17 September 2020
EMA/541236/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lynparza

International non-proprietary name: olaparib

Procedure No. EMEA/H/C/003726/II/0036

Note

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

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Table of contents

List of abbreviations

Abbreviation or special term	Explanation
ADR	Adverse drug reaction
AE(s)	Adverse event(s)
AML	Acute myeloid leukaemia
AQA	Analgesic Quantification Algorithm
ATM	Ataxia telangiectasia mutated
ATR	Ataxia telangiectasia and Rad3-related protein
AUC	Area under plasma concentration-time curve
AUC_{ss}	Area under plasma concentration-time curve during any dosing interval at steady state
BARD1	BRCA1 associated ring domain protein
bd	Twice daily
BICR	Blinded independent central review
BoR	Best overall response
BPI-SF	Brief Pain Inventory Short Form
BRCA	Breast cancer susceptibility gene (in accordance with scientific convention, gene and mutation is italicised whereas protein is not italicised)
BRACAnalysis CDx®	The test consists of gene sequencing and large rearrangement analysis of the *BRCA1* and *BRCA2* genes performed by Myriad Genetics, Inc in their Quality Systems Regulation (QSR) facility
BRCAm	*gBRCA* or *sBRCA* mutated
BRCAwt/VUS	*gBRCA* and *sBRCA* wild type/variant of uncertain significance
BRIP1	BRCA1 interacting protein C-terminal helicase 1
BTD	Breakthrough Therapy Designation
CDK12	Cyclin-dependent kinase 12
CDx	Companion diagnostic
CHEK1	Checkpoint kinase 1
CHEK2	Checkpoint kinase 2
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
CrCL	Creatinine clearance
CR	Complete response
CRF	Case report form
CRPC	Castration-resistant prostate cancer
CSR	Clinical study report

CTA	Clinical trial assay
CTC	Circulating tumour cell(s)
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Common technical document
ctDNA	Circulating tumour DNA
CYP	Cytochrome P450
dAUC	Daily AUC
DCO	Data cut-off
DDI	Drug-drug interaction
DDR	DNA damage response
DHPC	Direct Healthcare Professional Communication
DoR	Duration of Response
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EFR	Evaluable for response
EMA	European Medicines Agency
ePRO	Electronic patient reported outcome
EU	European Union
F1CDx	FoundationOne® CDx
FACT	Functional Assessment of Cancer Therapy
FACT-G	Functional Assessment of Cancer Therapy - General
FACT-P	Functional Assessment of Cancer Therapy - Prostate Cancer
FANCL	FA complementation group L
FAPSI-6	FACT Advanced Prostate Symptom Index 6
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIGO	Fédération Internationale de Gynécologie Obstétrique (International Federation of Gynaecology and Obstetrics)
FMI	Foundation Medicine Inc.
FMI CLIA HRR CTA	Foundation Medicine Inc CLIA Homologous Recombination Repair Clinical Trial assay. The test uses DNA extracted from formalin-fixed, paraffin-embedded tumour samples and next generation sequencing to detect alterations in a total of 324 genes, including *BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D* and *RAD54L.* Testing is performed in a CLIA facility
FWB	Functional well-being
gBRCA	Germline *BRCA*
gBRCAm	Germline *BRCA* mutated
GCP	Good Clinical Practice
Gmean	Geometric mean

h	Hours
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRQoL	Health-related quality of life
HRR	Homologous recombination repair
HRRm	Homologous recombination repair gene mutated
IC_{90}	90% inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ILD	Interstitial lung disease
IND	Investigational new drug
ITT	Intention-to-treat
IVIVC	in vitro-in vivo correlation
Ka	Absorption rate constant
MATE	Human Multi-Drug And Toxin Extrusion Transporter
mCRPC	Metastatic castration-resistant prostate cancer
MCV	Mean corpuscular volume
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MTP	Multiple testing procedure
N	Total number of patients
n	Number of patients
NA	Not applicable
NHA(s)	New hormonal agent(s)
NR	Not reported
OAT	Organic anion transporter
OATP	Organic anion-transporting polypeptide
OCT	Organic cation-transporter
od	Once daily
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PALB2	Partner and localizer of *BRCA2*
PARP	Polyadenosine 5'diphosphoribose polymerase
PBPK	Physiologically-based pharmacokinetic
PBRER	Periodic benefit-risk evaluation report
PCS	Prostate cancer subscale
PCWG3	Prostate Cancer Working Groups 3
PD	Pharmacodynamic

PFS	Progression-free survival
PFS2	Time from randomisation to second progression or death
P-gp	P-glycoprotein
PK	Pharmacokinetic
PPP2R2A	Protein phosphatase 2 regulatory subunit Balpha
PR	Partial response
PRO	Patient reported outcome
PSA	Prostate specific antigen
PSA_{50}	A ≥50% decline in PSA from baseline
PSR	Platinum-sensitive relapsed
PT	Preferred term
PWB	Physical well-being
Q	Quarter
QC	Quality control
QSR	Quality Systems Regulation
QT	ECG interval measured from the beginning of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia correction
QTcI	QT interval corrected for heart rate using individual-specific correction
RAD51B	RAD51 paralog B
RAD51C	RAD51 paralog C
RAD51D	RAD51 paralog D
RAD54L	RAD54 Like
RECIST	Response Evaluation Criteria in Solid Tumours
rPFS	Radiological progression-free survival
SAE	Serious adverse event
SAP	Statistical analysis plan
SAWP	Scientific Advice Working Party
sBRCA	Somatic *BRCA* (*BRCA* variant found in the tumour but not in the germline)
sBRCAm	Somatic *BRCA* mutated
sBRCA VUS	Somatic *BRCA* variant of uncertain significance
sNDA	Supplemental New Drug Application
SOC	System organ class
SSRE	Symptomatic skeletal-related event
std	Standard deviation
tBRCA	Tumour *BRCA* (mutations detected in the tumour)
tBRCAm	Tumour *BRCA* mutated
TEAE	Treatment emergent adverse event

TTPP	Time to pain progression
UGT	UDP-glucuronosyltransferase
ULN	Upper limit of normal
US/USA	United States/United States of America
vs	Versus
VUS	Variants of uncertain significance
wt	Wild type

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AstraZeneca AB submitted to the European Medicines Agency on 22 November 2019 an application for a variation.

The following variation was requested:

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

Extension of indication to include the use of Lynparza tablets as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene mutations (germline and/or somatic) who have progressed following a prior new hormonal agent. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC are updated. The PL is updated accordingly. In addition, sections 4.4 and 4.8 of the SmPC for Lynparza hard capsules are revised based on updated safety data analysis.
The RMP version 20 has also been submitted.

Information on paediatric requirements

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

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

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH 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 MAH received Scientific Advice from the CHMP on 21 July 2016 (EMEA/H/SA/1215/4/2016/II). The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Alexandre Moreau Co-Rapporteur: Koenraad Norga

Timetable	Actual dates
Submission date	22 November 2019
Start of procedure:	28 December 2019
CHMP Co-Rapporteur Assessment Report	21 February 2020
CHMP Rapporteur Assessment Report	21 February 2020
PRAC Rapporteur Assessment Report	28 February 2020
PRAC Outcome	12 March 2020
CHMP members comments	05 March 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	19 March 2020
Request for supplementary information (RSI)	26 March 2020
CHMP Rapporteur Assessment Report	28 May 2020
PRAC Rapporteur Assessment Report	29 May 2020
PRAC Outcome	11 June 2020
CHMP members comments	04 June 2020
Updated CHMP Rapporteur Assessment Report	22 June 2020
Request for supplementary information (RSI)	25 June 2020
PRAC Rapporteur Assessment Report	n/a
CHMP Rapporteur Assessment Report	4 September 2020
CHMP members comments	07 September 2020
Updated CHMP Rapporteur Assessment Report	11 September 2020
Opinion	17 September 2020

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The applied indication is for the treatment of adult patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene mutations (germline and/or somatic) who have progressed following a prior new hormonal agent.

Epidemiology

Worldwide in 2018, prostate cancer was estimated to be the fifth most common cause of cancer death in men (358,989 deaths) and the second most common newly diagnosed cancer in men (1,276,106 new

cases) (Globocan 2018). In Europe in 2018, prostate cancer was estimated to be the third most common cause of cancer death in men (107,315 deaths) and the most common newly diagnosed cancer in men (449,761 new cases) (ECIS 2018).

Almost all patients dying from prostate cancer will have mCRPC, and 90% of overall mortality in mCRPC patients is attributable to the underlying malignant disease (Scher et al 2015). For patients diagnosed with metastatic disease, the 5-year survival rate is 30% (American Society of Cancer 2019, Siegel et al 2019).

Biologic features

Most prostate cancers are adenocarcinomas. Following the initial evaluation and diagnosis, approximately 90% of men undergo primary localized treatment with curative intent (Cooperberg et al, 2010). Androgen deprivation therapy (ADT) (i.e., surgical or medical castration) is often initiated in men with rising prostate-specific antigen (PSA) after primary therapy. Following ADT, the next most frequent clinical state in the current model of prostate cancer progression is that of CRPC, defined as disease progression despite castrate hormone levels (testosterone $\leq$ 50 ng/dL). Men with CRPC can have metastatic or non-metastatic disease. In the majority of patients, metastatic CRPC evolves from non-metastatic CRPC and PSA doubling time has been shown to be a strong predictor of the development of metastases in these patients (Moreira et al, 2015; Scher et al, 2015).

Between 24% to 30% of mCRPCs have loss of function mutations in genes involved in homologous recombination repair (HRR) of DNA damage response (Abida et al 2017, Armenia et al 2018, Chung et al 2019, Mateo et al 2015, Robinson et al 2015).

In this application, the HRR genes refer to a family of 15 pre-specified genes with a biological rationale for loss of function to predict sensitivity to olaparib.

Enrichment of BRCA1/2, ATM and CDK12 mutations in advanced prostate cancer has been documented in the literature by several studies (Abida et al 2017, Armenia et al 2018, Chung et al 2019, Mateo et al 2018). Mutations in the breast cancer susceptibility genes ([BRCA] BRCA1 and/or BRCA2) are the most prevalent HRR gene mutations in mCRPC (with BRCA2 more prevalent than BRCA1) with ataxia telangiectasia mutated (ATM) the second most frequently mutated HRR gene in mCRPC (Armenia et al 2018, Chung et al 2019, Mateo et al 2015, Robinson et al 2015). Based on literature, the prevalence of BRCA1/BRCA2 gene mutations is expected to be between 8.4% and 16%. The high representation of BRCA2 mutations in advanced/metastatic prostate cancer is considered to be a consequence of BRCA2 mutations being associated with a particular aggressive phenotype (Castro et al 2013, Castro et al 2015, Chung et al 2019, Mateo et al 2018) rather than these mutations being acquired under treatment with standard therapies (e.g., androgen receptor mutations and amplifications [Mateo et al 2018]).

Management

New hormonal agents (NHAs) such as abiraterone acetate and enzalutamide are the preferred choice for first-line therapy for mCRPC patients.

However, once mCRPC patients have failed NHA, the benefit from approved second-line treatment options such as taxanes or switching to another NHA, appears substantially diminished and no clear single standard of care exists. Considering the currently available treatments, there is a high unmet clinical need for an effective treatment option that is tolerable, suitable for long-term use, convenient for administration, able to significantly extend radiological progression-free survival (rPFS), delay symptom progression, without detriment to overall survival (OS) or health-related quality of life (HRQoL), particularly after failure of NHAs, especially among the patient population who previously received the taxanes or were not eligible for this toxic regimen.

2.1.2. About the product

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

Lynparza is approved in EU for the treatment of ovarian cancer, breast cancer and adenocarcinoma of the pancreas.

The MAH applied for a new indication for olaparib tablets formulation as follows: "Lynparza is indicated as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene mutations (germline and/ or somatic) who have progressed following a prior new hormonal agent."

The final recommended indication is: "Lynparza is indicated as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer and BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent."

The recommended dose of Lynparza in monotherapy 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. Medical castration with luteinising hormone releasing hormone (LHRH) analogue should be continued during treatment in patients not surgically castrated.

For BRCA1/2-mutated metastatic castration-resistant prostate cancer (mCRPC), patients must have confirmation of a deleterious or suspected deleterious BRCA1/2 mutation (using either tumour or blood sample) before Lynparza treatment is initiated. BRCA1/2 mutation status should be determined by an experienced laboratory using a validated test method.

Genetic testing should be conducted by an experienced laboratory using a validated test. Local or central testing of blood and/or tumour samples for germline and/or somatic *BRCA1/2* mutations have been used in different studies. DNA obtained from a tissue or blood sample has been tested in most of the studies, with testing of ctDNA being used for exploratory purposes. Depending on the test used and the international classification consensus, the *BRCA1/2* mutations have been classified as deleterious/suspected deleterious or pathogenic/likely pathogenic.

2.2. Non-clinical aspects

Apart from an updated environmental risk assessment, no new non-clinical data were provided in the initial submission supporting this application, which was considered acceptable by the CHMP.

During the procedure, the MAH provided a discussion on the biological rationale for the HRRm gene panel-based selection approach supported by non-clinical (data not shown) and clinical data from the literature. In summary, clinical efficacy data from TOPARP (an open label, two part, Phase II study) were presented to support the sensitivity to olaparib in mCRPC patients with tumours harbouring defects in some genes associated with defects in homologous recombination DNA repair (Mateo et al, 2015 and 2020). Results in mCRPC patients with BRCA1/ BRCA2 mutations are discussed further under the section on clinical aspects.

2.2.1. Ecotoxicity/environmental risk assessment

The potential environmental impact from use of the drug substance olaparib has already been evaluated and supported approval of the capsule (ovarian, fallopian tube, or primary peritoneal cancer) as a monotherapy and the tablet formulation (epithelial ovarian, fallopian tube or primary peritoneal cancer, metastatic adenocarcinoma of the pancreas) as a monotherapy.

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

The PECsurfacewater (0.16 µg/L) is above the Phase I action limit (0.01 µg/L) therefore the risk assessment for olaparib enters Phase II. The Log Pow (1.55 at pH 7) value is <4.5, therefore, it can be concluded that olaparib is not PBT or vPvB, as such, no further screening for PBT potential of olaparib is required in Phase I.

It is predicted that in domestic sewage, olaparib will not significantly partition into the solid phase during waste water treatment. The measured Kd in active sludge was <3700 L/Kg, therefore an environmental risk assessment in the terrestrial compartment is not required in Tier B.

Olaparib is not expected to undergo significant biodegradation during sewage treatment and is considered hydrolytically stable. It is therefore expected to pass into the aquatic environment where the results from the water sediment study showed that olaparib is predicted to partition into the sediment phase. Greater than 10% of the applied radioactivity was associated with the sediment phase; therefore, the effects of olaparib on sediment dwelling organisms was investigated in Tier B.

The PEC/PNEC ratios for microorganisms (1.6×10^{-5}), ground water (1.2×10^{-3}) and surface water (5.0×10^{-3}) are below the trigger ratios of 0.1, 1 and 1 respectively, indicating no significant environmental risk in these compartments. Therefore, no further evaluation of the drug substance and/or its metabolites on microorganisms or pelagic aquatic organisms is needed in Tier B.

Olaparib is not expected to undergo significant biodegradation or adsorb to sludge solids during sewage treatment. Therefore, olaparib is expected to enter the aquatic environment and partition into aquatic sediments where it is unlikely to be significantly degraded. Whilst the DT50 data for the persistence of olaparib (251-551 days) are above the criterion for a very persistent compound (DT50 >180 days for total system), the octanol-water partition coefficient (Log Pow = 1.55) value for olaparib is <3 indicating that the risk of bioaccumulation in aquatic organisms is low. Based on these results, olaparib does not fulfil the criteria to be classified as a PBT or vPvB compound.

The PEC/PNEC ratios for ground water, surface water and sediment are below 1, and the PEC/PNEC for microorganisms is below 0.1, indicating that olaparib is unlikely to present a risk to biological sewage treatment processes or aquatic environment.

2.2.2. Discussion on non-clinical aspects

An updated ERA covering this extension of indication has been submitted. Olaparib is not a PBT or vPvB substance. The total PEC surfacewater value is above the action limit. Considering the phase I and phase II data, olaparib is not expected to pose a risk to the environment.

The MAH also provided a discussion on the biological rationale for the HRRm gene panel-based selection approach supported by non-clinical data (data not shown; see discussion on clinical efficacy).

2.2.3. Conclusion on the non-clinical aspects

Considering the above data, olaparib is not expected to pose a risk to the environment. Although the role of the selected gene mutations in the HRR pathway is acknowledged, the clinical benefit of a PARP inhibitor on the non-BRCA mutations remains unknown (see discussion on clinical efficacy).

