or AST. The olaparib-treated patient had transient concurrent elevated AST (CTCAE Grade 2) and bilirubin (> 2 x ULN) at Visit 10 (Day 129). No AEs were reported for this patient at the time of these laboratory findings. There were no dose interruptions or dose reductions and AST and ALT values were both normal at the next visit. The patient had hepatic metastases at screening.

In the 300 mg bd pool, the majority (695 [91.8%] patients) had combined AST or ALT below 3 × ULN. AST or ALT values above 3 × ULN were reported infrequently (37 [4.9%] patients had values of >3 ×

ULN to ≤5 × ULN; 17 [2.2%] patients had values >5 × ULN to ≤10 × ULN; 7 [0.9%] patients had values >10 × ULN to ≤20 × ULN, and 1 [0.1%] patient had a value of >20 × ULN).

In the 300 mg bd pool, the proportion of patients who had an AST or an ALT laboratory value of CTCAE Grade 3 is similar to that in the olaparib arm of the OlympiAD study (3.0% and 2.0% respectively).

An assessment of combined elevations of ALT and bilirubin was conducted for all patients in the 300 mg bd pool. Of these 759 patients, 15 (2.0%) reported elevations of both AST and ALT >3 × ULN and total bilirubin >2 × ULN, irrespective of ALP, at any point during their study treatment. A detailed evaluation of medical history, progression of disease, temporal association with elevated ALP (>2 × ULN for 8 patients and <1 × ULN for 1 patient) and other factors showed that all 9 patients had alternative explanations for elevations of ALT and bilirubin, generally suggestive of obstructive causes, or cancer disease progression, including disease progression in the liver.

Increase in creatinine

In the olaparib arm of OlympiAD, 96.1% of olaparib-treated patients had normal creatinine levels at baseline, 3.4% had CTCAE Grade 1 at baseline and 0.5% had CTCAE Grade 2 at baseline. A total of 31/204 (15.2%) patients had a single change in CTCAE Grade (most changes were normal to Grade 1) and no patients had 2 grade shifts in CTCAE Grade for creatinine; 1 patient had a shift from normal at baseline to CTCAE Grade 3 on treatment (this patient had hydronephrosis at baseline; no patients had a 4 grade shift.

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 OlympiAD. In the 300 mg bd pool, 90.0% of olaparib-treated patients had normal creatinine at baseline, 9.2% had CTCAE Grade 1 at baseline and 0.7% had CTCAE Grade 2 at baseline. A total of 594/757 (78.5%) patients had a single change in CTCAE Grade (changes were normal to Grade 1 in 568 of the 591 patients) and 96/757 (12.7%) had 2 CTCAE grade shifts (all were normal to Grade 2); one patient (0.1%) had a 3 grade shift in creatinine (from Grade 0 to Grade 3).

Safety in special populations

Effect of age

Table 71 shows the distribution of AEs by patient age.

Table 71: Number of patients reporting at least one adverse event by age group in the 300 mg bd pool

	Number (%) of patients			
MedDRA term	Age ≤65 years N=602	Age 65 to 74 years N=126	Age 75 to 84 years N=31	Age ≥85 years N=0
Total AEs	588 (97.7)	123 (97.6)	30 (96.8)	0
Total SAEs[a]	106 (17.6)	31 (24.6)	6 (19.4)	0
Fatal[b]	1 (0.2)	1 (0.8)	0	0
Hospitalisation/prolong existing hospitalisation	101 (16.8)	27 (21.4)	6 (19.4)	0
Life-threatening	11 (1.8)	2 (1.6)	0	0

Other (disability incapacity)	3 (0.5)	0	0	0
Other (medically significant)	30 (5.0)	6 (4.8)	1 (3.2)	0
Total DAEs	37 (6.1)	10 (7.9)	3 (9.7)	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

[b] Event was fatal within 30 days of the last dose of olaparib

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.

Data derived from Table 2.7.4.1.13.1, Table 2.7.4.1.6.1.4, Module 5.3.5.3 (DCO: 25 September 2017).

An analysis of AEs by the SOCs most relevant to elderly patients, and age is provided in Table 71. For the majority of the AEs, there were no differences in frequency of AEs by PT in patients aged <65 years when compared with patients aged 65 to 74 years and patients aged 75 to 84 years. ALT increased, leukopenia, headache and nausea were the only AEs that occurred at a higher incidence (≥5% difference) in the <65 years category compared with 65 to 74 and 75 to 84 year categories. For the 65 to 74 years age category, AEs that occurred at a higher incidence (≥5% difference) when compared with <65 years age category were: fatigue, oedema peripheral and urinary tract infection. For the 75 to 84 years age category, AEs that occurred at a higher incidence (≥5% difference) when compared with <65 years were: arthralgia, constipation, decreased appetite, dysgeusia, dyspnoea, dyspnoea exertional, fatigue, haematuria, hypomagnesaemia, hypotension, malaise, pharyngitis and thrombocytopenia.

Table 72: 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

Patients, n (%)	Age ≤65 years N=602	Age 65 to 74 years N=126	Age 75 to 84 years N=31	Age ≥85 years N=0
Total number of patients with AEs	588 (97.7)	123 (97.6)	30 (96.8)	0
Psychiatric disorders (SOC)	104 (17.5)	19 (15.1)	5 (16.1)	0
Accidents and injuries (SMQ)	37 (6.1)	4 (3.2)	2 (6.5)	0
Cardiac disorders (SOC)	32 (5.3)	11 (8.7)	1 (3.2)	0
Vascular disorders (SOC)	51 (8.5)	17 (13.5)	2 (6.5)	0
Central nervous system vascular disorders (SMQ)	3 (0.5)	0	0	0
Infections and infestations (SOC)	262 (43.5)	59 (46.8)	13 (41.9)	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	73 (12.1)	21 (16.7)	2 (6.5)	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 2.7.4.1.13.1, Table 2.7.4.1.13.2, Table 2.7.4.1.13.3, Table 2.7.4.1.13.4 and Table 2.7.4.1.6.2.4 Module 5.3.5.3 (DCO: 25 September 2017).

Effect of race

Safety data are presented for the 168 non-White patients who received the proposed dose of 300 mg bd as a monotherapy across the clinical programme. The majority of these patients 155 (92.3%) were of Asian origin, 5 (3.0%) patients were of Black or African American origin and 8 (4.8%) were of other racial origin.

Table 73: 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]	All patients (advanced solid tumours) N=759	Non-White patients[b] N=168
Any AE	741 (97.6)	163 (97.0)
Any AE causally related to study drug[c]	654 (86.2)	149 (88.7)
Any AE of CTCAE Grade 3 or higher	278 (36.6)	68 (40.5)
Any AE with outcome = death	3 (0.4)	1 (0.6)
Any SAE (including events with outcome = death)	143 (18.8)	30 (17.9)
AE leading to dose reduction of study treatment	134 (17.7)	25 (14.9)
Any AE leading to interruption/delay of study treatment	239 (31.5)	51 (30.4)
AE leading to discontinuation of study treatment	50 (6.6)	11 (6.5)

[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 168 Non-White patients, 5 patients were Black, 155 patients were Asian and 8 patients were 'other'.

c As assessed by the investigator

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

AE: Adverse event; bd: Twice daily; CTCAE: Common Terminology Criteria for Adverse Events; DCO: Data cut-off; N: Total number of patients; SAE: Serious adverse event.

Data derived from Table 2.7.4.1.1.1 and Table 2.7.4.1.11.1, 300 mg bd pool, Module 5.3.5.3 (DCO: 25 September 2017).

AEs that occurred at a higher incidence in non-White patients (≥5% difference) compared with White patients were: ALT increased, anaemia, AST increased, malaise, neutrophil count decreased, platelet count decreased, upper respiratory tract infection and WBC count decreased.

AEs with a CTCAE Grade ≥3 that occurred at a higher incidence in non-White patients (≥5% difference) compared with White patients were: anaemia, neutrophil count decreased, and WBC count decreased. Anaemia and WBC count decreased were the only AEs that resulted in a dose modification that occurred at a higher incidence in non-White patients (≥5% difference) compared with White patients.

Discontinuation due to adverse events

AEs leading to discontinuation of study treatment were similarly low in OlympiAD and in the 300 mg bd pool, and were reported for 4.9% and 6.6% of patients respectively. In the physician's choice chemotherapy arm, AEs leading to discontinuation of the study treatment were reported in 7.7% of patients. The most common SOCs reported for AEs leading to discontinuation were blood and lymphatic disorders. Anaemia was the most common AE leading to discontinuation in OlympiAD and in the 300 mg bd pool.

Dose reductions/interruptions due to adverse events

Dose interruptions or delay and dose reductions were reported respectively in 50.7% and 26.8% patients on olaparib and respectively in 38.5% and 30.8% patients on physician's choice of chemotherapy. A numerically higher proportion of patients in the olaparib arm (35.1%) had a dose interruption due to an AE compared with the proportion of patients in the physician's choice of chemotherapy arm (26.4%). However, a numerically lower proportion of patients in the olaparib arm (25.4%) compared to the physician's choice of chemotherapy arm (30.8%) had a dose reduction due to an AE.

AEs leading to dose reductions were reported for 134 (17.7%) of patients for the 300 mg bd pool and AEs leading to dose interruption were reported for 239 (31.5%) of patients for the 300 mg bd pool.

The types of AEs leading to dose modifications (anaemia, vomiting, neutropenia, nausea and fatigue) were comparable with those observed in OlympiAD.

Post marketing experience

The capsule formulation of olaparib is currently approved in more than 50 countries worldwide for the treatment of patients with ovarian cancer. The tablet formulation is approved in the US and Japan for patients with PSR ovarian cancer and was recently approved in the US for patients with gBRCAm HER2-negative metastatic breast cancer. The reports received do not change the benefit-risk profile of olaparib.