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 3 Summary of olaparib efficacy studies to support the proposed indication in mCRPC

Study number	Design	Patient population	Number of patients	Olaparib dose and formulation	Efficacy endpoints	Number of HRRm or *gBRCAm* prostate patients (mutation testing methods)	Study status
D081DC00007 (PROfound)	Phase III open-label, randomised, controlled, multicentre study	HRRm patients with mCRPC who have failed prior treatment with an NHA	Cohort A+B: 387 (256 olaparib; 131 investigators choice of NHA) Cohort A: 245 (162 olaparib; 83 investigators choice of NHA) Cohort B: 142 (94 olaparib; 48 investigators choice of NHA)	300 mg bd (oral) tablet formulation	Primary: rPFS (BICR) Secondary: Confirmed ORR, TTPP, OS, PFS2, Time to first SSRE, DoR, confirmed ORR in soft tissue, Time to opiate use for cancer related pain, PSA response, CTC conversion rate, PFS2, disease symptoms/HRQoL (pain severity progression, pain interference, pain palliation, FACT-P)	387 HRRm (FMI CLIA HRR CTA) 376 HRRm (FMI F1CDx® assay) 62 *gBRCAm* (Myriad BRACAnalysis CDx test)	Ongoing for OS follow-up
D0810C00042 (Study 42)	Phase II open-label, non-randomised, non-comparative, multicentre study	*gBRCAm* patients with advanced cancers (including prostate)	298 overall; 8 in prostate cancer cohort	400 mg bd (oral) capsule formulation	Primary: Tumour response rate Secondary: ORR, PFS, OS, DoR, DCR	8 (Local testing)[a]	Complete

[a] *gBRCA* mutation status was determined by local germline testing, as recorded on CRFs at study enrolment

In PROfound, a separate China cohort of patients with *BRCA1*, *BRCA2* or *ATM* mutations (Cohort A) is planned to be randomised as per the global study, however randomisation of the China cohort has not yet started.

bd Twice daily; BICR Blinded independent central review; *BRCA* Breast cancer susceptibility gene; CDx Companion diagnostic; CLIA Clinical Laboratory Improvement Amendments; CTA Clinical trial assay; CRF Case report form; CSR Clinical study report; CTC Circulating tumour cells; DoR Duration of response; FACT-P Functional Assessment of Cancer Therapy - Prostate Cancer; FMI Foundation Medicine Inc.; *gBRCAm* Germline *BRCA* mutated; HRQoL Health-related quality of life; HRR Homologous recombination repair; HRRm Homologous recombination repair gene mutated; mCRPC Metastatic castration-resistant prostate cancer; NHA New hormonal agent; ORR Objective response rate; OS Overall survival; rPFS Radiological progression-free survival; PFS2 Time from randomisation to second progression or death; PSA Prostate specific antigen; SSRE Symptomatic skeletal-related event; TTPP Time to pain progression.

Source: PROfound CSR, Module 5.3.5.1 and Study 42 CSR, Module 5.3.5.2

2.3.2. Pharmacokinetics

The submitted documentation consists of a compilation of the investigations conducted with olaparib and already assessed. There are no new formal PK studies submitted. The sparse sampling data collected in

the pivotal, phase 3 study (PROfound study) were integrated in order to update the previous version of the population-PK model. The refined model was used in order to predict the exposure (AUC and Cmax) in patients enrolled and analyzed from study PROfound. The predicted systemic exposure was used in order to test for Exposure-Response (Efficacy and Safety) relationship.

Population-PK Model

In order to describe the concentration-time profiles of olaparib after oral tablet administration all available data from patients who received olaparib as tablets, including data from 9 previous studies and data from PROfound, were pooled.

Clinical studies included in the present analyses are listed below. All studies were considered in the PopPK analysis. The table lists in addition if data from these studies (or parts of the studies) have been used in the efficacy and/or safety analysis.

Table 1: Clinical studies included in the analysis

Study number	Study phase and patient population	Dose regimen	Number of patients[a]	Efficacy analysis	Safety analysis
D081BC00001 (Study 01)	Phase I: Japanese patients with advanced solid tumours	olaparib 200, 300 mg qd or BID	11	No	Yes
D0816C00004 (Study 04)	Phase I: Patients with advanced solid tumours	olaparib 300 mg qd or BID	60	No	Yes
D0816C00007 (Study 07)	Phase I: Patients with advanced solid tumours	olaparib 100 mg qd, 300 mg BID	59	No	Yes
D0816C00008 (Study 08)	Phase I: Patients with advanced solid tumours	olaparib 300 mg qd	22	No	Yes
D0810C00024 (Study 24)	Phase I: Patients with advanced solid tumours	olaparib 200, 250, 300, 350, 400, 450 mg, qd or BID	144	No	Yes
D0816C00002 (SOLO2)	Phase III: Patients with PSR BRCA mutated ovarian cancer patients excluding gastric surgery patients	olaparib 300 mg BID / placebo	94 / 99	No / No	Yes / Yes
D0816C00010 (SOLO3)	Phase III: maintenance in 3L+ PSR gBRCAm ovarian cancer patients excluding gastric surgery patients	olaparib 300 mg BID (/ comparator)	81 (/ 76)	No (/ No)	Yes (/ No)
D0819C00003 (OlympiAD)	Phase III: treatment of gBRCA1/2m Metastatic Breast	olaparib 300 mg BID (/ comparator)	36 (/ 91)	No (/ No)	Yes (/ No)
D081DC00008	Phase II: metastatic castrateresistant prostate cancer who have received prior chemotherapy containing docetaxel	Abiraterone + olaparib 300 mg BID (/ placebo)	13 (/ 61)	No (/ No)	No (/ No)

D081DC00007 (PROfound)	Phase III, metastatic castrate resistant prostate cancer with homologous recombination repair gene mutations	olaparib 300 mg BID / enzalutamide or abiraterone acetate	74 / 131	Yes / Yes	Yes / No

[a] Numbers reported are number of patients in the master datasets provided by AstraZeneca (For patients treated with olaparib: population PK master data set, for patients in placebo group in SOLO2: safety master data set, for patients treated with enzalutamide or abiraterone acetate: efficacy master data set). Numbers in parenthesis are numbers of non-olaparib treatment groups that were not included in the master datasets.

Model development (Refinement)

The previous established population PK model was reduced to contain only the absorption route for tablets and used as initial model with the same covariance (i.e., correlation of CL/F and Vc/F, as well as Q/F and Vp/F) and covariate structure. The current population PK analysis included only data collected with olaparib oral tablet formulation.

As a first step in the covariate model building, the significance of the previous covariates (i.e., tablet strength on Ka and ECOG performance status on CL/F) was confirmed. Baseline values of age, creatinine clearance, and body weight, sex, race, ECOG performance status, tumour location, and BRCA mutation status were tested as covariates on selected model parameters. Since no additional covariates were found to be statistically significant, the final model was

The following model was chosen as final model:

- Linear two-compartmental distribution model with first order absorption from dosing into central compartment and zero-order absorption into dosing compartment.
- Correlation of individual random effects for apparent clearance (CL/F) and apparent central volume (Vc/F). And separately of apparent intercompartmental clearance (Q/F) and apparent peripheral volume (Vp/F).
- Proportional residual error model.
- Time dependent CL/F, mimicking difference for single dose and steady-state conditions implemented by assuming single dose clearance up to 96 hours post first dose and steadystate clearance from 96 hours post first dose on.
- Mild ECOG status (ECOG1) and Moderate ECOG status (ECOG2) as categorical covariates on CL/F.
- Tablet strength as time-dependent covariate on tablet absorption rate (Ka). Two groups of tablet strength were used (with 50 and 150 mg tablet strength being the reference group). Group 1: tablet strength of 100 mg. Group 2: 125, 200, 225, 250, and 300 mg tablet strength.

The parameter estimates for the final updated model are reported in **Table 2**. In this table "CL, Vc, Q, Vp" should be understood as representing the apparent parameters "CL/F, Vc/F, Q/F, Vp/F.

Table 2: Population parameter estimates for final PopPK model

PARAMETER	VALUE	RSE	SHRINKAGE	COMMENT
Typical parameters				
CL [L/hour]				
	7.81	3.12%	-	Apparent Clearance post single dose (L/hour)
Vc [L]	4.55	5.49%	-	Apparent Central volume (L)

Q [L/hour]	1.44	5.33%	-	Apparent Intercompartmental clearance (L/hour)
Vp [L]	19	6.35%	-	Apparent Peripheral volume (L)
Frel [fraction]	1 (FIX)	-	-	Oral bioavailability (fraction)
Ka [1/hour]	0.21	0.0684%	-	First-order absorption rate parameter (1/hour)
Tk0 [hour]	0.489	5.56%	-	Zero order absorption duration (hours)
CLSCALE [.]	-0.225	-2.75%	-	log(Scaling factor) for CL above 96 hours post first dose
Inter-individual variability				
omega(CL)	0.476	2.82%	4.3%	LogNormal
omega(Vc)	0.731	4.96%	34%	LogNormal
omega(Q)	0.709	6.17%	37%	LogNormal
omega(Vp)	0.784	5.55%	38%	LogNormal
omega(Frel)	0 (FIX)	-	-	LogNormal
omega(Ka)	0.173	10%	44%	LogNormal
omega(Tk0)	0.865	3.79%	28%	LogNormal
omega(CLSCALE)	0 (FIX)	-	-	Normal
Correlation of random effects				
corr(CL,Vc)	0.0878	69.2%	-	Correlation coefficient
corr(Q,Vp)	0.546	11.9%	-	Correlation coefficient
Parameter-Covariate relationships				
beta_Ka(STRGRP1_1)	0.582	3.5%	-	100 mg Tablet Yes on Ka
beta_Ka(STRGRP2_1)	0.294	10.9%	-	125,200,225,250,300 mg Tablet Yes on Ka
beta_CL(ECOG1_1)	-0.195	22.7%	-	ECOG performance status=1 Yes on CL
beta_CL(ECOG2_1)	-0.578	21.7%	-	ECOG performance status>=2 Yes on CL
Residual Variability				
error_PROP1	0.346	0.647%	-	Proportional Error (fraction) - Concentration
Objective function	10749	-	-	-
AIC	10789	-	-	-
BIC	10928	-	-	-

Model: ../Output/FINAL_MODELS/03_Final_Model, Significant digits: 3 (Objective function rounded to closest integer value), omega values reported in standard deviation. Covariate equations (X refers to non-reference covariate level. I_X is 0 for the reference level and 1 otherwise.):

Model Qualification/Validation

Model diagnostics were provided. The random effects appeared to be adequately normally distributed (**Figure 1**) and the predicted and observed individual concentrations were generally symmetrically distributed around the line of identity (**Figure 2**). The different residuals and the NPDE did not show any trends, both over time and over the population prediction. Individual plots of observations, individual and population predictions were provided on linear and logarithmic scale, respectively.

A dose-normalized VPC was generated for the final model as shown in **Figure 1**, supporting the adequacy of the model to describe the observed data. VPCs stratified by study are shown in **Figure 3**.

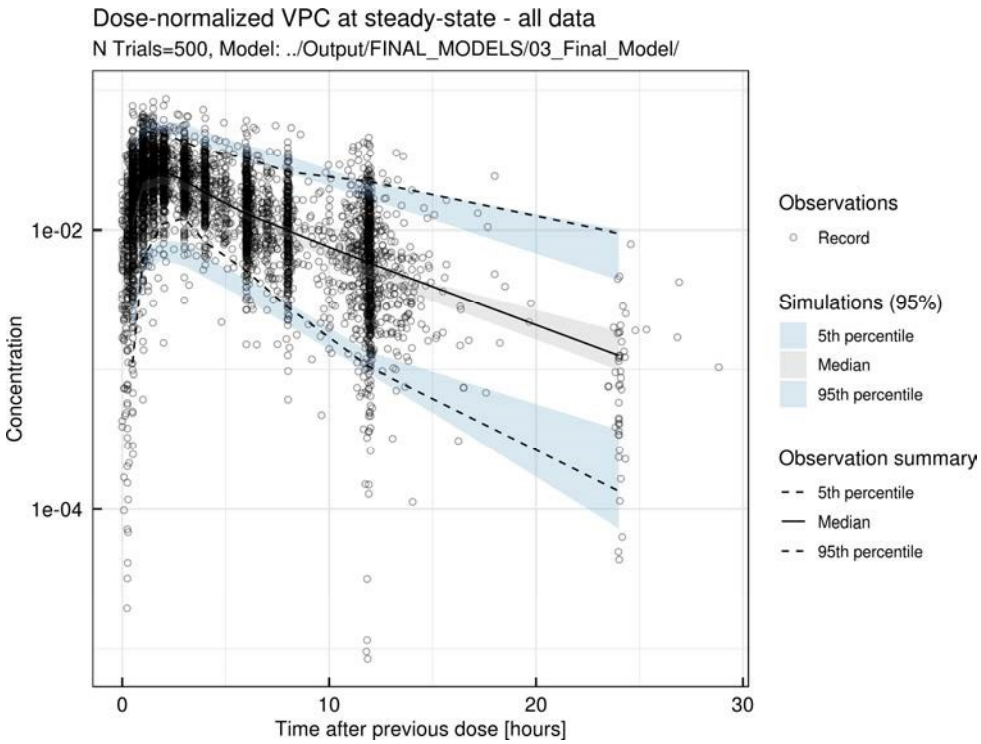


Figure 1: Dose-normalized VPC for steady-state data following QD and BID administrations of olaparib

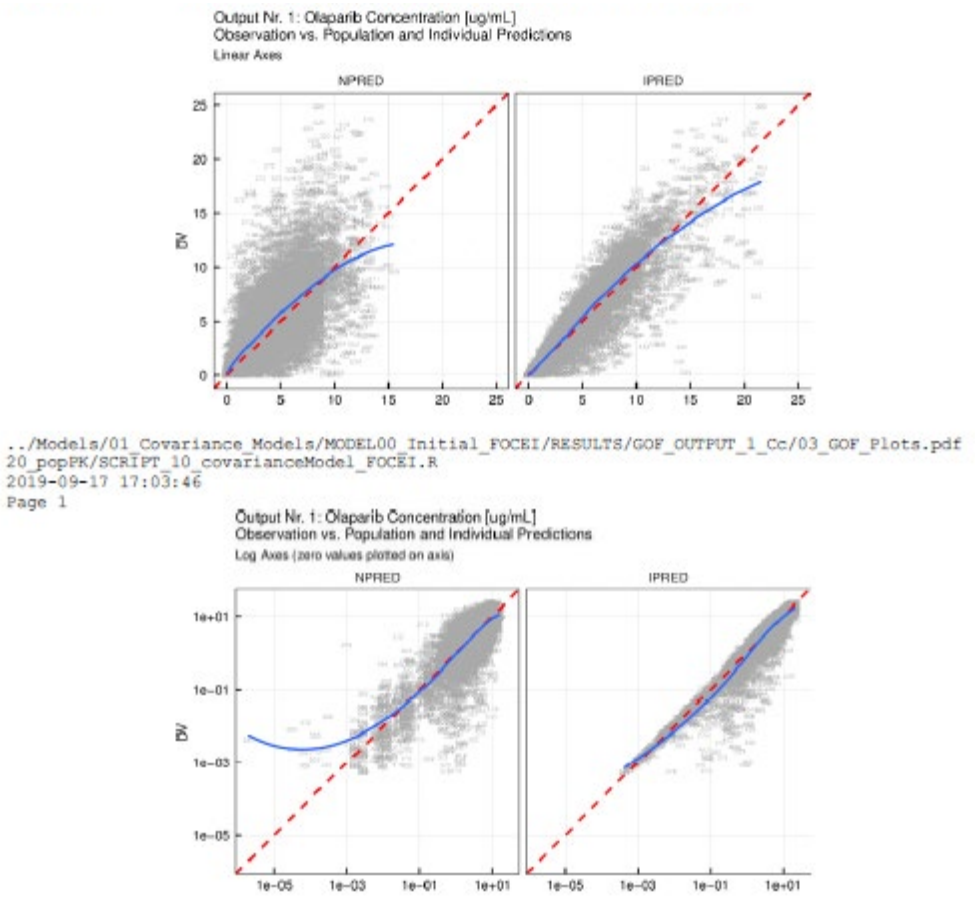
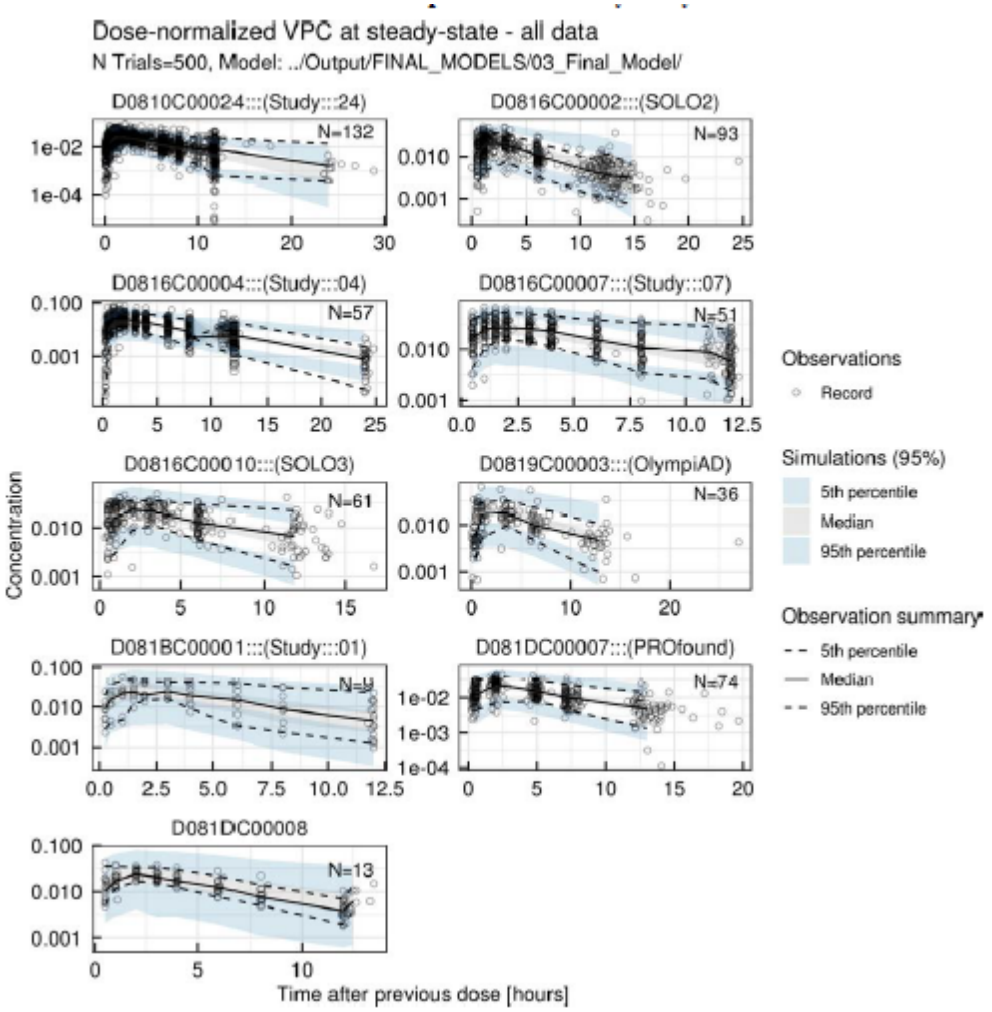


Figure 2: Goodness-of-fit model diagnostics – final PK model



Goodness-of-fit plots and visual predictive checks (VPCs) demonstrated an adequate description of the data by the model. The estimated apparent clearance (7.81 L/hour) and the central volume (4.55 L) were comparable (less than 16% difference) to the values from the previous population PK model for the tablet formulation (Olaparib-MS-06). There was a 20% lower clearance for doses at steady state compared to the clearance after a single dose.

Figure 3: Dose-normalised VPC for steady-state data following QD and BID administrations of olaparib stratified by study

Model-Based Systemic exposure predictions

Simulations of the model were performed to determine the exposure in terms of area under the concentration time curve at steady state (AUCss) as well as maximum and/or minimum concentration within a dosing interval at steady state (Cmaxss and/or Cminss) for twice daily dosing for various dose levels. For patients at a 300 mg bid dosing regimen the geometric means (and %CVs) for individually predicted Cmaxss, AUCss, and Cminss were 7.63 µg/mL (34.6%), 49.2 µg.h/mL (44.1%), and 1.55 µg/mL (72%) respectively. These values were similar to values reported based on the previous PopPK model which were 7.67 µg/mL (40.2%), 49.0 µg.h/mL (51.6%), and 1.57 µg/mL (86.2%). Individual exposure metrics were determined based on the empirical Bayes estimates of the model parameters.

Model predicted individual AUC(0-infinity) and Cmax post single dose

Model predicted AUC(0-infinity) and Cmax post single dose, obtained through simulation of the individual patient parameters (based on EBEs) have been summarized in **Table 3** for doses of 100, 200, 250, 300, and 400 mg olaparib. For each individual patient a single dose was simulated over 3 weeks to allow for adequate washout. Chosen dose level was the same dose as the patient had received as first dose in the analysis dataset. **Table 3** reports the number of patients in each dose group, the geometric mean and CV% and the min and max values within each dose group.

Table 3: Summary of model predicted individual AUC and Cmax after single dose administrations of different olaparib doses

Regimen	Na	Cmax [ug/mL][b]	AUC(0-inf) [ug*hour/mL][b]
100 mg single dose	59	2.85 (42.9%) [1.1,9.35]	15.6 (64.5%) [5.93,76.1]
200 mg single dose	32	5.58 (39.6%) [3.05,18.6]	35 (63.1%) [13.8,362]
250 mg single dose	27	6.63 (26.1%) [4.31,12.1]	42.5 (40.8%) [19,78.4]
300 mg single dose	402	5.37 (31.7%) [2.57,14.2]	39.2 (44.2%) [13.8,183]
400 mg single dose	53	9.51 (34%) [4.1,20.5]	69.7 (57.5%) [14.6,206]

[a] Number of patients in group

[b] Geometric mean (Geometric CV%) [minimum, maximum] Values rounded to 3 significant digits

Model predicted individual AUC, Cmax, and Cmin at steady state

Model predicted AUC, Cmax, and Cmin at steady state, obtained through simulation of the individual patient parameters (based on EBEs) have been summarized in **Table 4** for doses of 100, 200, 250, 300, and 400 mg BID olaparib. Steady-state conditions were assumed to be achieved after 5 days of continuous BID dosing. Table 13 reports the number of patients in each dose group, the geometric mean and CV% and the min and max values within each dose group.

Table 4: Summary of model predicted individual steady-state AUC, Cmax, and Cmin after multiple dose administrations of different olaparib doses

Regimen	Na	Cmaxss [ug/mL][b]	AUCss [ug*hour/mL][b]	Cminss [ug/mL][b]
100 mg bid	59	3.72 (46%) [1.71,14.3]	19.6 (64.6%) [7.44,95.7]	0.402 (158%) [0.0489,4.41]
200 mg bid	32	7.61 (48.2%) [3.76,46.7]	43.9 (63%) [17.3,451]	1.21 (111%) [0.232,29.2]
250 mg bid	27	8.94 (28%) [5.8,16.6]	53.1 (40.7%) [23.9,98.5]	1.49 (75.3%) [0.358,4.2]
300 mg bid	402	7.63 (34.6%) [3.45,24.3]	49.2 (44.1%) [17.3,227]	1.55 (72%) [0.283,14.4]
400 mg bid	53	13.5 (38.4%) [5.06,31.3]	87.5 (57.6%) [18.3,259]	2.86 (105%) [0.269,17.6]

[a] Number of patients in group

[b] Geometric mean (Geometric CV%) [minimum, maximum] Values rounded to 3 significant digits

Population simulations of AUC, Cmax, and Cmin at steady state

Simulations of 200, 300, and 400 mg BID dosing were performed for N=5000 patients per dose group and Cmax, Cmin, and AUC at steady state were determined. It was assumed that 5 days of continuous BID dosing allowed to reach steady- state conditions. Individual parameters for the 5000 patients per dose were sampled from the individual parameter distribution, estimated in the final PopPK model. 200

mg dose was assumed to be given with 100 mg tablet strength, 300 mg dose with 150 mg tablet strength, and 400 mg dose with two 150 mg and one 100 mg tablet.

Table 5 reports the geometric mean and CV% and the 5th and 95th percentiles of the steadystate AUC in each dose group.

Table 5: Summary of model predicted population steady-state AUC, Cmax, and Cmin after multiple dose administrations of different olaparib doses

Regimen	Tablets	Na	Cmaxss [ug/mL][b]	AUCss [ug*hour/mL][b]	Cminss [ug/mL][b]
200 mg bid	2x 100mg	5000	6.71 (42.6%) [3.44,13]	34.4 (51.7%) [15.4,76.4]	0.708 (110%) [0.157,2.87]
300 mg bid	2x 150mg	5000	7.58 (43.8%) [3.82,15]	52.4 (51.6%) [23.6,118]	1.85 (77.6%) [0.606,5.93]
400 mg bid	2x 150mg + 1x 100mg	5000	11 (43.7%) [5.59,21.7]	69.8 (51.3%) [31.6,155]	2.21 (81%) [0.688,7.31]

[a] Number of simulated patients in group

[b] Geometric mean (Geometric CV%) [5th percentile, 95th percentile] Values rounded to 3 significant digits

2.3.3. Pharmacodynamics

No new primary or secondary studies were provided which was considered acceptable by the CHMP.

The MAH provided a discussion on the biological rationale for the HRRm gene panel-based selection approach supported by clinical data (data not shown; see discussion on clinical efficacy).

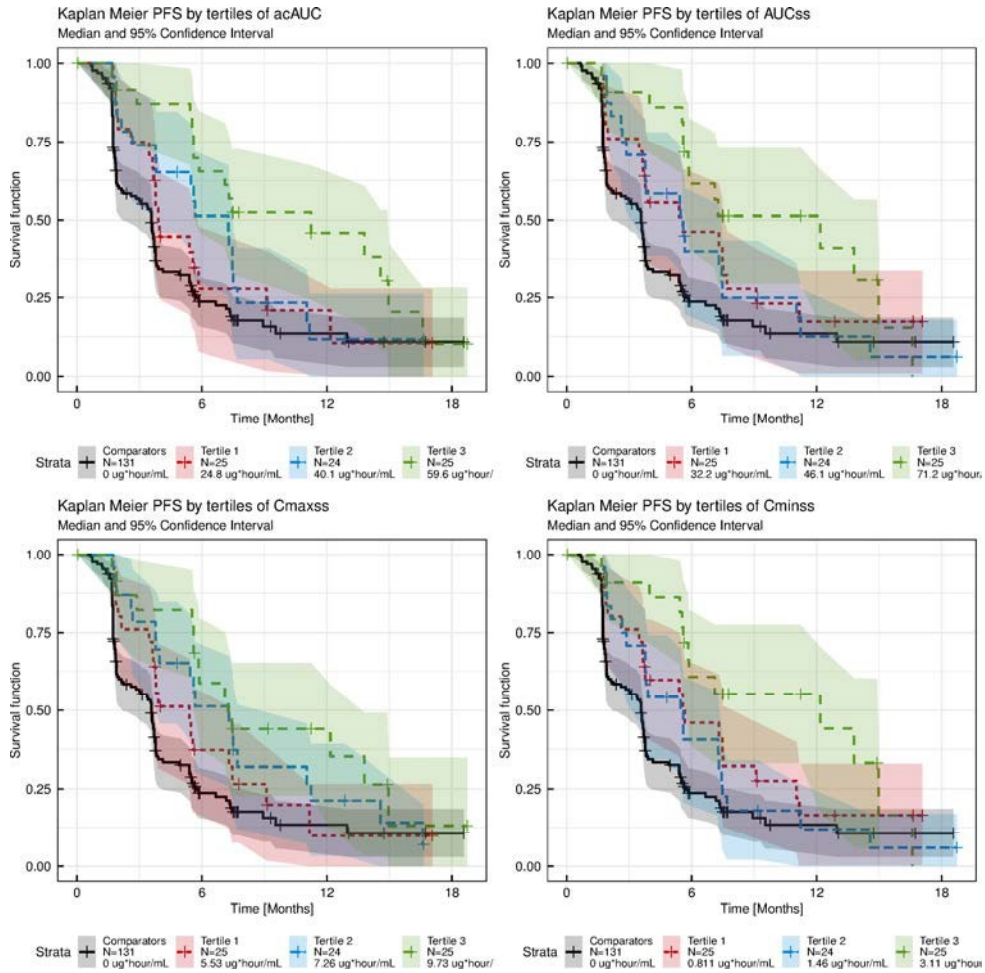
2.3.4. PK/PD modelling

Exposure-Efficacy Relationship

Correlation between olaparib exposure and PFS

The correlation between olaparib exposure and PFS was explored by plotting Kaplan-Meier (KM) curves with each of the considered olaparib exposure metrics (acAUC, AUCss, Cmaxss, and Cminss) stratified by tertiles (see **Figure 4**).

All exposure metrics indicated an on average longer progression free survival time for the olaparib treated patients compared to the control group and for patients with a higher olaparib exposure compared to a lower olaparib exposure. Still, confidence intervals partly overlapped between the control group and the lower exposure group and the three exposure groups. At the end of the observation period of 18 months the fraction of progression free patients was about 10% for all groups.



Comparators group: patients treated with enzalutamide or abiraterone acetate. The other groups are determined based on the median of the considered exposure metric. N=number in the legend reports the number of patients in the respective group. The last number for each legend in the group reports the mean olaparib exposure within the respective group with 3 significant digits.

Figure 4: Kaplan-Meier plots for exposure-efficacy in prostate cancer patients, stratified by tertiles of olaparib exposure metric of acAUC, AUCss, Cmaxss, and Cminss

Modeling efficacy by Cox regression

As the KM curves suggested a potential olaparib exposure/response relationship on PFS Cox proportional hazard regression models were fitted to assess whether a significant relationship of exposure and PFS can be detected. Enzalutamide or abiraterone acetate treated patients were not considered in this analysis.

Base model

Univariate models with one covariate (BAGE, BWTKG, PSABASE, RACE, DISSEV,BRCAM2, ATM, CDK12) respectively were fitted to include all relevant covariates into the base model. Only showed a hazard ratio (HR) significantly different ($p<0.01$) from. The base model including the two significant covariates, BRCAM2 and CDK12, is shown in **Table 6**.

Table 6: Base model for the Cox proportional hazard regression of PFS

Parameter	Value	95% CI	P_value	P_value_PH
BRCAM2=1	0.5577	[0.2848, 1.092]	0.08856	0.06909

CDK12=1	2.211	[1.094, 4.469]	0.02715	0.1305

Metrics	OBJ	DF	DeltaOBJ	P_value_PH
	360.1	2	-12.34	0.127

Model: COX~BRCAM2+CDK12
Implemented as: fit <- survival::coxph(COX~BRCAM2+CDK12, data=data__, x=TRUE, y=TRUE)
Reference category for BRCAM2: 0
Reference category for CDK12: 0
Value: Hazard ratio estimate for predictor. OBJ: -2*log-likelihood, DeltaOBJ: OBJ difference to null model. P_value: statistical significance of predictor variable. P-value_PH: p-value for testing proportional hazard assumption (valid assumption if >0.05, value in OBJ row is global value). Values rounded to 4 significant digits.

Exposure metrics models

Cox proportional hazard model including either acAUC, AUCss, Cmaxss, or Cminss were fitted to the data. The estimation results are shown in **Table 7**. Inclusion of none of the exposure metrics led to a significant improvement of the model fit. The estimated HRs were smaller than one suggesting a lower risk of disease progression with increasing exposure. However, the 95%-CIs of the HR estimates for all exposure metrics include 1 indicating that no statistically significant correlation of exposure and PFS could be detected based on the PROfound data.

The total number of olaparib patients included in this analysis was 74, this may limit the power to detect statistically significant trends.

Table 7: Comparison of Cox proportional hazard regression model using different exposure metrics

Model	**OBJ**	**DF**	**DeltaOBJ**	**DeltaDF**	**P_value_PH**	**HR**
Base	360.1	2	(base)	(base)	0.127	-
acAUC	357.3	3	-2.827	1	0.1635	0.9853 (0.9683,1.003)
AUCss	357.1	3	-3.054	1	0.1377	0.9849 (0.9676,1.003)
Cmaxss	357.2	3	-2.923	1	0.1785	0.8785 (0.7549,1.022)
Cminss	357.1	3	-2.976	1	0.0974	0.7661 (0.5552,1.057)

Estimates with 95%-confidence intervals
Significance: * <0.05, ** <0.01, *** <0.001
Values rounded to 4 digits.
OBJ: -2*log-likelihood; DF: Degrees of freedom; P_value_PH: global test for proportional hazards (valid assumption if >0.05); DeltaOBJ: OBJ difference to base model; DeltaDF: DF difference to base model.

Exposure-Safety Relationship

The relationship of safety events and olaparib exposure was analysed based on a pooled data set from the same studies as the population PK analysis, with exception of the study D081DC00008. In this study (D081DC00008), olaparib had been administered only in combination with abiraterone and the safety analysis concerned olaparib only treatment. The safety analysis also included the data from the placebo arm in one study (SOLO2) which was not considered in the PK analysis. The data set included 576 patients on active olaparib treatment and 99 patients in the placebo maintenance group in SOLO2. Patients had adverse event information recorded as a function of the CTC grade, with 0 for no event and 1, 2, 3 and 4 for mild, moderate, severe, and life threatening, respectively.