2.5.1. Discussion on clinical safety

Across the entire clinical programme, as of 15 December 2017, an estimated 8319 patients are estimated to have received treatment with olaparib. The safety of olaparib 300 mg bid tablet is mainly based on the phase III OlympiAD study. The OlympiAD data have been pooled with the data from patients receiving olaparib 300 mg bid tablet in additional 10 monotherapy studies providing a pooled safety database of about 759 patients (268 of whom had breast cancer). These safety data are considered supplementary to the presentation of data from the OlympiAD study.

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

In study OlympiAD, the median total treatment duration was more than twice as long in the olaparib arm (approximately 8.2 months) compared with the physician's choice of chemotherapy arm (approximately 3.4 months). 27.8% of patients in the olaparib arm remained on treatment for ≥1 year compared with 9.9% of patients in the physician's choice of chemotherapy arm.

The most common AEs in the olaparib arm were: nausea (58.0%), anaemia (39.5%), vomiting (32.2%), fatigue (29.8%), diarrhoea (20.5%), headache (20.5%), neutropenia (18.0%), cough (17.1%), decreased appetite (17.1%), WBC decreased (16.1%), pyrexia (14.6%), back pain (14.6%), upper respiratory tract infection (13.2%), constipation (12.7%), neutrophil count decreased (11.2%), ALT increased (11.7%), arthralgia (11.2%) and leukopenia (11.2%).

It can be noticed than in OlympiAD, anaemia, nausea and vomiting were reported at a significantly higher frequency in olaparib arm than in the physician's choice of chemotherapy arm whereas neutropenia, PPE syndrome and alopecia were reported at a significantly higher frequency in the physician's choice of chemotherapy arm than in olaparib arm.

In OlympiAD, approximately 40% of patients in either treatment arm of the OlympiAD study had AEs leading to either dose reduction or dose interruptions/delays. The proportion of patients who had AEs leading to either dose reduction or dose interruptions were similar for OlympiAD and the 300 mg bd pool.

The proportion of patients who reported AEs leading to discontinuation of treatment was low in both treatment arms.

Grade ≥3 AEs had a higher incidence in the physician's choice of chemotherapy arm (49.5% of patients) than in the olaparib arm (38.0%). Anaemia and neutropenia were the only AEs Grade ≥3 reported in ≥5% of patients in the olaparib arm (respectively 15.6% and 5.4% in the olaparib arm vs. 4.4% and 13.2% in the physician's choice of chemotherapy arm). AEs of CTCAE Grade 3 or higher were similar and occurred at similar frequencies in olaparib between treatment arm of OlympiAD and the 300 mg bid pool.

SAEs were reported in a similar proportion of patients in the olaparib arm (16.6%) compared with the physician's choice of chemotherapy arm (16.5%). The highest frequency of reported SAEs at the system organ class (SOC) level was blood and lymphatic system disorders (2.9% olaparib vs. 6.6% physician's choice of chemotherapy). The most common SAE in both arms was anaemia (2.4% olaparib vs 2.2% physician's choice of chemotherapy). The only SAEs considered by the Investigator to be causally related to olaparib in >1 patient was anaemia (5 [2.4%] patients). The only other SAEs reported in ≥2 patients in olaparib arm only were: dyspnoea (1.5%), pyrexia (1.5%), neutrophil count decreased (1.0%) and platelet count decreased (1.0%). The majority of SAEs had resolved with either no action taken or following a temporary dose interruption or delay/dose change, or were recovering. SAEs were reported at a similar frequency in OlympiAD and in the 300 mg bd pooled dataset.

Most deaths occurring on study were related to the disease under investigation with only one patient in the olaparib arm with an AE leading to death (sepsis) which was not considered related to study treatment by the Investigator. The frequency of deaths for any reason was similar for olaparib-treated patients over patients in the physician's choice of chemotherapy arm (63.4% vs. 63.9% respectively). The frequency of deaths for any reason was twice as large as for olaparib-treated patients (63.4%) in OlympiAD over the 300 mg bd pool (27.0%). But the majority of deaths concern death related to disease under investigation which was twice as many in the olaparib arm than in the physician's choice of chemotherapy arm (respectively 58.5% and 25.0%).

The adverse drug reactions (ADRs) identified for olaparib tablets are the same as previously described in the SmPC of olaparib. Section 4.8 of the SmPC has been revised to reflect updated frequencies based on pooled data from 1525 patients with solid tumours treated with lynparza monotherapy in clinical trials at the recommended dose. The most frequently observed adverse reactions across clinical trials in patients receiving Lynparza monotherapy (≥ 10%) were nausea, fatigue (including asthenia), vomiting, anaemia, diarrhoea, decreased appetite, headache, cough, dysgeusia, dyspepsia, neutropenia, dizziness, and leukopenia.

Back pain was the only AE not listed as an ADR that occurred at a frequency of 10% in the olaparib 300 mg bd arm and a 5% or greater frequency compared with the physician's choice of chemotherapy arm.

However, back pain is a common disease-related symptom in metastatic breast cancer patients and the event rate data suggests that the difference in crude incidence observed in OlympiAD is likely due to differences in exposure/observation time between arms.

The adverse events of special interest (AESIs) for olaparib are myelodysplastic syndrome (MDS)/AML, pneumonitis and new primary malignancies. These adverse events have been classified in the RMP as important potential risks supported by pharmacovigilance activities.

Investigators in OlympiAD were required to record MDS/AML and new primary malignancies events beyond 30 days after the last dose of olaparib at any point in OS follow-up. A causal relationship between olaparib treatment and the development or acceleration of MDS/AML, new primary malignancies and pneumonitis has not been established.

There were no reports of MDS or AML in either treatment arm of OlympiAD, either on treatment, or within the 30-day follow-up period.

In the OlympiAD study, there was 1 event of new primary malignancy (malignant melanoma in situ of CTCAE Grade 1) reported in the olaparib arm (0.5% of patients) compared with no event in physician's choice of chemotherapy arm. The incidence of new primary malignancies in the pool of patients who received olaparib in monotherapy studies (tablet and capsule formulations; all doses of olaparib) is 1.23% for olaparib (24 patients in a total of 1957 patients, of whom 13 patients had skin cancers).There have also been reports of new primary malignancies from post marketing surveillance, consistent with the characterisation of the events reported from monotherapy clinical studies. Patients enrolled into the olaparib clinical studies had already received prior chemotherapy with multiple cycles of platinum containing chemotherapy. Whilst it is not possible to exclude a contribution of olaparib, there were other contributory factors for all reports.

In the OlympiAD study, there were no pneumonitis cases reported. There were 8 patients with events of pneumonitis in the pool of patients who received olaparib in monotherapy studies (tablet and capsule formulations; all doses of olaparib) giving an incidence rate of 8 in 1525 patients (0.52%).

Regarding laboratory parameters, changes in haemoglobin, neutrophils, lymphocytes, platelets and mean corpuscular volume were the only significant haematological parameters with clinically relevant changes; these parameters are recognised ADRs for olaparib. Anaemia is the only one important identified risk in the RMP, whereas neutropenia and thrombocytopenia are no longer considered as important identified risk in the RMP.

Additional safety measures have been incorporated into the Phase III programme and these measures have also been implemented where olaparib is marketed: specified haematological values are required before inclusion into the studies or treatment and regular monitoring is continued while on treatment to detect haematological abnormalities early. In case of, prolonged cytopenias, patients are to be referred to a haematologist and bone marrow analysis should be considered. If a diagnosis of MDS is confirmed, olaparib treatment must be discontinued and the event, treatment, course and outcome must be reported as an SAE. Based on the updated analysis of MDS/AML, with a DCO date of 15 December 2017, these measures are considered to remain appropriate for minimization of the risk for MDS/AML, and do not require any further amendment. Section 4.4 of the SmPC has also been updated to reflect that the incidence of MDS/AML cases was similar among gBRCA1m and gBRCA2m patients (1.4% versus 1.6%).

At the exception of anaemia and neutropenia (see above, paragraph on AEs grade ≥ 3) the changes in the laboratory values for the haematology parameters in the olaparib arm were generally reported in low numbers of patients with a maximum CTCAE Grade of 3 or 4 (leukopenia 2.4%, neutrophil count 4.9%, %, WBC decreased 3.4% and platelet count decreased 2.4%). These changes in haematological parameters are generally mild or moderate, manageable, and reversible.

The only significant change in clinical chemistry parameters occurred for creatinine: increase in blood creatinine is a recognised ADR for olaparib and is no longer considered important identified risk in the RMP. AEs of increased creatinine were predominantly Grade 1 in severity and none led to permanent discontinuation of treatment. The laboratory observations of elevated serum creatinine were not associated with renal impairment and had apparently no clinical sequelae. The changes in creatinine are consistent with the finding that olaparib is known to be an inhibitor of organic cation-transporter (OCT)-2 and multi-drug and toxin extrusion protein (MATE)-1.

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

Regarding special populations, although there are limited data in elderly patients ≥75 years of age, assessment of the safety of olaparib in patient subgroups showed an acceptable safety profile regardless of age, race, gender, or body weight. No dose adjustment is required on the basis of patient age, racial origin, gender or body weight.

Based on the mode of action of olaparib, women of childbearing potential should not become pregnant while on Lynparza and not be pregnant at the beginning of treatment. A pregnancy test should be performed on all women of childbearing potential prior to treatment and considered regularly throughout treatment.

Women of childbearing potential must use two forms of reliable contraception before starting Lynparza therapy, during therapy and for 1 month after receiving the last dose of Lynparza, unless abstinence is the chosen method of contraception (see section 4.4). Two highly effective and complementary forms of contraception are recommended.

Since it cannot be excluded that olaparib may reduce exposure to substrates of CYP2C9 through enzyme induction, the efficacy of some hormonal contraceptives may be reduced if co-administered with olaparib. Therefore, an additional non-hormonal contraceptive method should be considered during treatment (see section 4.5). For women with hormone dependent cancer, two non-hormonal contraceptive methods should be considered.