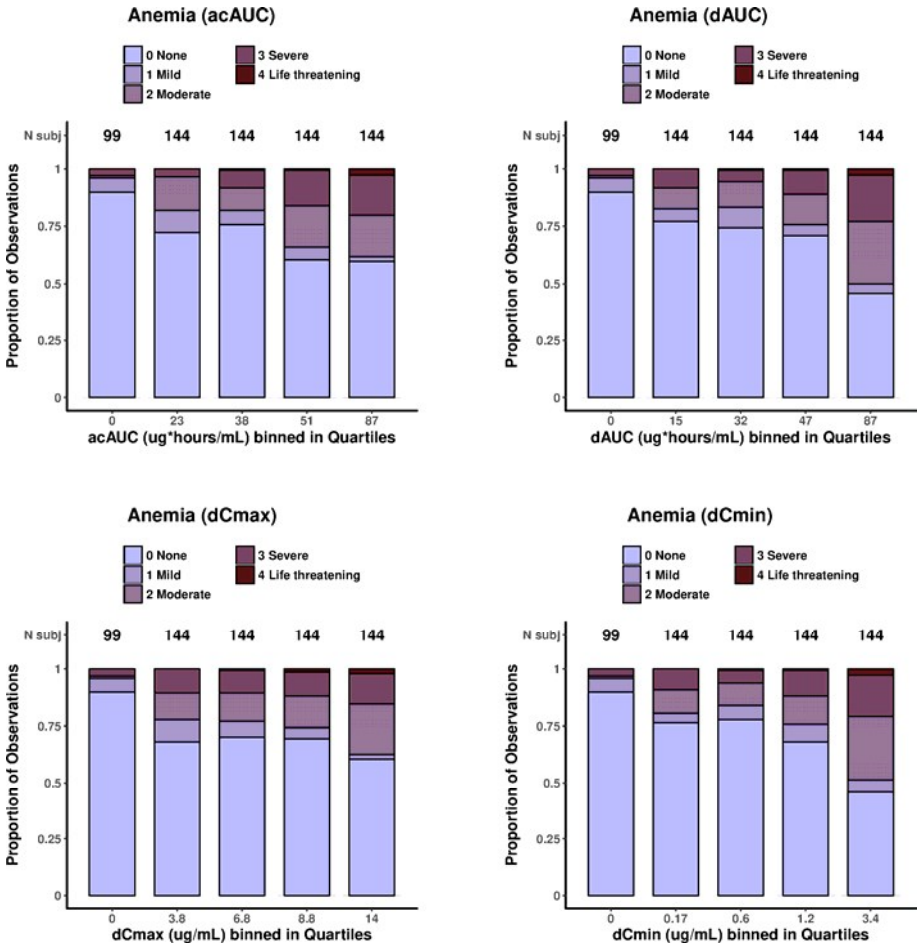
Adverse events (AEs) for anaemia, decreased appetite, diarrhoea, dysgeusia, fatigue, headache, nausea, neutropenia, and vomiting were evaluated. The considered event per patient and adverse event type was the first event of the maximum severity grade observed for the respective patient. The AEs were summarized by severity grade and type of AE for placebo patients and olaparib treated patients separately indicating moderately higher AE rates for olaparib treated patients in general. As in previous analyses, the exposure/AE response relationship was analysed based on Cmax, Cmin, and AUC at day of occurrence of considered safety event (dCmax, dCmin, dAUC) as well as the acAUC at day of occurrence of the considered safety event. First, proportions of the AEs by grade and stratified by quartiles of the exposure metrics (in comparison to the placebo patients) were graphically explored. Second, ordinal logistic regression was used to evaluate significant correlations ($p<0.001$) of the severity grades of the AEs and the different exposure metric values.

Graphical investigation of Exposure-AE Relationship:

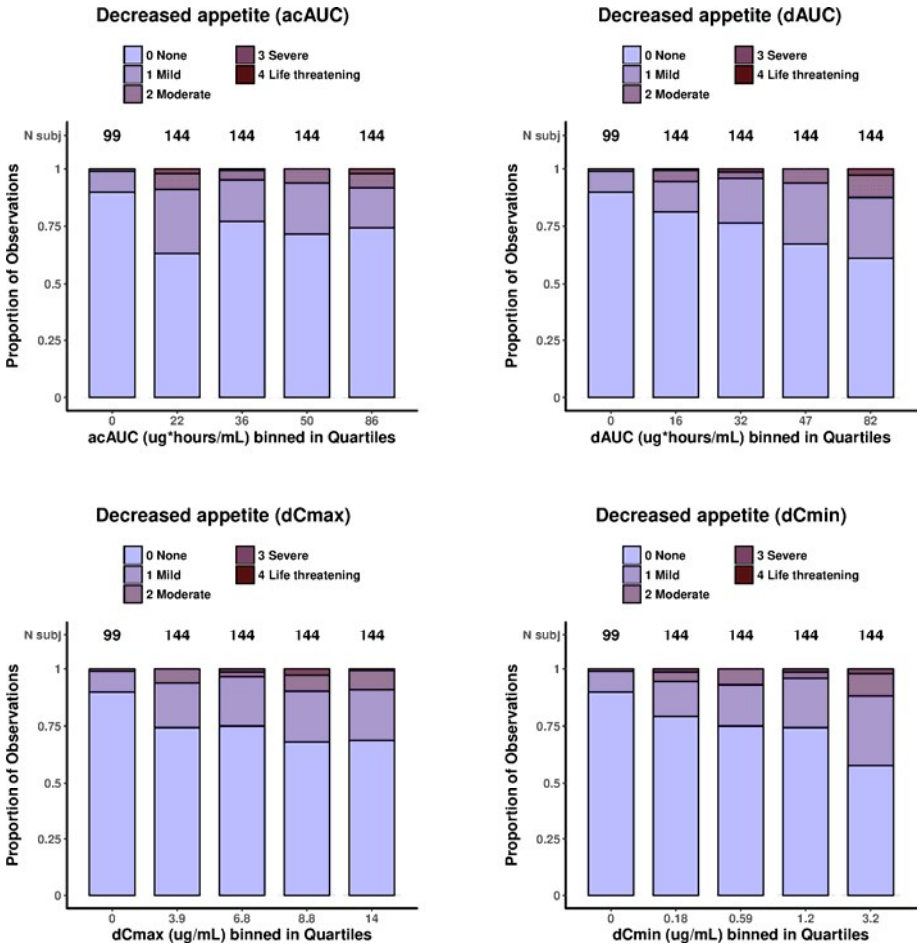
Anaemia AEs were significantly correlated with all exposure metrics, while decreased appetite, fatigue, and vomiting showed a significant correlation with dAUC and dCmin. dAUC showed also to be a significant predictor for nausea. The pattern of AE to olaparib exposure relationship found by the current analysis was comparable to the pattern found in the previous analysis. Significant relationships to exposure were found for anaemia, decreased appetite, fatigue, nausea, vomiting and no relationship was detected for neutropenia by both analyses. Comparable results were also found for diarrhoea (i.e., weak relationship). Dysgeusia was suggested to be significantly correlated with exposure based on the previous analysis while only a weak correlation could be detected by the current analysis. The current analysis also found a weak correlation of exposure and headache while none was detected previously. Based on the current analysis, the best predictor of AEs was dAUC while it was acAUC and dCmax in the previous analysis.

Adverse event as a function of the CTC grade, with 0 for no event and 1, 2, 3 and 4 for mild, moderate, severe, and life threatening, for each exposure metric is illustrated below.

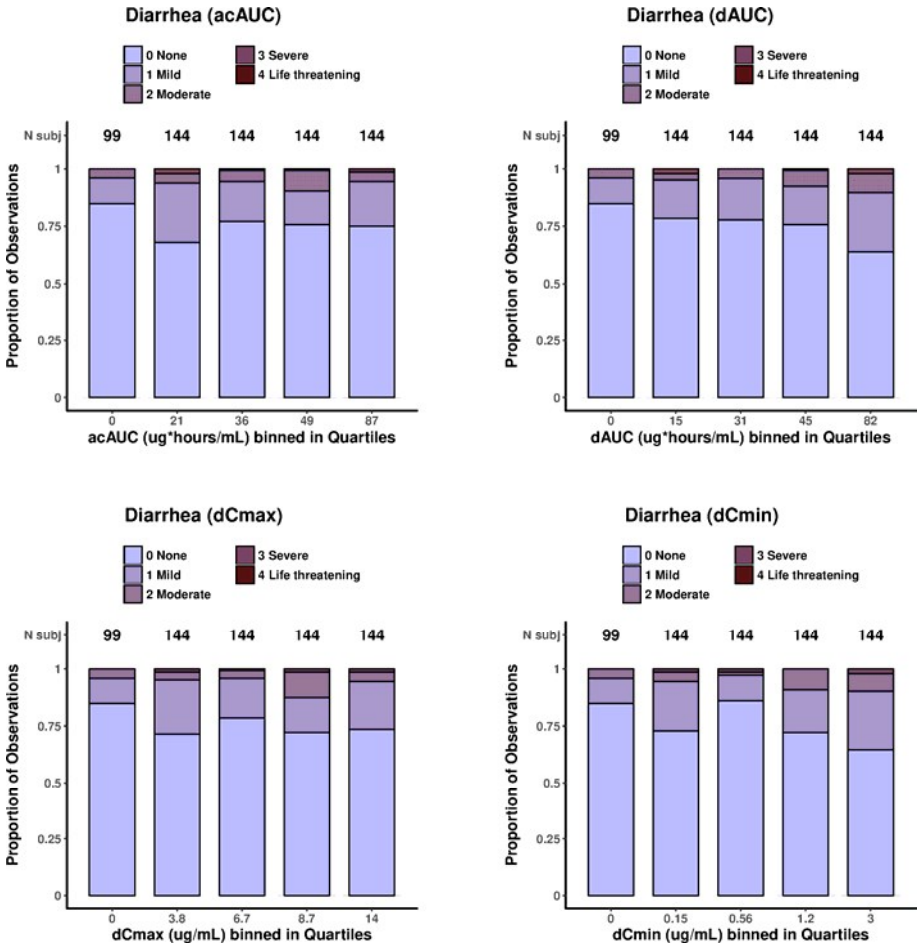
Proportion of observed anaemia grades versus olaparib exposure



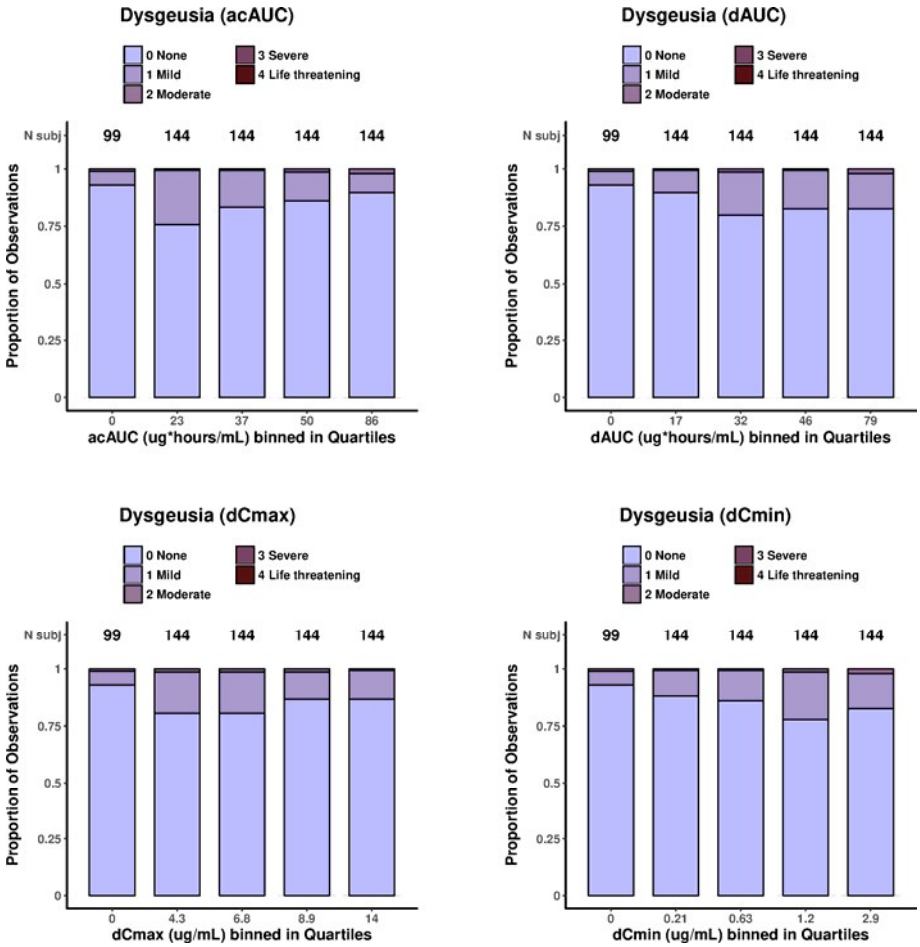
Proportion of observed decreased appetite grades versus olaparib exposure



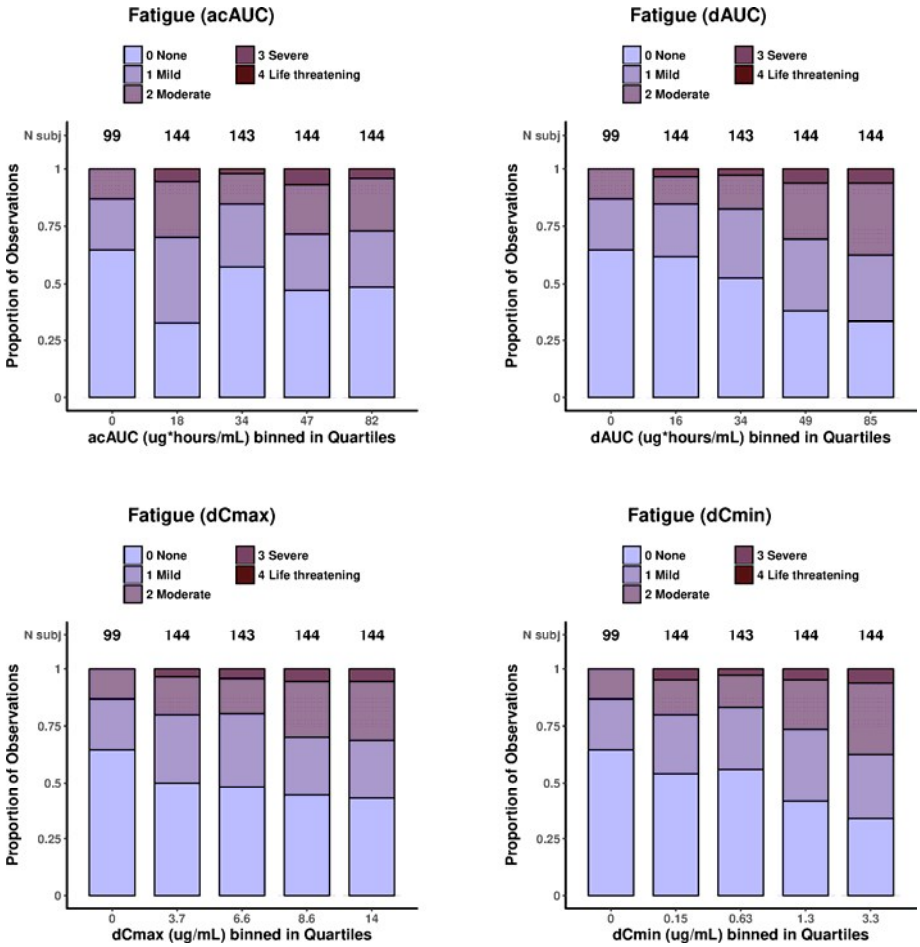
Proportion of observed diarrhea grades versus olaparib exposure



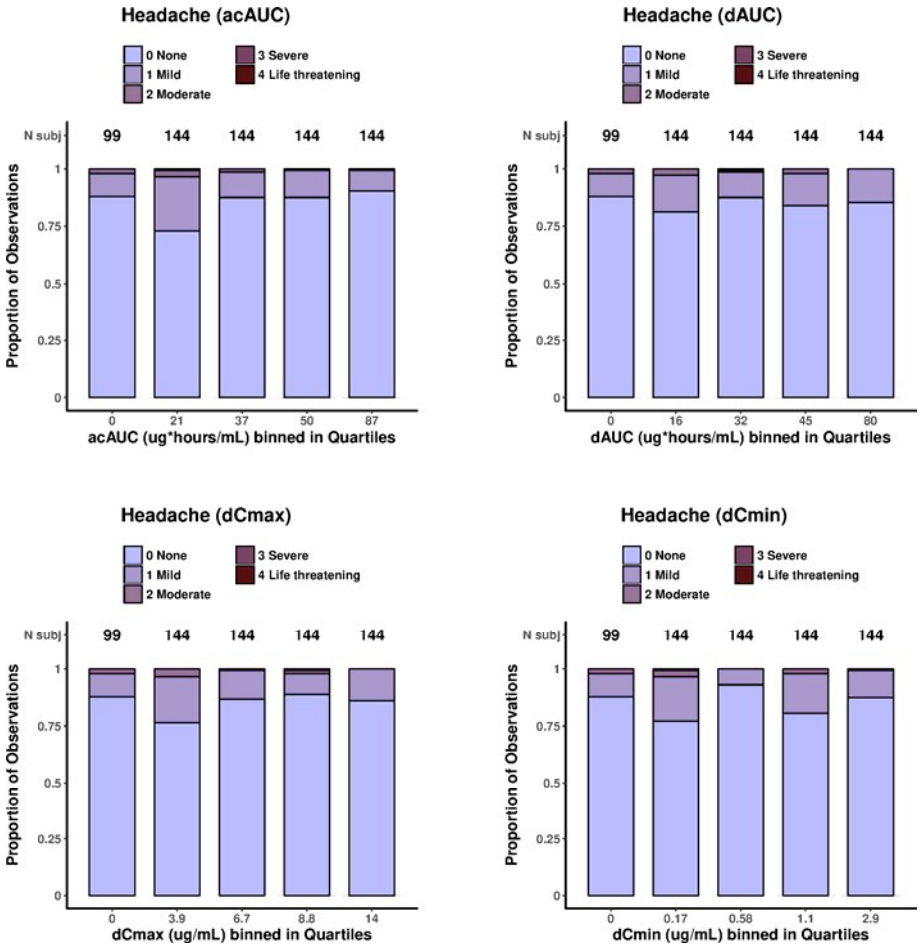
Proportion of observed dysgeusia grades versus olaparib exposure



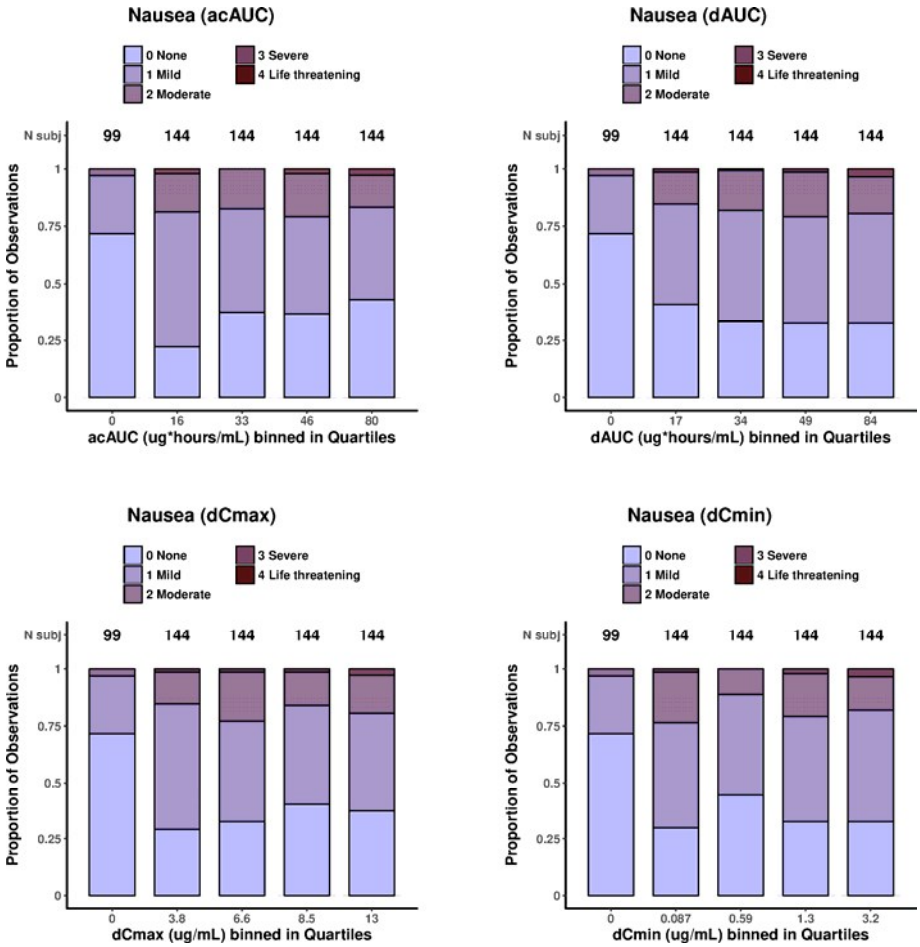
Proportion of observed fatigue grades versus olaparib exposure



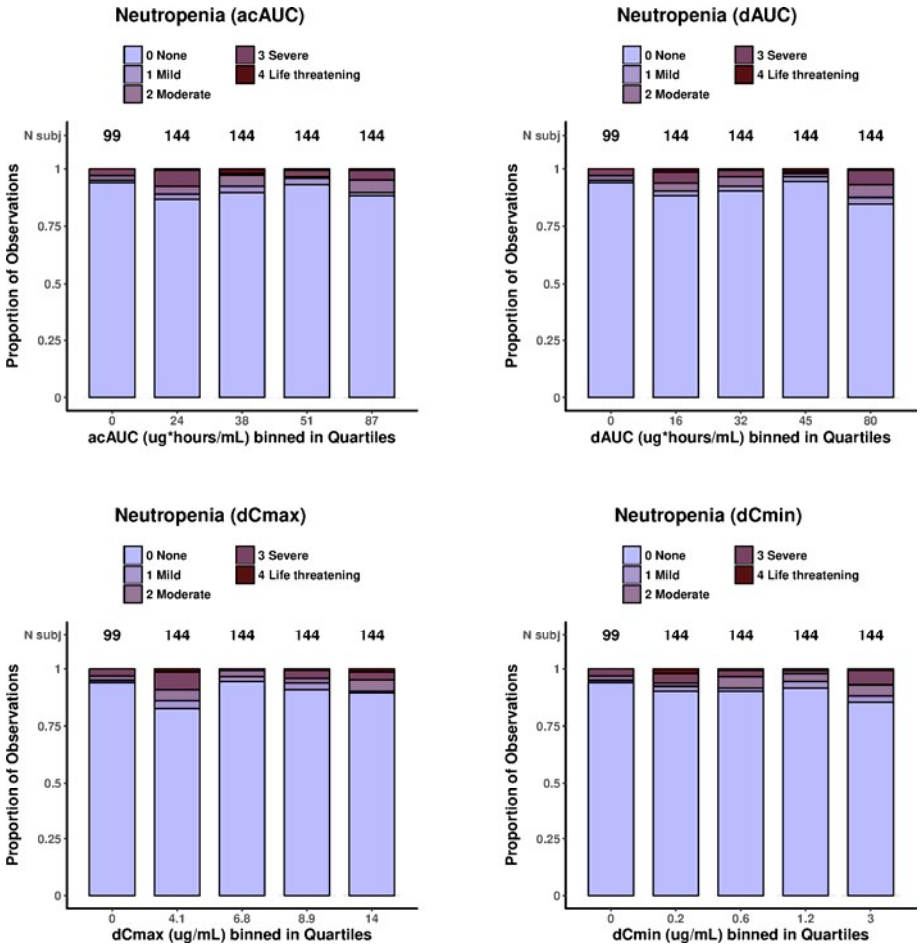
Proportion of observed headache grades versus olaparib exposure



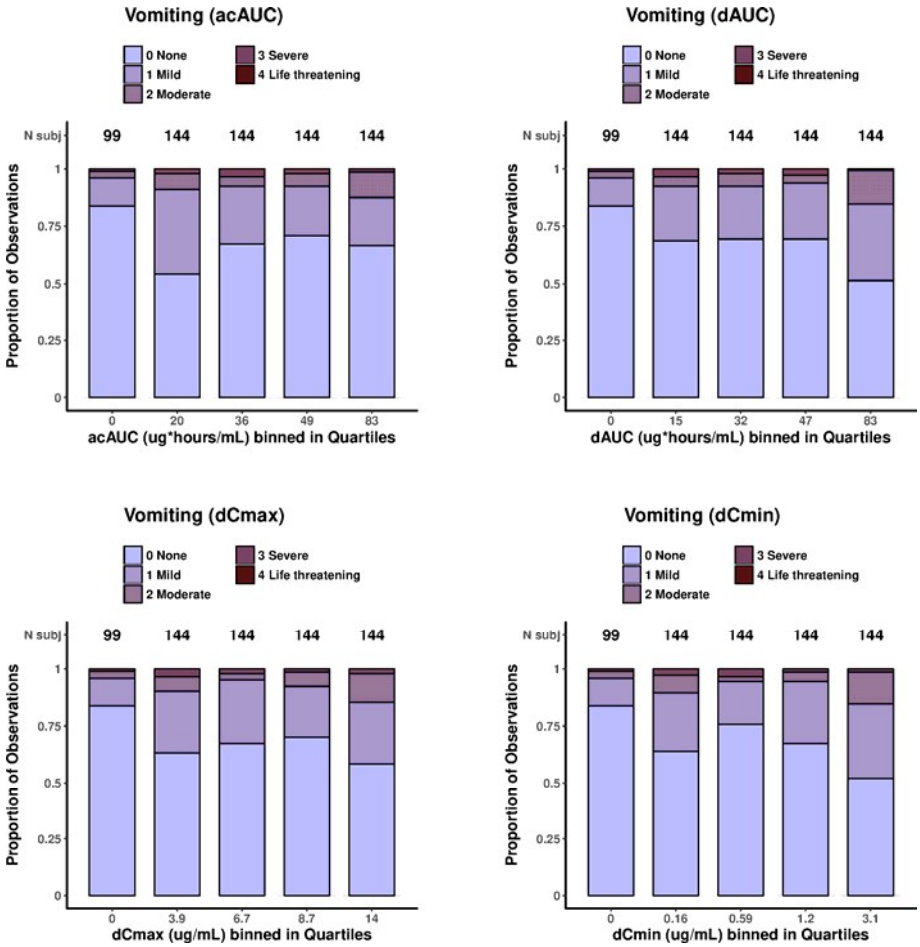
Proportion of observed nausea grades versus olaparib exposure



Proportion of observed neutropenia grades versus olaparib exposure



Proportion of observed vomiting grades versus olaparib exposure



Note: The 5 vertical bars from left to right represent the placebo, the first, second, third, and fourth quartile of considered olaparib exposure metric, respectively. Within each vertical bar, the stacked segment bars from bottom to top with different colors represent proportions of observed maximum individual AE Grade from 0 (None) to 4 (Life threatening). Above each bar the number of unique subjects contributing to each vertical bar is shown. acAUC: average cumulative AUC at the day of observed adverse event; dAUC/dCmax/dCmin: AUC/Cmax/Cmin at the day observed adverse event. The numeric values on the x axis represent the mean of the considered exposure metric within the bin.

Figure 5: Proportion of observed adverse event as a function of the CTC grade versus olaparib exposure

Modeling safety by ordinal logistic regression

The exploratory plots indicated apparent relationships of proportions of observed safety grades for some of the adverse events (e.g., anaemia, nausea, fatigue) to olaparib exposure measured by dCmin or dAUC. Ordinal logistic regression analyses for all adverse events were conducted to further explore potential correlation between the exposure metrics and the frequency or severity of the different AEs.

A full covariate modeling approach was chosen, in which the base model consisted of a model that considered BAGE, BWTKG, RACE, SEX, DISSEV, TUMGRP, and BRCA as predictors for the occurrence of the different adverse events. Subsequently, the different exposure metrics were introduced into the model as additional predictors and the change in objective function (-2xLogLikelihood) from the base model to the models including exposure was determined. Results are shown in **Table 8**. Following this analysis dAUC appeared to be the best predictor for occurrence of adverse events. Models for anemia,

decreased appetite, fatigue, nausea, and vomiting improved on the 0.001 significance level, i.e., by a drop of the objective function of more than 10.83 points, when including dAUC in the model. Anemia adverse events showed the strongest relationship with exposure in general as any of the exposure metrics improved the model fit on the 0.001 significance level.

Table 8: Comparison of delta-objective functions for models with different exposure metrics in all adverse events

AENAME	acAUC	dAUC	dCmax	dCmin
Anemia	-33.94	-54.8	-17.97	-46.97
Decreased appetite	-0.91	-21.28	-5.57	-14.88
Diarrhea	0	-8.45	-0.52	-7.82
Dysgeusia	-0.85	-5.49	-0.11	-2.3
Fatigue	-2.07	-36.29	-9.37	-23.13
Headache	-6.67	-0.13	-4.01	-0.25
Nausea	-1.66	-21.89	-8.73	-6.43
Neutropenia	-0.26	-2.2	-0.11	-4.06
Vomiting	-0.62	-21.69	-5.76	-13.02

Delta objective function calculated relative to a model without exposure metric included but with the same covariates. The objective functions were calculated as -2xLogLikelihood. Results rounded to 2 digits.

2.3.5. Discussion on clinical pharmacology

Olaparib presented as tablets as monotherapy, is already approved in adult patients with breast cancer, adenocarcinoma of the pancreas and advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy. Olaparib pharmacokinetics (ADME) as well as the influencing intrinsic factors have been fully characterised and already evaluated with the hard gelatine capsules and the tablets.

The variation under review concerns the use of olaparib tablets as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene mutations (germline and/or somatic) who have progressed following a prior new hormonal agent. The claimed dose of olaparib in this indication is the same than the dose approved for other solid tumours indications. This extension indication is not claimed for the hard gelatine capsule.

The MAH provided the results of an updated population PK analysis integrating the sparse data from study PROfound. The population PK of olaparib after oral administration using tablets was well described by a two-compartmental distribution model with linear elimination from the central compartment and consecutive zero and first order absorption.

The model characteristics are in line with previous results. However, the Omega-Shrinkage (Inter Individual Variability) was too high (more than 25%) for most of the model parameters: Vc, Q, Vp, Ka, Tk0. As a consequence, the predictive power of the model is questionable. Therefore, the model-based prediction of the individual exposure should be considered cautiously and as such the exposure-Response relationship investigations should also be.

In the current analysis, the clearance was 20% smaller for steady-state administration compared to single doses.

Covariate analysis of the latest pooled tablet formulation data was consistent with the previous covariate analysis of pooled tablet and capsule formulation data. The estimated effects were comparable to the previous population PK analysis (Olaparib-MS-06).

Patients with an ECOG performance status of 1 had a 18% smaller apparent clearance and patients with an ECOG performance status of 2 had a 44% smaller apparent clearance compared to patients with an ECOG performance status of 0.

The absorption rate was dependent on the tablet strength. Compared to tablets of 50 or 150 mg olaparib tablets with 125, 200, 225, 250, or 300 mg had a faster first order absorption and tablets with 100 mg olaparib had a faster first order absorption than any other tablets.

No additional covariate relationships for age, body weight, creatinine clearance, sex, ethnicity, disease severity, tumour location, hepatic impairment status, tablet strength, BRCA mutation type were detected.

The analysis of exposure-efficacy relationship of data from pivotal PROfound study revealed no clear correlation between exposure and efficacy endpoint PFS. However, the outcome of such analysis should be considered cautiously, as the reliability of the model-based prediction of exposure is questionable (see comments on the pop-PK model).

The graphical analysis visualizing the event rates by exposure quartile and a model-based analysis using ordinal logistic regression indicated a similar safety pattern as was detected in a previous safety analysis (Olaparib-MS-07). This updated analysis of exposure-AE relationship (including data from the pivotal PROfound study) revealed no particular concern by comparison to the previous investigations. However, the outcome of such analysis should be considered cautiously, as the reliability of the model-based prediction of exposure is questionable (see comments on the pop-PK model)

2.3.6. Conclusions on clinical pharmacology

No new biopharmaceutical or clinical pharmacology study has been submitted to support the proposed indication. The current clinical pharmacology package provides sufficient characterisation of the key PK characteristics of olaparib and when combined with *in vitro* drug metabolism and PK profiling data and *in vivo* DDI studies, it provides sufficient data in support of an adequate labelling for special populations and DDI. The results of the Pop PK analysis and exposure-efficacy/ safety analysis should be considered cautiously.

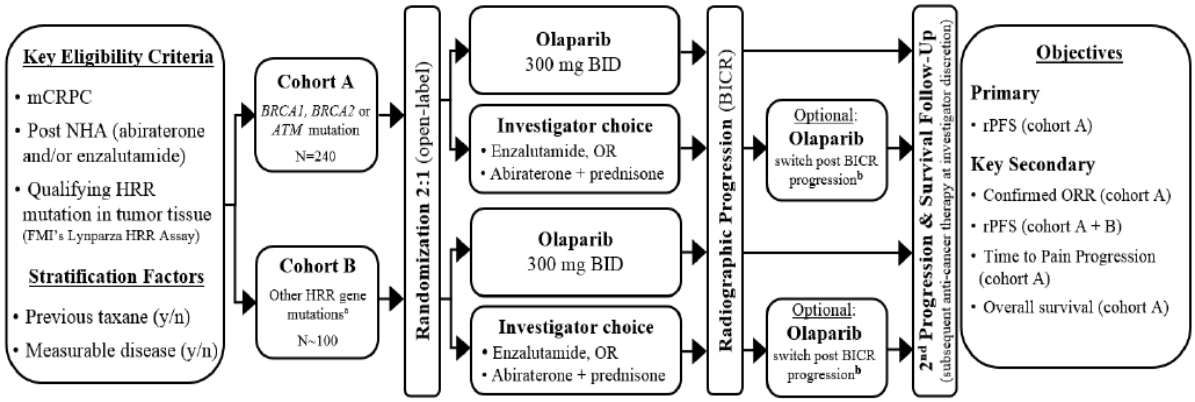
2.4. Clinical efficacy

2.4.1. Main study

Study D081DC00007 (PROfound)

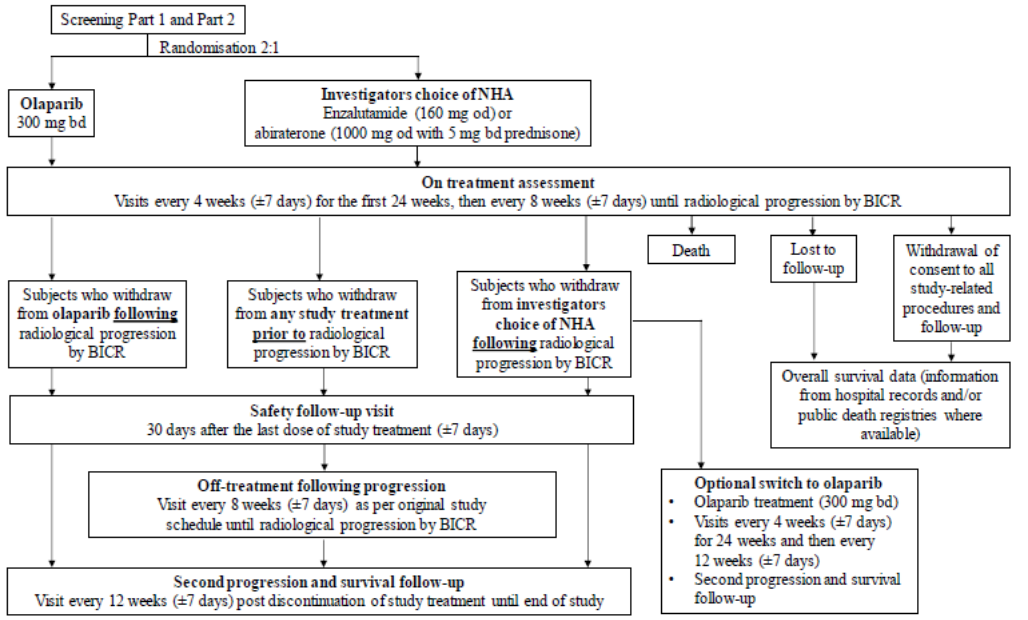
Methods

This was a Phase III, randomised, open-label, multicentre trial to assess the efficacy and safety of olaparib monotherapy in patients with mCRPC that have qualifying HRR gene mutations that were predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function) who have failed prior treatment with an NHA.