Olaparib has clastogenic potential it is not known whether olaparib or its metabolites are found in seminal fluid. Therefore, male patients must use a condom during therapy and for 3 months after receiving the last dose of Lynparza when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male patients must also use highly effective contraception if they are of childbearing potential. Male patients should not donate sperm during therapy and for 3 months after receiving the last dose of Lynparza (see sections 4.4 and 4.6).

Additional expert consultations

See under discussion on clinical efficacy.

2.5.2. Conclusions on clinical safety

The safety profile of olaparib including patients from OlympiAD is generally consistent with the known safety profile of olaparib. It includes gastrointestinal AEs, hematologic toxicity and general disorders. No new safety signals were identified from patients with gBRCAm HER2-negative metastatic breast cancer. AEs associated with olaparib are generally mild or moderate, manageable with dose modification or standard supportive treatment and rarely requiring treatment discontinuation.

Regarding MDS/AML, pneumonitis and new primary malignancies, a causal relationship between olaparib treatment and these adverse events has not been established. Therefore, they are still considered as important potential risk for olaparib with ongoing surveillance activities detailed in the RMP.

The SmPC and RMP have been adequately updated to reflect available safety data.

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 16.3 with the following content:

Safety concerns

Table 74: 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 Potential inhibitory effect of olaparib on UGT1A4 and UGT1A9

Pharmacovigilance plan

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

Risk minimisation measures

Table 75: 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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Medication errors associated with dual availability of capsules and tablets	Routine risk communication in: • SmPC Section 4.2 • PL Section 3 Routine risk minimisation activities recommending specific clinical measures to address the risk: **SmPC Section 4.2:** Statement informing that olaparib is available as tablets and capsules which are not to be used interchangeably due to differences in the dosing and bioavailability of each formulation. **PL Section 3:** Statement informing that olaparib is available as tablets and capsules which are not the same and not to be used interchangeably. **Additional risk minimisation measures:** Distribution of a DHPC to prescribers and pharmacists providing clear information on the 2 formulations.	Routine
Effects on embryofoetal survival and abnormal development	Routine risk communication in: • SmPC Sections 4.4, 4.6 • PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: **SmPC Section 4.4, 4.**6: Advice on contraception and pregnancy. **PL Section 2:** Advice on contraception and pregnancy.	Routine
Long term exposure to/potential toxicity to olaparib	None	Routine
Potential inhibitory effect of olaparib on UGT1A4 and UGT1A9	None	None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.6, 4.8, 5.1 and 5.2 of the SmPC of Lynparza tablets have been updated. Particularly, the warning with regard to women of childbearing potential/contraception in females has been modified to the product information. The SmPC of Lynparza capsule has been revised accordingly to reflect updated safety information.

The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the SmPC guideline and excipients guideline which were reviewed by QRD and accepted by the CHMP.

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The indication is for Lynparza in monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments. Patient with hormone receptor (HR)-positive breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy.

Breast cancer is a life-threatening disease and is the second leading cause of cancer death among women and the fourth leading cause of cancer death overall (American Cancer Society 2018).

Approximately 5% of breast cancers are associated with a germline mutation in the BRCA1 and/or BRCA2 gene with approximately 3% associated with the BRCA2 gene (generally hormone receptor positive). In the general population, BRCA1/2 mutation carriers have an increased relative risk of breast cancer. The presence of gBRCA1 mutations is associated with a lifetime risk of breast cancer ranging from 60% to 70%. gBRCA2 mutations are associated with a lifetime risk of breast cancer between 40% to 60% in women and 5% to 10% in men. Rare individuals carry deleterious mutations in both BRCA1 and BRCA2 genes.

3.1.2. Available therapies and unmet medical need

The selection of appropriate therapy for advanced breast cancer comprising locally advanced and metastatic breast cancer is complex because of the many treatment options and biologic heterogeneity of the disease (ABC4 consensus guidelines). The potential treatment options are determined in accordance with ER and PR and HER2 status of the tumour. Treatment options for patients presenting with metastatic

breast cancer may also be influenced by what adjuvant therapy was used, how soon after adjuvant therapy the patient relapses, and by sites of metastasis.

Currently, single agent chemotherapy after previous exposure to anthracyclines and taxanes has a median progression free survival (PFS) of approximately 4 months and an overall survival (OS) of 9 to 16 months when given early in the metastatic setting.

For patients with HER2-negative metastatic breast cancer, there is no one preferred first-line chemotherapy. Sequential monotherapy with single agents such as capecitabine, vinorelbine, or eribulin are among the preferred choices in metastatic breast cancer patients previously treated with an anthracycline and a taxane in the adjuvant or metastatic setting and for whom further hormonal treatments are not indicated (NCCN 2018). Combination chemotherapy is reserved for select patients with high tumour burden, rapid clinical progression, life-threatening visceral metastases, or need for rapid symptom and/or disease control.