[a] Cohort B HRR genes include *BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L.*
[b] Subjects randomized to investigator choice arm will be given the opportunity to begin treatment with open-label olaparib (300 mg bid) only after objective radiographic progression by blinded independent central reader (BICR). No intervening systemic anti-cancer therapy following discontinuation of randomized treatment will be permitted. Subjects may continue on olaparib as long as they show clinical benefit as judged by the investigator.

Figure 6: PROfound study design



Confirmation of radiological progression by BICR was only required prior to the data cut-off date of the primary analysis. After this date, confirmation of radiological progression by investigator assessment was sufficient.
bd Twice daily; BICR Blinded Independent Central Review; NHA New hormonal agent; od Once daily.

Figure 7: Flow chart of PROfound study design

Study participants

Inclusion criteria

For inclusion in the study, patients had to fulfil all the following criteria:

1. Provision of informed consent prior to any study-specific procedures

2. Male ≥18 years of age

3. Histologically confirmed diagnosis of prostate cancer.

4. Candidate for treatment with enzalutamide or abiraterone acetate with documented current evidence of metastatic castration-resistant prostate cancer, where metastatic status was defined as at least 1 documented metastatic lesion on either bone scan or computed tomography (CT)/magnetic resonance imaging (MRI) scan. Patients whose disease spread is limited to regional pelvic lymph nodes or local recurrence (e.g., bladder, rectum) were not eligible.

5. Patients must have progressed on prior NHA (e.g., abiraterone acetate and/or enzalutamide) for the treatment of metastatic prostate cancer and/or CRPC. Determination of progression was done per local investigator.

6. Serum testosterone levels ≤50 ng/dL (≤1.75 nmol/L) within 28 days before randomisation.

7. Patients without prior surgical castration must have been currently taking and willing to continue LHRH analog (agonist or antagonist) therapy throughout the duration of study treatment.

8. Radiological progression at study entry while on androgen deprivation therapy (or after bilateral orchiectomy). Determination of progression was done per local investigator.

9. Qualifying HRR gene mutation in tumour tissue by the FMI CLIA HRR Clinical Trial Assay (CTA)

- Either archival or de novo biopsies were acceptable.
- If patients had a mutation in 1 of the 15 HRR genes based on prior prostate cancer tissue specimen testing by the commercially available FoundationOne assay, they must have had the mutation confirmed as a qualifying mutation by FMI. Residual DNA (stored at FMI) from the original FoundationOne test was to be used for confirmation. Patients who did not have sufficient residual DNA from their original test were to be analysed in-silico for qualifying HRR gene mutations, according to the criteria in place for determining eligible mutations in PROfound, based on their original FoundationOne test data, but these patients must have supplied a sufficient formalin fixed, paraffin embedded tumour sample to carry out retrospective central confirmation using the FMI CLIA HRR CTA.

10. Patients must have had 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 in the past 28 days
- Absolute neutrophil count ≥1.5×10^9/L
- Platelet count ≥100×10^9/L
- Total bilirubin ≤1.5×institutional upper limit of normal (ULN)
- Aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase/alanine aminotransferase (ALT) serum glutamic pyruvate transaminase) ≤2.5×institutional ULN unless liver metastases were present in which case they must be ≤5×ULN
- Patients must have creatinine clearance estimated of ≥51 mL/min using the Cockcroft-Gault equation for males or based on a 24 hour urine test.
- Estimated creatinine clearance = (140-age [years])×weight (kg) serum creatinine (mg/dL)×72

11. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2.

12. Patients must have had a life expectancy of ≥16 weeks.

13. Must have used a condom during treatment and for 3 months after the last dose of olaparib when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female

partners of male patients should also have used a highly effective form of contraception if they are of childbearing potential.

14. Patient was willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations at the institution, and completing electronic patient reported outcomes (ePRO) instruments.

Exclusion criteria

Any of the following was regarded as a criterion for exclusion from the study:

1. Involvement in the planning and/or conduct of the study

2. Previous randomisation in the present study

3. Participation in another clinical study with an investigational product during the last 30 days prior to randomisation

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

5. Patients who have had any previous treatment with DNA-damaging cytotoxic chemotherapy, except if for non-prostate cancer indication and last dose >5 years prior to randomisation. For example, patients who received prior mitoxantrone or platinum-based chemotherapy for prostate cancer were excluded.

- Prior estramustine was allowed.

6. Other malignancy (including MDS and monoclonal gammopathy of unknown significance) within the last 5 years except: adequately treated non-melanoma skin cancer or other solid tumours including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for ≥5 years

7. Patients with MDS/AML or with features suggestive of MDS/AML

8. Resting electrocardiogram (ECG) indicating uncontrolled, potentially reversible cardiac conditions, as judged by the investigator (e.g., unstable ischaemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QT interval corrected for heart rate using Fridericia's correction prolongation >500 ms, electrolyte disturbances, etc), or patients with congenital long QT syndrome

9. Patients who were receiving any systemic anti-cancer therapy (except radiotherapy) within 3 weeks prior to study treatment

- Agents to maintain castrate status were authorised as detailed in inclusion criterion #7. Agents such as 5-α reductase inhibitors (finasteride, dutasteride), oestrogen compounds (including estramustine) and megesterol were considered anti-cancer agents and prohibited within 3 weeks prior to study treatment.
- Bone-targeted therapy with denosumab or zoledronic acid was allowed. If patients were being treated with these agents, they should have been on a stable regimen when entering the study.

10. Concomitant use of known strong cytochrome P450 (CYP)3A inhibitors (e.g., itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (e.g., ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting olaparib was 2 weeks.

11. Concomitant use of known strong (eg, phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (e.g., bosentan,

efavirenz, modafinil). The required washout period prior to starting olaparib was 5 weeks for phenobarbital and 3 weeks for other agents.

12. Persistent toxicities (>Grade 2, per the Common Terminology Criteria for Adverse Event [CTCAE]) caused by previous cancer therapy, excluding alopecia or toxicities related to the use of LHRH agonist or antagonist

13. Patients with known brain metastases. A scan to confirm the absence of brain metastases was not required.

14. Patients with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease (SD) for 28 days.

15. Patients unevaluable for both bone and soft tissue progression as defined by meeting both of the following criteria:

(a) A bone scan referred to as a superscan showing an intense symmetric activity in the bones.

(b) No soft tissue lesion (measurable or non-measurable) that can be assessed by RECIST.

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

17. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, 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 interstitial bilateral lung disease on high resolution computed tomography scan or any psychiatric disorder that prohibited obtaining informed consent.

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

19. Immunocompromised patients, e.g., patients who were known to be serologically positive for human immunodeficiency virus (HIV)

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

21. Patients with known active hepatitis (i.e., hepatitis B or C)

- Active hepatitis B virus (HBV) was defined by a known positive HBV surface antigen (HBsAg) result. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody and absence of HBsAg) were eligible.
- Patients positive for hepatitis C virus (HCV) antibody were eligible only if polymerase chain reaction is negative for HCV RNA.

22. Previous allogeneic bone marrow transplant or double umbilical cord blood transplantation

23. Whole blood transfusions in the last 120 days prior to entry into the study (packed red blood cells and platelet transfusions were acceptable, for timing, refer to inclusion criteria #10).

Mutation status

The procedure for assignment of HRR mutation status in PROfound was as follows:

- Screening part 1

- **Prospective tHRR testing for patient selection using the FMI CLIA HRR CTA**: HRR mutation status was determined through central tumour tissue testing performed by Foundation Medicine Inc. using the CLIA HRR CTA. For this purpose, either an archival tumour block, or a *de novo* tumour biopsy sample was required.
- **Patients with prior FoundationOne test result:** Patients could also enter screening if they had a prior FoundationOne test result which confirmed an eligible tHRRm result. These patients required generation of a **confirmatory CLIA HRR CTA result**. Confirmatory CLIA HRR CTA testing was performed on **residual DNA samples**, if available. Patients who did not have sufficient residual DNA available were able to proceed to screening part 2 following **reanalysis of the existing FoundationOne result** using the CLIA HRR CTA mutation calling and classification process.

Patients with a tHRRm result were eligible to participate in screening part 2.

- Screening part 2
  - **Confirmed FMI F1CDx subgroup**: To determine the patient population who would comprise the FoundationOne CDx positive subgroup (called "Confirmed FMI F1CDx subgroup"), results obtained for tHRR status using the CLIA HRR CTA were **evaluated prior to database lock** to determine if the patient was tHRRm according to the **FoundationOne CDx quality control (QC) criteria and classification rules**. No retesting of study samples using the FoundationOne CDx test was performed in PROfound.
  - **Confirmed Myriad gBRCAm subgroup**: The germline mutation status of the **BRCA1/2** genes was assessed **retrospectively**, prior to database lock, through central testing performed using the **BRACAnalysis CDx test**.

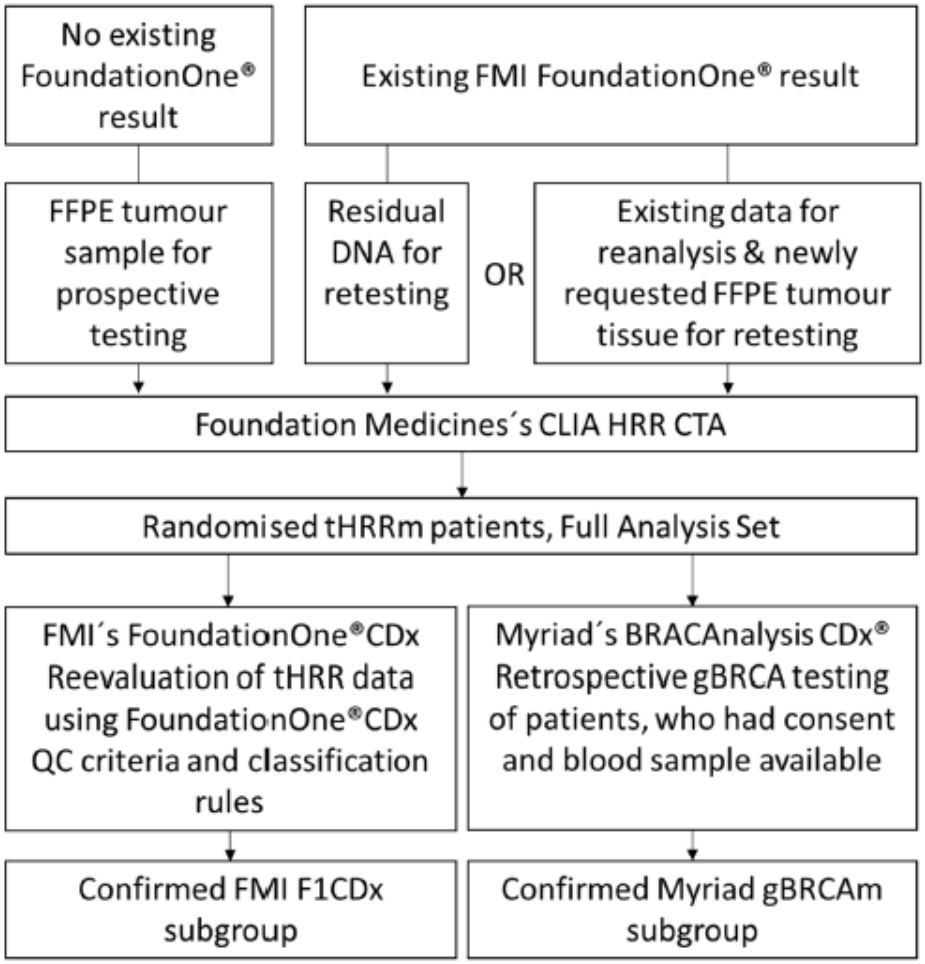


Figure 8: Test methods and resulting planned subgroups of PROfound study

Treatments

Patients were randomised in a 2:1 ratio to the treatments as specified below:

- Olaparib tablets orally 300 mg [2 x 150 mg tablets] twice daily [bd], tablet formulation

- Investigators choice of NHA with either enzalutamide 160 mg orally once daily (od) or abiraterone acetate 1000 mg orally od with prednisone 5 mg orally bd (prednisolone was permitted for use instead of prednisone, if necessary)

Treatment continued until objective radiological disease progression or until patients were unable to tolerate study treatment.

Once patients receiving investigators choice of NHA were determined to have objective radiological progression by a blinded independent central radiological (BICR), or by investigator assessment if after the date of DCO for the primary analysis, they were eligible to switch to treatment with olaparib.

Objectives and endpoints

Table 9: Objectives and endpoints

Objective	Endpoint/variable
Primary objective	
• To determine the efficacy (as assessed by rPFS) of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with mCRPC with *BRCA1*, *BRCA2* or *ATM* qualifying mutations (**Cohort A**).	• **rPFS by BICR** using **RECIST 1.1** (soft tissue) and **PCWG-3** (bone) criteria
Key secondary objectives	
• To determine the efficacy (as assessed by ORR) of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with BRCA1, BRCA2 or ATM qualifying gene mutations (**Cohort A**).	• **Confirmed ORR by BICR** assessment in patients with measurable disease using **RECIST 1.1** (soft tissue) and **PCWG-3** (bone) criteria
• To determine the efficacy (as assessed by rPFS) of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with HRR qualifying mutations (**Cohort A+B**). Note: this objective is not applicable for the potential future China cohort.	• **rPFS by BICR** using RECIST 1.1 (soft tissue) and PCWG-3 (bone) criteria
• To determine the efficacy (as assessed by time to pain progression) of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with BRCA1, BRCA2 or ATM qualifying gene mutations (**Cohort A**).	• **Pain progression** based on BPI-SF Item 3 "worst pain in 24 hours" and opiate analgesic use (AQA score)
• To determine the efficacy (as assessed by overall survival) of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with BRCA1, BRCA2 or ATM qualifying gene mutations (**Cohort A**).	• **OS**
Other secondary objectives	

• To further assess the efficacy of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with BRCA1, BRCA2 or ATM qualifying gene mutations (**Cohort A**).	• Time from randomisation to the **first SSRE** • Time from partial or complete response in patients with measurable disease (RECIST 1.1) to progression by BICR (**DoR**) • Time from randomisation to **opiate use for cancer-related pain** • Confirmed **ORR (RECIST 1.1) in soft tissue** by BICR in patients with measurable disease (soft tissue response) • Proportion of patients achieving a ≥50% decrease in PSA from baseline to the lowest post-baseline PSA result, confirmed by a second consecutive PSA assessment at least 3 weeks later (**PSA_{50} response**) • Proportion of patients achieving a decline in the number of CTCs from ≥5 cells/7.5mL to <5 cells/7.5mL whole blood (**CTC conversion rate**) • Time from randomisation to second progression **by investigator assessment** of radiological or clinical progression or death (**PFS2**)
• To further assess the effect of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with BRCA1, BRCA2 or ATM qualifying gene mutations (**Cohort A**) on disease-related symptoms and health-related quality of life (**HRQoL**).	• Pain severity progression based on BPI-SF pain severity domain and opiate use (AQA score) • Pain interference based on BPI-SF pain interference domain • FACT-P (FACT-P Total score, TOI, FWB, PWB, PCS and FACT Advanced Prostate Symptom Index 6 [FAPSI-6]) • Proportion of patients with pain (BPI-SF Item 3) score ≥4 points at baseline who have a decrease of ≥2 points in pain (BPI-SF Item 3) and without ≥1 point increase in analgesic score (AQA score) at 12 weeks, confirmed at least 3 weeks later (pain palliation)
• To assess the efficacy of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with HRR qualifying gene mutations other than BRCA1, BRCA2 or ATM (**Cohort B**). Note: this objective is not applicable for the potential future China cohort.	• **rPFS by BICR** using RECIST 1.1 (soft tissue) and PCWG-3 (bone) criteria • **Confirmed ORR by BICR** assessment in patients with measurable disease using RECIST 1.1 (soft tissue) and PCWG-3 (bone) criteria • **Pain progression** based on BPI-SF Item 3 "worst pain in 24 hours" and opiate analgesic use (AQA score) • **OS**

• To further assess the efficacy of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with HRR qualifying gene mutations **(Cohort A+B**). Note: this objective is not applicable for the potential future China cohort.	• Confirmed ORR by BICR assessment in patients with measurable disease using RECIST 1.1 (soft tissue) and PCWG-3 (bone) criteria • Time from randomisation to the first SSRE • Time from partial or complete response in patients with measurable disease (RECIST 1.1) to progression by BICR (DoR) • Time from randomisation to opiate use for cancer-related pain • Confirmed ORR (RECIST 1.1) in soft tissue by BICR in patients with measurable disease (soft tissue response) • Proportion of patients achieving a ≥50% decrease in PSA from baseline to the lowest post-baseline PSA result, confirmed by a second consecutive PSA assessment at least 3 weeks later (PSA50 response) • Proportion of patients achieving a decline in the number of CTCs from ≥5 cells/7.5mL to <5 cells/7.5mL whole blood (CTC conversion rate) • Time from randomisation to second progression by investigator assessment of radiological or clinical progression or death (PFS2) • OS
• To further assess the effect of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with HRR qualifying gene mutations **(Cohort A+B**) on disease-related symptoms and health-related quality of life (**HRQoL**). Note: this objective is not applicable for the potential future China cohort.	• Pain progression based on BPI-SF Item 3 "worst pain in 24 hours" and opiate analgesic use (AQA score) • Pain severity progression based on BPI-SF pain severity domain and opiate use (AQA score). • Pain interference based on BPI-SF pain interference domain • FACT-P (FACT-P Total score, TOI, FWB, PWB, PCS and FACT Advanced Prostate Symptom Index 6 [FAPSI-6]) • Proportion of patients with pain (BPI-SF Item 3) score ≥4 points at baseline who have a decrease of ≥2 points in pain (BPI-SF Item 3) and without ≥1 point increase in analgesic score (AQA score) at 12 weeks, confirmed at least 3 weeks later (pain palliation)
• To determine the exposure to olaparib in a subset of subjects receiving olaparib. • Note: this objective is not applicable for the potential future China cohort.	• Olaparib plasma concentration data

Sample size

The primary endpoint of the study was rPFS in Cohort A. It was planned to randomise approximately 240 patients (2:1 ratio of olaparib:investigators choice of NHA), with the rPFS analysis occurring once approximately 143 rPFS events (confirmed by BICR) had occurred.