There is no targeted therapy available to date for a treatment of TNBC. The prognosis for patients with TNBC and/or those who carry gBRCA1 mutations with metastatic disease may even be worse than the overall metastatic breast cancer population. According to current NCCN guidelines (2018), carboplatin is considered as one of recommended regimens for recurrent or metastatic disease.

For the treatment of hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer, CDK4/6 inhibitors have recently been approved in combination with endocrine therapy in first line and in women who have received prior endocrine therapy. Everolimus, an mTOR inhibitor, is also approved for the treatment of hormone receptor-positive, HER2 negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor.

There are currently no treatments approved in the European Union (EU) specifically for gBRCAm patients with metastatic breast cancer and these patients are treated depending on the hormone receptor and HER2 status determined in their tumours.

3.1.3. Main clinical studies

This application is based on results from the pivotal Phase III, randomised, controlled, open-label, multicentre study D0819C00003 (OlympiAD) (n=302), in which gBRCAm patients who had previously received chemotherapy in the neoadjuvant, adjuvant or metastatic setting (no more than 2 prior lines of chemotherapy for metastatic breast cancer) and were HER2-negative were randomised 2:1 to receive either olaparib (300 mg bd, tablet formulation) or physician's choice of chemotherapy (capecitabine, eribulin, or vinorelbine). Patients with hormone receptor-positive breast cancer should have been treated with a prior endocrine therapy or should be patients for whom endocrine therapy is not an appropriate option.

Patients with somatic BRCA1/2-mutated tumours were not eligible and have not been included.

The primary endpoint was PFS as determined by blinded independent central review (BICR). OS, PFS2 (investigator assessment) and ORR (by BICR) were secondary endpoints. TFST and TSST were also analysed as supportive endpoints for PFS and PFS2, respectively.

3.2. Favourable effects

OlympiAD met its primary endpoint demonstrating a statistically significant and clinically relevant 3-months improvement in PFS based on BICR in the FAS population treated with olaparib compared to physician's choice of chemotherapy (HR 0.58; 95% CI: 0.43, 0.80; p<0.0001; median 7.03 vs 4.17

months) which was supported by investigator assessment (HR 0.50; 95% CI: 0.36, 0.68; p=0.0009; median 7.8 vs 3.8 months).

Following the subgroup analyses of PFS, no subgroups appeared to derive a differential benefit compared with the overall population. The treatment effects observed in individual chemotherapies (capecitabin, vinorelbin or eribulin) were similar to that observed in the intention-to-treat (ITT) set.

A statistical significant improvement on PFS2 was observed in the olaparib arm (HR: 0.57, 95% CI 0.40 – 0.87; p=0.0033) with a median second PFS 13.17 months in the olaparib arm compared to 9.26 months in the comparator arm. Final post-hoc PFS2 analysis was consistent with PFS2 at the DCO for primary analysis.

Final OS analysis was conducted at 64% maturity of the FAS population. There was no suggestion of a detrimental effect on OS, with the HR numerically favouring olaparib [HR 0.90 (95% CI: 0.66, 1.23; p=0.5131; median OS 19.3 months in the olaparib arm versus 17.1 months in the physician's choice of chemotherapy arm].

Confirmed ORR (CR or PR) in patients with measurable disease was 52 % (87/167) in the olaparib arm and 23% (15/66) in the chemotherapy arm. A complete response was observed in 13 patients (8%) in the olaparib arm and 1 patient (1.5%) in the comparator arm.

The median DoR was 6.9 months (95%CI 4.2, 10.2) in the olaparib arm and 7.9 months (95%CI 4.5, 12.2) in the chemotherapy arm.

3.3. Uncertainties and limitations about favourable effects

Due to the lack of a direct comparison with platinum chemotherapy, the relative efficacy of olaparib with such treatment has not been defined. Furthermore, the efficacy of olaparib has not been evaluated in patients defined as resistant to prior platinum therapy. Patients who had received platinum (cisplatin or carboplatin, either as monotherapy or in combination) for advanced breast cancer were eligible to enter the study provided there had been no evidence of disease progression during the platinum chemotherapy in metastatic setting or as (neo)adjuvant treatment at least 12 months before the randomisation. Thus there is a general uncertainty about the optimal sequence of treatment with olaparib in a treatment context where platinum based chemotherapy is an option. Information about prior and subsequent platinum therapy received is considered relevant for the prescribers and has been included in the section 5.1 SmPC.

Resistance mechanisms to DNA-damaging agents including PARP inhibitors has not been sufficiently investigated to date and would be of value to determine the optimal sequence of use for PARP inhibitors and chemotherapy for breast cancer and to elaborate more effective therapeutic strategies in advanced BRCAm breast cancer. The investigation of efficacy in platinum-resistant tumours and comparative efficacy to platinum agents is recommended

3.1. Unfavourable effects

The most common ADRs in the olaparib arm were: nausea (58.0%), anaemia (39.5%), vomiting (32.2%), fatigue (29.8%), diarrhoea (20.5%), headache (20.5%), neutropenia (18.0%), cough (17.1%), decreased appetite (17.1%), WBC decreased (16.1%), neutrophil count decreased (11.2%) and leukopenia (11.2%). These were generally mild to moderate in severity and did not lead to discontinuation.