The PROfound study was designed to enrol approximately 340 subjects with 240 subjects in Cohort A and approximately 100 subjects in Cohort B. The study sample size calculation was based on Cohort A with the ratio of patients between Cohort A and Cohort B based on an assessment of natural prevalence of the genes in the literature at the time of study design (Robinson et al 2015).

It was expected that the targeted sample size of 240 patients in Cohort A with approximately 143 rPFS events (60% maturity) would provide 95% power to demonstrate a statistically significant difference in rPFS at a 2-sided alpha level of 5% assuming true treatment effect was a HR=0.53. This translates to an approximate 4.5-month improvement in median rPFS over an assumed 5-month median rPFS on enzalutamide or abiraterone acetate assuming rPFS was exponentially distributed.

Cohort B of the study was to consist of approximately 100 patients with qualifying HRR gene mutations other than BRCA1, BRCA2 and ATM. These patients were to be randomised in a 2:1 ratio to olaparib:investigators choice of either enzalutamide or abiraterone acetate.

The number of patients enrolled in Cohort B was not driven by a formal sample size calculation and was determined by the enrolment period for Cohort A.

Randomisation

Patients were randomized 2:1 to either olaparib or pre-declared investigator choice of either enzalutamide or abiraterone acetate in each of the Cohorts A and B.

Patients with mutations in BRCA1, BRCA2 or ATM were randomised in Cohort A (irrespective of co-occurring mutations in one of the 12 other HRR genes), whereas patients with mutations among other genes were randomised in Cohort B.

Randomization was stratified based on prior receipt of taxane chemotherapy (yes vs no) and presence of measurable disease at baseline (yes vs no).

Blinding (masking)

This is an open-label study.

Statistical methods

Hypotheses were to be tested using a MTP with an alpha-exhaustive recycling strategy (Burman et al 2009). Upon achieving statistical significance on the primary endpoint rPFS in Cohort A, testing of each of the secondary endpoints, ORR (Cohort A), rPFS (Cohort A+B), time to pain progression (Cohort A), and overall survival (Cohort A) were to be performed sequentially with the 2-sided 5% level of alpha recycled from the primary rPFS (Cohort A) endpoint. This testing procedure was to stop when the entire test mass is allocated to non-rejected hypotheses. Implementation of this pre-defined ordered testing procedure, including recycling, was to strongly control type I error at 5% (2-sided), among all key hypotheses.

Analysis populations

- **Full analysis set (FAS)** (all randomised patients) for analysis of the efficacy and HRQoL endpoints (except for ORR, duration of response [DoR] and best overall response [BoR])
- **Patients evaluable for response (EFS):** a subset of the FAS population who had measurable disease at baseline as per the RECIST 1.1 criteria (the EFR analysis set) for the analysis of ORR, DoR and BoR
- **Safety analysis set (SAS):** All patients who were randomised as part of the global enrolment and received at least one dose of randomised study treatment in Cohort A or in Cohort B were included in the safety analysis set (SAS) in their respective cohorts.
- **Safety Switch Analysis Set:** All patients randomised to investigator choice, who received at least one dose of study treatment in Cohort A or in Cohort B, who subsequently switched to olaparib upon progression and received at least one dose of olaparib were included in the safety switch analysis set.

Analysis methods

The study was designed to provide at least 95% power to demonstrate a statistically significant difference in rPFS at a 2-sided alpha level of 5% assuming a true treatment effect was indicated by a hazard ratio (HR) of 0.53 in Cohort A.

- **rPFS**

  Primary analysis

  The rPFS analysis was planned for when approximately 143 events (confirmed by BICR) had occurred in Cohort A.

  rPFS was defined as the time from randomization until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the subject withdraws from randomized therapy or receives another anti-cancer therapy prior to progression.

  Objective progression in soft tissue by RECIST 1.1 was defined as a ≥20% increase in the sum of the diameters of the target lesions (compared to previous minimum sum) and an absolute increase of ≥5 mm, or an overall non-target lesions assessment of progression or a new lesion. Patients had tumour assessments at baseline and every 8 weeks relative to the date of randomisation until objective radiological disease progression by BICR.

  Bone lesions were assessed by bone scan using PCWG-3 (prostate cancer working group 3). If 2 or more new metastatic bone lesions were observed compared to the 8-week assessment, the confirmatory scan performed at least 6 weeks later and preferably at the next scheduled assessment, must have shown the persistence of or an increase in the number of metastatic bone lesions compared to the prior scan for progression to be documented.

  rPFS was analysed using a log-rank test. Patients who had not progressed (defined as complete response [CR], partial response [PR] or stable disease [SD] by RECIST 1.1 for soft tissue disease, or non-progressive disease [PD] for bone disease) or died at the time of analysis were censored at the time of the earliest date of their last evaluable RECIST 1.1 assessment (taking the latest target lesion, non-target lesion or new lesion scan date) or bone scan assessment that showed non-PD. If performed at the same visit, the latest of the previous RECIST 1.1 assessment or bone scan assessment was used.

Table 10: Primary endpoint and sensitivity analyses

Endpoints analysed	Cohort	Notes
Radiologic progression-free survival	Cohort A Cohort B Cohort A+B	• Stratified log-rank test: -Primary analysis (based on BICR [RECIST 1.1 and PCWG3] assessments and stratified in accordance with the pooling strategy defined in section 4.2.2 • Hazard ratio using Cox proportional hazards model (with ties=Efron and the stratification variables determined by the pooling strategy as covariates) • Plots and summaries of number (%) patients with progression or death events using Kaplan-Meier (KM) method. • Stratified log tank test and cox proportional hazards model will be repeated for confirmed FMI F1CDx patients and confirmed myriad *gBRCA*m patients. • KM plot will be produced for confirmed FMI F1CDx patients and confirmed myriad *gBRCA*m patients.
rPFS sensitivity analysis: (a) Evaluation-time bias (b) Attrition bias (c) Censoring bias (d) Ascertainment bias (e) Sensitivity analysis using unequivocal clinical progression in addition to radiological progression (f) Sensitivity analysis for confirmation of bone progression (g) Sensitivity analysis censoring patients with subsequent therapy or discontinuation of study drug	Cohort A Cohort B Cohort A+B	• Stratified log-rank test stratified in accordance with the pooling strategy (all sensitivity analyses except for censoring bias) • Hazard ratio using Cox proportional hazards model with ties=Efron and the stratification variables determined by the pooling strategy as covariates (all sensitivity analyses except for censoring bias) • KM plot (censoring bias and ascertainment

Subgroup analysis

The following subgroups of the FAS in Cohort A and Cohort A+B were analysed for rPFS for stratification factors:

- Previous taxane use (yes, no)
- Measurable disease at baseline (yes, no)

Values collected on the eCRF were used to define subgroups for stratification factors. Additional subgroups of interest included:

- HRR gene mutations using all patients (Cohort A+B) in the FAS; each individual gene and pre-specified combinations
- Metastases at baseline: bone only vs visceral vs other - Cohort A and Cohort A+B
- ECOG performance status at baseline (0, 1 or 2) - Cohort A and Cohort A+B
- Age at randomisation (<65, ≥65) - Cohort A and Cohort A+B

- Region (Asia, Europe, North and South America) - Cohort A and Cohort A+B
- Race (White, Black/African-American, Asian, Other) - Cohort A and Cohort A+B
- Baseline prostate-specific antigen (PSA; above/below median baseline PSA of the patients across both treatment groups) - Cohort A and Cohort A+B

- **Confirmed ORR** assessed based on **BICR** assessed RECIST and bone scan data using PCWG-3 only patients with measurable disease (target lesions) at entry were to be included in the analysis. A patient was classified as a responder if the RECIST 1.1 criteria for a CR or PR are satisfied (as well as the absence of confirmed progression on bone scan assessed by PCWG-3) at any time up to and including the defined analysis cut-off point. For each treatment group, the ORR was the number of patients with a CR and PR divided by the number of patients in the treatment group in the FAS with measurable disease at baseline.

- **TTPP,** analysed using log-rank test. Pain was assessed using Brief Pain Inventory – Short Form [BPI-SF] worst pain [Item 3] and quantified with a 0 to 10 numeric rating scale (NRS) where 0="no pain" and 10="worst pain imaginable". An analgesic log in ePRO handheld devices was used by subjects to electronically record all analgesic medication doses and dosage times to track pain medication use. Only changes in opiate use were considered in pain progression evaluation. Opiates taken by patients were converted into oral morphine equivalents (OME) as defined by Chung et al using the Analgesic Quantification Algorithm (AQA). For each visit or time point, pain score and opiate analgesic use (AQA score) were averaged over 7 days of assessments. A minimum of 4 days assessments was required to compute the average pain score. Pain progression was defined as an increase of 2 or more points from baseline in average BPI-SF worst pain [Item 3] score on the 0 to 10 NRS.

- **OS** was defined as the time from the date of randomisation until death due to any cause. Any patient not known to have died at the time of analysis was censored based on the last recorded date on which the patient was known to be alive. An interim analysis of OS was carried out at the time of the rPFS analysis, with the final OS analysis scheduled to take place when approximately 146 deaths have occurred (61% maturity) in Cohort A, which is estimated to occur in 2Q2020. Exploratory analyses of OS in Cohort A, adjusting for impact of subsequent PARP inhibitor trial or treatment (or other potentially active investigational agents), may be performed if a sufficient proportion of patients switch.

In PROfound, pre-specified sensitivity analyses to the main analyses of rPFS, confirmed ORR, TTPP and OS were performed in the subset of patients whose qualifying gene mutation status was confirmed positive according to the testing QC metrics and mutation classification process approved for the FMI F1CDx test or the subset of patients whose gBRCAm status was confirmed by the Myriad test. The FMI F1CDx subgroup analysis was performed for Cohort A, Cohort B and Cohort A+B; however, the Myriad gBRCAm subroup analysis was performed for Cohort A+B only.

- **Time to first Symptomatic Skeletal-Related Event SSRE**

Time to first Symptomatic Skeletal-Related Event	Cohort A Cohort A+B	• Stratified log-rank test stratified in accordance with the pooling strategy • Hazard ratio using a Cox proportional hazards model (with ties=Efron and the stratification variables determined by the pooling strategy as covariates) • Plots and summaries of number (%) patients with events using KM method.

- **DoR**

Duration of Response: • Confirmed response • Unconfirmed response	Cohort A Cohort B Cohort A+B	• Summarized using descriptive statistics • KM plots

- **Time to Opiate use for Cancer related Pain**

Time to Opiate use for Cancer related Pain	Cohort A Cohort A+B	• Stratified log-rank test stratified in accordance with the pooling strategy • Hazard ratio using a Cox proportional hazards model (with ties=Efron and the stratification variables determined by the pooling strategy as covariates) • Plots and summaries of number (%) patients with events using KM method.

- **Prostate specific antigen (PSA) response**

Prostate Specific Antigen (PSA) Response	Cohort A
	Cohort A+B
		• Summarized using descriptive statistics
		• Waterfall plots
		  • Best percentage change from baseline
		  • Percentage change from baseline at Week 12
		• Confirmed PSA best response presented with 95% CIs

- **Circulating Tumour Cell (CTC) conversion rate**

Circulating Tumor Cell (CTC) conversion rate	Cohort A
	Cohort A+B
		• Summarized using descriptive statistics
		• Waterfall plots
		  • Best change from baseline
		  • Best percentage change from baseline
		• Proportion of patients achieving CTC conversion at any time presented with 95% CIs

- **PFS2**

Time from randomization to second progression or death	Cohort A Cohort A+B	• Stratified log-rank test stratified in accordance with the pooling strategy • Hazard ratio using a Cox proportional hazards model (with ties=Efron and the stratification variables determined by the pooling strategy as covariates) • Plots and summaries of number (%) patients with events using KM method.

Results

Results from cohort B are not presented.

Participant flow

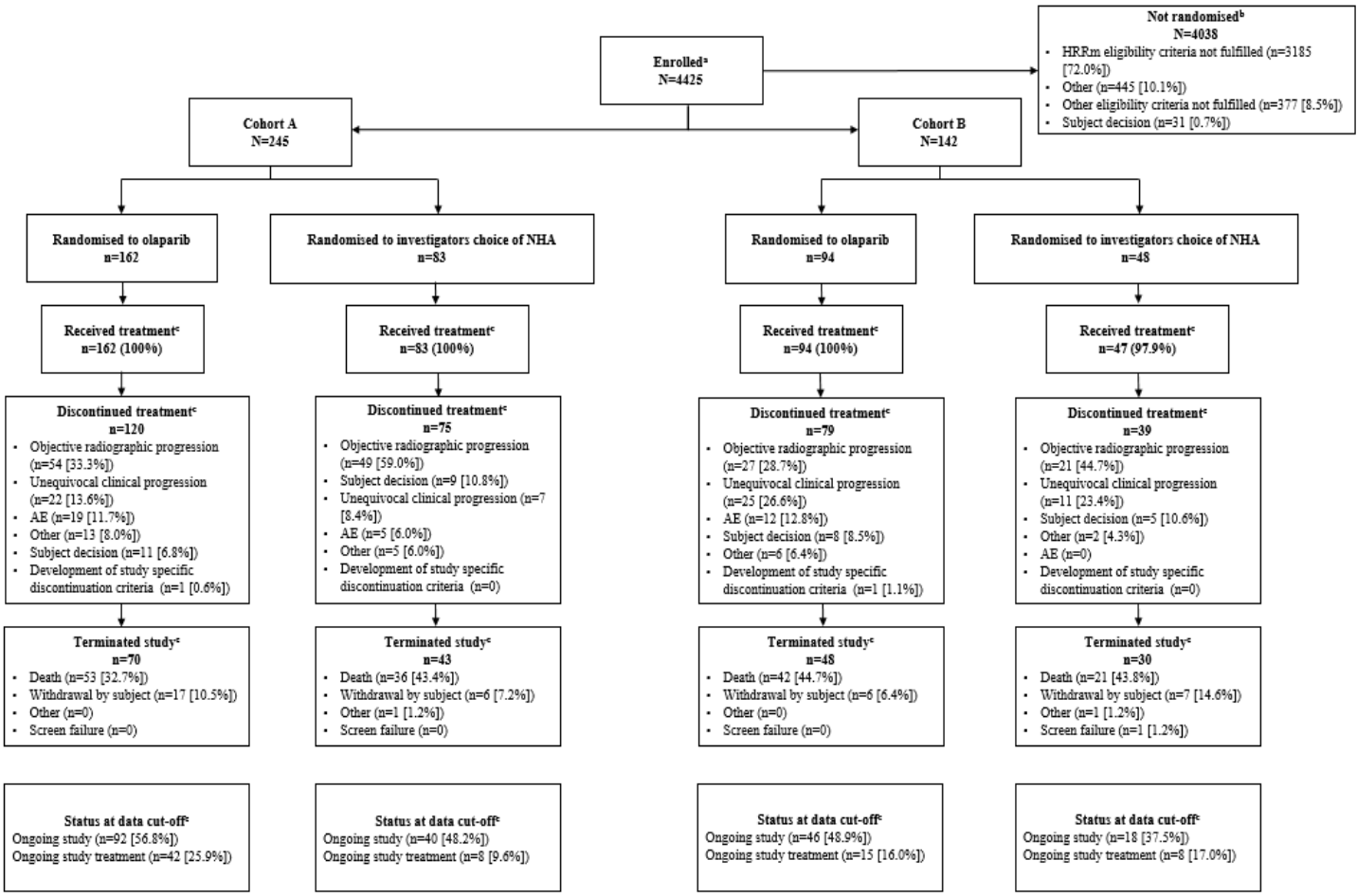


Figure 9: Patient disposition (all patients)

a Main informed consent received.
b Percentages were calculated from the number of patients signing the main ICF.
c Percentages were calculated from the number of patients randomised.
AE adverse event; HRRm homologous recombination repair gene mutated; ICF informed consent form; NHA new hormonal agent.