Gastrointestinal toxicity (nausea, vomiting and diarrhoea), hematologic toxicity (anaemia), fatigue, headache are considered the main risks with olaparib. Nausea and vomiting were reported at a significantly higher frequency in olaparib arm than in the physician's choice of chemotherapy arm.

The toxicity of olaparib was manageable by dose interruptions, dose reductions and standard supportive treatment as required. Discontinuation due to adverse events occurred for 4.9% of the patients in olaparib arm and 7.7% of the patients in the physician's choice of chemotherapy arm. In olaparib arm and in the physician's choice of chemotherapy arm, anaemia was the most common AE leading to discontinuation (2.0% and 2.2% respectively).

AEs of anaemia were reported for a higher proportion of patients in the olaparib arm (40.0%) compared with the physician's choice of chemotherapy arm (26.4%). These events were predominantly Grade 1 or 2 in severity and approximately half of the patients in the olaparib arm and one third in the chemotherapy arm have been treated for this AE. CTCAE Grade ≥ 3 anaemia was reported in 16.1% patients in olaparib arm vs. 4.4% patients in the physician's choice of chemotherapy arm. In total, 18.0% patients in the olaparib arm, and 5.5% patients in the physician's choice of chemotherapy arm had blood transfusions.

Grade ≥3 AEs had a higher incidence in the physician's choice of chemotherapy arm (49.5% of patients) than in the olaparib arm (38.0%).

There were no reports of MDS/AML or pneumonitis in the study. A new primary malignancy was reported for 1 patient (0.5%) in the olaparib arm. This was a non-serious, CTCAE grade 1 event of malignant melanoma in situ. The patient also had a medical history of melanoma.

Most deaths occurring on study were related to the disease under investigation with only one patient in the olaparib arm with an AE leading to death (sepsis) which was not considered related to study treatment by the investigator.

The safety profile of olaparib in patients with gBRCA mutations in the OlympiAD trial was generally consistent with the known safety profile of olaparib.

3.2. Uncertainties and limitations about unfavourable effects

Available long-term safety data are still limited. Long-term exposure to/potential toxicity to olaparib remains classified as missing information in the risk management plan supported by pharmacovigilance activities. MDS/AML and NPM will also continue to be closely monitored as reflected in the RMP.

There was no report of myelodysplastic syndrome (MDS)/AML. The causality of olaparib in occurrence of these events has not been established. Long-term exposure to/potential toxicity to olaparib are currently classified in the risk management plan as important potential risks addressed by pharmacovigilance activities. MDS/AML and the risk of new primary malignancies will continue to be closely monitored as reflected in the RMP.

3.3. Effects Table

Table 76: Effects Table for olaparib tablet formulation in gBRCA1/2-mutated HER2-negative metastatic breast cancer (data cut-off 16 December 2017, updated data cut-off 25 September 2017)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
DCO at 16 December 2016						
PFS median	From randomisation to progression or death	months	7.03	4.17		OlympiAD
HR		(95% CI)	0.58 (0.43-0.80)		p = 0.0009 by BICR	
Confirmed ORR	CR or PR	%	52	23	By BICR	OlympiAD
DCO at 25 September 2017						
PFS 2 Median	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	months	12.8	9.4	p = 0.0005	OlympiAD
HR		(95% CI)	0.55 (0.39, 0.77)		Consistent the primary analysis	
OS Median	the time from the date of randomisation until death due to any cause	months	19.3	17.1	p=0.5131 64% maturity Consistent with interim analysis	OlympiAD
HR		(95% CI)	0.90 (0.66, 1.23)			

Unfavourable Effects

Adverse Effect	Short description	Unit	Study OlympiAD		Pool	Uncertainties / Strength of evidence	References
			Olaparib 300 mg tablets bd N=205	Physician's choice of chemotherapy N=91	Olaparib 300 mg tablets N=759		
Blood and lymphatic disorders;	Anaemia All grades	Pts (%)	81 (39.5)	23 (25.3)	277 (36.5)		OlympiAD
	Grade 3 and 4		32 (15.6)	4 (4.4)	111 (14.6)		
	Treatment discontinuation		4 (2.0)	2 (2.2)	12 (1.6)		
	Neutropenia All grade	Pts (%)	37 (18)	28 (30.8)	94 (12.4)		"
	Grade 3 and 4		11 (5.4)	12 (13.2)	29 (3.8)		

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence		References
	Leukopenia All grade	Pts (%)	23 (11.2)	9 (9.9)	61 (8.0)		"
	Grade 3 and 4		5 (2.4)	3 (3.3)	12 (1.6)		
General disorders;	Fatigue All grade	Pts (%)	61 (29.8)	22 (24.2)	297 (39.1)		"
	Grade 3 and 4		7 (3.4)	1 (1.1)	24 (3.2)		
Nervous system disorders;	Headache All grade	Pts (%)	42 (20.5)	14 (15.4)	129 (17.0)		"
	Grade 3 and 4		7 (3.4)	1 (1.1)	24 (3.2)		
Gastrointestinal disorders;	Nausea All grade	Pts (%)	119 (58.0)	32 (35.2)	455 (59.9)		"
	Vomiting All grade	Pts (%)	66 (32.2)	14 (15.4)	260 (34.3)		"
	Diarrhoea All grade	Pts (%)	42 (20.5)	20 (22.0)	187 (24.6)		"

3.4. Benefit-risk assessment and discussion

3.4.1. Importance of favourable and unfavourable effects

The benefits of olaparib in germline BRCA mutated metastatic breast cancer are supported by a statistically significant improvement in PFS supported by consistent results in PFS2 and ORR compared with chemotherapy. There was no suggestion of a detrimental effect on OS with the HR numerically favouring olaparib. Results appear robust and consistent in the different sensitivity and subgroup analyses provided. The magnitude of the improvement in the ITT population (3-months for median PFS translating into a 67% relative prolongation of median PFS) is of potential clinical relevance in both HER2 negative/ER and/or PgR positive breast cancer and TNBC.

The safety profile of olaparib including patients from OlympiAD is generally consistent with the known safety profile of olaparib. No new safety signals were identified from patients with gBRCAm HER2-negative metastatic breast cancer and safety findings in olaparib arm of OlympiAD were consistent with the 300 mg tablet pool. The toxicity of olaparib was manageable with dose interruptions, dose reductions and standard supportive treatment as required. However, it should be highlight that nausea and vomiting were reported at a significantly higher frequency in olaparib arm than in the physician's choice of chemotherapy arm. Among haematological toxicities, anaemia is the most prominent. It was reported at higher frequency in the olaparib arm, lead to discontinuation in some patients and resulted in blood transfusions in 18% of patients in the olaparib arm.

3.4.2. Balance of benefits and risks

In view of the poor prognosis of the germinal BRCAm HER2-negative metastatic breast cancer in patients previously treated with an anthracycline and a taxane in the adjuvant /neoadjuvant or metastatic setting and for whom hormonal treatments are not indicated, the results of the pivotal OlympiAD trial are considered of clinical relevance. The observed 3 months gain in median PFS, supported by consistent improvement in PFS2 and no detriment to OS compared with chemotherapy, is considered of clinical benefit and able to outweigh the treatment related toxicity which compares favourably with chemotherapy-related toxicity.

3.4.3. Additional considerations on the benefit-risk balance

Patients with locally advanced disease with a generally better prognosis have not been included in the pivotal trial, but the extrapolation to this patient population was considered acceptable by the CHMP given a similar clinical management for locally advanced and metastatic disease and based on a biological and pharmacological rationale.

There are no clinical data available on the responsiveness of breast tumours with somatic BRCA mutation to PARPi. The MAH is recommended to collect clinical data in this population. In line with the SAG Oncology advice, extrapolation of results from patients with germline BRCA mutations that developed breast cancer to patients with sporadic breast cancers that harbour somatic BRCA mutations in their tumours is not justified for the time being in the absence of any clinical data and other data supporting the proposed mechanistic rationale. Although the mechanistic theoretical rationale is acknowledged, the magnitude of the potential effect in the context of breast cancer is uncertain. The indication has therefore been restricted to gBRCAm patients only until clinical outcome data for sBRCAm patients become available.

Substantial clinical benefit including OS benefit has been shown for anthracyclines and taxanes that are current standard of care. As per eligibly criteria, nearly all patients enrolled in the study had prior anthracycline and taxane therapy. It is therefore considered that anthracycline and taxane should be specified prior regimens in the indication unless patients were not suitable for these treatments. In line with the studied population, the indication also reflects that HR+ breast cancer patients should have progressed on a prior endocrine therapy or be considered unsuitable for endocrine therapy.

gBRCA mutations are found in 10% of male breast cancer patients with the majority with mutations in BRCA2. Despite the limited number of male patients included in the OlympiAD study (n=7), the CHMP considers that the extrapolation to a very rare population of male breast cancer patients with germline BRCA mutations, predominantly BRCA2 and characterised by high grade and aggressive phenotype (Silvestri et al, 2016) is acceptable based on the common biological and pharmacological rationale.

3.5. Conclusions

The overall B/R of Lynparza is positive for the following indication: Lynparza in monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments. Patient with hormone receptor (HR)-positive breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy.

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 tablets as monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer; patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments. Patient with hormone receptor (HR)-positive breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy. As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.6, 4.8, 5.1 and 5.2 of the SmPC of Lynparza tablets have been updated. The SmPC of Lynparza capsule has been revised to reflect updated safety information and the Package Leaflet has been updated accordingly. Furthermore, RMP version 16.3 has also been accepted. Changes were also made to the PI to bring it in line with the SmPC guideline and excipients guideline which were reviewed by QRD and accepted by the CHMP.

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