Table 11. Patient disposition (Cohort A)

	Number (%) of patients		
	Olaparib 300 mg bd	**Investigators choice of NHA**	**Total**
Patients randomised	162 (100)	83 (100)	245 (100)
Patients who were not randomised[a]			4038
Patient decision			31
HRRm eligibility criteria not fulfilled			3185
Other eligibility criteria not fulfilled			377
Other			445[b]
Full analysis set[c]	162 (100)	83 (100)	245 (100)
Patients who received study treatment	162 (100)	83 (100)	245 (100)
Enzalutamide		37 (44.6)	
Abiraterone		46 (55.4)	
Patients who did not receive study treatment	0	0	0
Patients ongoing study treatment at DCO[c]	42 (25.9)	8 (9.6)	50 (20.4)
Patients who discontinued study treatment[c]	120 (74.1)	75 (90.4)	195 (79.6)
Adverse event	19 (11.7)	5 (6.0)	24 (9.8)
Objective radiographic progression	54 (33.3)	49 (59.0)	103 (42.0)
Unequivocal clinical progression	22 (13.6)	7 (8.4)	29 (11.8)
Patient decision	11 (6.8)	9 (10.8)	20 (8.2)
Development of study specific discontinuation criteria	1 (0.6)	0	1 (0.4)
Other	13 (8.0)	5 (6.0)	18 (7.3)
Patients ongoing study at DCO[c]	92 (56.8)	40 (48.2)	132 (53.9)
Patients who withdrew from the study[c]	70 (43.2)	43 (51.8)	113 (46.1)
Patient decision	17 (10.5)	6 (7.2)	23 (9.4)
Death	53 (32.7)	36 (43.4)	89 (36.3)
Other	0	1 (1.2)	1 (0.4)

a) Percentages were calculated from number of patients signing the main ICF.
b) Investigator selected 'Other' on the eCRF. Reasons included (but were not limited to): patient was HRRm negative; HRRm positive results were received after Screening Period 2 closed; patient died; patient had not had radiological progression with the ongoing treatment; patient withdrew consent prior to Screening Period 2).
c) Percentages were calculated from number of patients randomised.
bd twice daily; DCO data cut off; eCRF electronic case report form; HRRm homologous recombination repair gene mutated; ICF informed consent form; NHA new hormonal agent.

Recruitment

This was an international multicentre study conducted in 206 study centres in 20 countries (of these, 139 centres randomised patients): Argentina (6 sites), Australia (10 sites), Austria (5 sites), Brazil (14 sites), Canada (12 sites), Denmark (1 site), France (13 sites), Germany (15 sites), Israel (6 sites), Italy (10 sites), Japan (30 sites), Netherlands (6 sites), Norway (1 site), South Korea (9 sites), Spain (7 sites), Sweden (2 sites), Taiwan (9 sites), Turkey (8 sites), United Kingdom (5 sites) and United States (37 sites).

First subject enrolled: 06 February 2017

Last patient enrolled: 18 September 2018

Data cut-off date: 04 June 2019

The analyses presented in this report are based on a data cut-off date of 4 June 2019 and a database lock date of 15 July 2019.

Conduct of the study

Protocol amendments

Table 12. 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	Person(s)/ group(s) responsible for amendment[a]
Amendments made after the start of patient recruitment			
3.0 (4 June 2018)	Exploratory endpoints were added to compare the effect of olaparib versus investigator's choice of treatment in patients with *BRCA1*, *BRCA2*, *ATM* or HRR qualifying mutations as detected by ctDNA analysis	To assess the validity of using ctDNA analysis.	Study delivery team
	Inclusion criterion 5 was updated to clarify patients were to have progressed on prior NHA for the treatment of metastatic prostate cancer and/or CRPC; previously this was mCRPC only	To clarify that patients were to have metastatic or non-metastatic CRPC: previously this was mCRPC only.	Study delivery team
	Inclusion criterion 10 was updated to state creatinine clearance could be estimated by Cockcroft-Gault equation for males or based on a 24 hour urine test	To allow determination of creatinine clearance by 24 hour urine test as well as Cockcroft-Gault equation.	Study delivery team

	Exclusion criterion 5 was updated to clarify that patients could have received prior treatment with DNA-damaging cytotoxic chemotherapy for non-prostate cancer	To clarify that patients could have received previous treatment with DNA-damaging cytotoxic chemotherapy for non-prostate cancer if the last dose was given >5 years prior to randomisation.	Study delivery team
	Exclusion criterion 8 was updated to define resting ECG limits	To update ECG requirements for entry into the study.	Study delivery team
	An optional blood sample for germline testing was added	To allow for future testing to explore diagnostic test development.	Study delivery team
4.0 (7 March 2019)	A potential cohort of 42 patients randomised in China was added Note: data from this cohort are not reported in this CSR.	To gather data in the Chinese population.	Study delivery team
	Access to olaparib after DCO for patients randomised to the comparator group was clarified	To clarify that access to olaparib for patients in the comparator arm was only possible upon BICR-assessed progression, or after the DCO for the primary analysis, upon investigator-assessed radiological progression, prior to initiation of subsequent anti-cancer therapy.	Study delivery team

[a] All protocol amendments were approved by AstraZeneca before being submitted to a regulatory authority and/or an Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

ATM ataxia telangiectasia mutated; BICR blinded independent central review; *BRCA* breast cancer susceptibility gene; CRPC castration-resistant prostate cancer; CSR Clinical Study Report; ctDNA circulating tumour DNA; DCO data cut-off; ECG electrocardiogram; HRR homologous recombination repair; mCRPC metastatic castration-resistant prostate cancer; NHA new hormonal agent.

Changes to planned analyses

Table 13. Changes to planned analyses

Key details of change (Section of this report affected)	Reason for change	Person(s)/ group(s) responsible for change

Updated definitions and added information about how scores are derived for TTTP and endpoints using the BPI-SF	To allow the most appropriate statistical testing based on the data.	Study delivery team
Removed the text which required the 2 consecutive subsequent TTPP and BPI-SF assessments to be separated by 3-4 weeks. The requirement is 2 consecutive follow-up assessments (with at least 2 weeks between the end of the initial visit and the start of the subsequent visit)	To allow the most appropriate statistical testing based on the data.	Study delivery team
Added additional information for the imputation rules for OME and AQA scores	To describe how missing data was imputed.	Study delivery team
Specified that there needs to be at least 5 responses to perform logistic regression analyses throughout, otherwise a fisher's exact test will be used	To allow the most appropriate statistical testing based on the data.	Study delivery team
Added evaluable for response (EFR) analysis set for Cohort A, B and A+B (for ORR, DoR and BoR)	To allow assessment of data in patients in the FAS who had measurable disease at baseline.	Study delivery team
Updated the rPFS censoring approach for censoring patients who have not progressed or died at the time of analysis and for censoring patients who progress or die immediately after 2 or more consecutive missed visits	The updated approach takes account of the earliest date of their last evaluable RECIST 1.1 assessment (taking the latest target lesion, non-target lesion or new lesion scan date) or bone scan assessment that showed fewer than two new lesions.	Study delivery team
Patients who have not experienced any symptomatic skeletal-related event will be censored at time of death or time of last SSRE assessment (not time of analysis if the patient is living)	To allow the most appropriate statistical testing based on the data.	Study delivery team
Updated the subgroup analysis to only provide descriptive statistics if there are less than 5 events across both treatment groups	To allow the most appropriate statistical testing based on the data.	Study delivery team

Added safety switch analysis set	To allow assessment of safety data in patients who received at least one dose of study treatment who subsequently switched to olaparib upon progression and received at least one dose of olaparib.	Study delivery team
Total Functional Assessment of Cancer Therapy - General (FACT-G) score, sum of PWB, SWB, EWB and FWB was added	To allow more complete assessment of HRQoL data.	Study delivery team
The protocol stated safety data (including adverse events, laboratory data, concomitant medications and exposure) will be summarised for Cohort A, Cohort B and Cohort A+B. This was updated in the SAP to be produced for Cohort A+B only	To allow safety data to be presented for the largest population.	Study delivery team

AQA Analgesic Quantification Algorithm; BoR best objective response; BPI-SF Brief Pain Inventory – Short Form; DoR duration of response; EFR evaluable for response; EWB emotional well-being; FAS full analysis set; FWB functional well-being; OME oral morphine equivalents; ORR objective response rate; PWB physical well-being; RECIST Response Evaluation Criteria in Solid Tumours; rPFS radiological progression-free survival; SAP Statistical Analysis Plan; SWB social well-being; TTPP time to pain progression.

Protocol deviations

The important protocol deviations were identified and classified prior to unblinding for the primary DCO (4 June 2019).

The number of patients with important protocol deviations in each treatment group of Cohort A, Cohort B and Cohort A+B are summarised in the tables below.

Table 14. Important protocol deviations (FAS; Cohort A)

	Number (%) of patients		
	Olaparib 300 mg bd (N=162)	**Investigators choice of NHA (N=83)**	**Total (N=245)**
Number of patients with at least 1 important deviation[a]	8 (4.9)	5 (6.0)	13 (5.3)
Met Exclusion Criteria: Participation in another clinical study with an investigational product during the last 30 days prior to randomisation.	2 (1.2)	0	2 (0.8)
Met Exclusion Criteria: Previous treatment with DNA damaging cytotoxic chemotherapy, except if for non-prostate cancer indication and last dose >5 years prior to randomisation.	1 (0.6)	0	1 (0.4)

Met Exclusion Criteria: Other malignancy (including MDS and MGUS) within the last 5 years (see exceptions)	1 (0.6)	0	1 (0.4)
Met Exclusion Criteria: Patients receiving any systemic anti-cancer therapy (except radiotherapy) within 3 weeks prior to study treatment	2 (1.2)	0	2 (0.8)
Met Exclusion Criteria: Concomitant use of known strong or moderate CYP3A inducers. The required washout period prior to starting olaparib was 5 weeks for phenobarbital and 3 weeks for other agents.	0	1 (1.2)	1 (0.4)
Study medication administration instructions not followed, as defined in CSP.	1 (0.6)	0	1 (0.4)
Patient switched to olaparib without meeting CSP Section 4.2.1 criteria (ie, BICR confirmed progression, written consent for switch to olaparib)	0	2 (2.4)	2 (0.8)
Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline. Study treatment should be discontinued and restarted per CSP (Section 7.7).	0	1 (1.2)	1 (0.4)
Baseline tumour asessment performed >42 days before start date of randomised treatment	1 (0.6)	1 (1.2)	2 (0.8)

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

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

bd twice daily; BICR blinded independent central review; CSP Clinical Study Protocol; CYP cytochrome P450; FAS full analysis set; MDS myelodysplastic syndrome; MGUS monoclonal gammopathy of unknown significance; NHA new hormonal agent; RECIST Response Evaluation Criteria in Solid Tumours.

Table 15. Important protocol deviations (FAS; Cohort A+B)

	Number (%) of patients		
	Olaparib 300 mg bd (N=256)	**Investigators choice of NHA (N=131)**	**Total (N=387)**
Number of patients with at least 1 important deviation[a]	20 (7.8)	10 (7.6)	30 (7.8)
Failed Inclusion Criteria: Radiographic progression at study entry while on androgen deprivation therapy (or after bilateral orchiectomy)	2 (0.8)	0	2 (0.5)
Failed Inclusion Criteria: ECOG performance status 0-2	0	1 (0.8)	1 (0.3)

Met Exclusion Criteria: Participation in another clinical study with an investigational product during the last 30 days prior to randomisation	3 (1.2)	0	3 (0.8)
Met Exclusion Criteria: Previous treatment with DNA damaging cytotoxic chemotherapy, except if for non-prostate cancer indication and last dose >5 years prior to randomisation	2 (0.8)	0	2 (0.5)
Met Exclusion Criteria: Other malignancy (including MDS and MGUS) within the last 5 years (see exceptions)	1 (0.4)	0	1 (0.3)
Met Exclusion Criteria: Resting ECG indicating uncontrolled, potentially reversible cardiac conditions, as judged by the investigator, or patients with congenital long QT syndrome	0	1 (0.8)	1 (0.3)
Met Exclusion Criteria: Patients receiving any systemic anti-cancer therapy (except radiotherapy) within 3 weeks prior to study treatment.	4 (1.6)	1 (0.8)	5 (1.3)
Met Exclusion Criteria: Concomitant use of known strong CYP3A inhibitors or moderate CYP3A inhibitors. The required washout period prior to starting olaparib was 2 weeks.	2 (0.8)	0	2 (0.5)
Met Exclusion Criteria: Concomitant use of known strong or moderate CYP3A inducers. The required washout period prior to starting olaparib was 5 weeks for phenobarbital and 3 weeks for other agents.	0	2 (1.5)	2 (0.5)
Study medication administration instructions not followed, as defined in the CSP.	1 (0.4)	0	1 (0.3)
Patient was assigned to the incorrect cohort	3 (1.2)	1 (0.8)	4 (1.0)

Baseline data

Demographic characteristics

Table 16. PROfound demographic characteristics - Cohort A+B and Cohort A (FAS) (DCO 04 June 2019)

		Cohort A+B		Cohort A	
		Olaparib 300 mg bd (N=256)	**Investigators choice of NHA (N=131)**	**Olaparib 300 mg bd (N=162)**	**Investigators choice of NHA (N=83)**
Age (years)	n[a]	256	131	162	83

	Mean	68.5	68.9	68.0	68.1
	std	8.44	7.58	8.23	7.36
	Median	69.0	69.0	68.0	67.0
	Min	47	49	47	49
	Max	91	87	86	86
Age group (years), n (%)	n[a]	256 (100)	131 (100)	162 (100)	83 (100)
	<65	82 (32.0)	34 (26.0)	54 (33.3)	23 (27.7)
	≥65	174 (68.0)	97 (74.0)	108 (66.7)	60 (72.3)
Race, n (%)	n[a]	256 (100)	131 (100)	162 (100)	83 (100)
	White	163 (63.7)	85 (64.9)	109 (67.3)	55 (66.3)
	Black or African American	7 (2.7)	1 (0.8)	2 (1.2)	1 (1.2)
	Asian	69 (27.0)	36 (27.5)	43 (26.5)	19 (22.9)
	Other	2 (0.8)	1 (0.8)	1 (0.6)	1 (1.2)
	Missing	15 (5.9)	8 (6.1)	7 (4.3)	7 (8.4)
Ethnic group, n (%)	n[a]	256 (100)	131 (100)	162 (100)	83 (100)
	Hispanic or Latino	17 (6.6)	12 (9.2)	12 (7.4)	9 (10.8)
	Not Hispanic or Latino	228 (89.1)	112 (85.5)	145 (89.5)	69 (83.1)
	Missing	11 (4.3)	7 (5.3)	5 (3.1)	5 (6.0)

Disease characteristics

Table 17. PROfound disease characteristics - Cohort A+B and Cohort A (FAS) (DCO 04 June 2019)

		Cohort A+B		Cohort A	
		Olaparib 300 mg bd (N=256)	**Investigators choice of NHA (N=131)**	**Olaparib 300 mg bd (N=162)**	**Investigators choice of NHA (N=83)**
Time from CRPC to randomisation (months)	Median	24.8	23.7	24.2	23.7
	Min, Max	-6, 189	1, 177	-6, 189	1, 175
Time from mCRPC to randomisation (months)	Median	23.3	21.9	23.3	22.5
	Min, Max	-6, 125	1, 105	-6, 121	1, 105
Histology type at diagnosis	Adenocarcinoma	253 (98.8)	127 (96.9)	160 (98.8)	80 (96.4)
	Small cell carcinoma	0	0	0	0
	Other	1 (0.4)	3 (2.3)	0	2 (2.4)
	Missing	2 (0.8)	1 (0.8)	2 (1.2)	1 (1.2)
	2	1 (0.4)	0	1 (0.6)	0

Total Gleason Score at diagnosis	3	0	0	0	0
	4	2 (0.8)	0	2 (1.2)	0
	5	2 (0.8)	1 (0.8)	2 (1.2)	1 (1.2)
	6	6 (2.3)	4 (3.1)	6 (3.7)	3 (3.6)
	7	57 (22.3)	27 (20.6)	41 (25.3)	22 (26.5)
	8	61 (23.8)	28 (21.4)	36 (22.2)	12 (14.5)
	9	101 (39.5)	56 (42.7)	59 (36.4)	35 (42.2)
	10	21 (8.2)	11 (8.4)	10 (6.2)	7 (8.4)
	Missing	5 (2.0)	4 (3.1)	5 (3.1)	3 (3.6)
Sites of disease at baseline[b]	Total	255 (99.6)	131 (100)	162 (100)	83 (100)
	Prostate	41 (16.0)	21 (16.0)	27 (16.7)	12 (14.5)
	Locoregional lymph nodes	54 (21.1)	31 (23.7)	35 (21.6)	17 (20.5)
	Distant lymph nodes	99 (85.2)	51 (38.9)	59 (36.4)	35 (42.2)
	Bone	218 (85.2)	113 (86.2)	140 (86.4)	73 (88.0)
	Respiratory	43 (16.8)	15 (11.5)	30 (18.5)	11 (13.3)
	Liver	25 (9.8)	18 (13.7)	18 (11.1)	13 (15.7)
	Other distant sites	57 (22.2)	31 (23.7)	34 (21.0)	15 (18.1)
	Bone only	65 (25.4)	36 (27.5)	42 (25.9)	25 (30.1)
	Lymph node only	18 (7.0)	9 (6.9)	13 (8.0)	5 (6.0)
	Bone and lymph node only	46 (18.0)	19 (14.5)	26 (16.0)	14 (16.9)
ECOG PS at baseline	(0) Fully active	131 (51.2)	55 (42.0)	84 (51.9)	34 (41.0)
	(1) Restricted in physically strenuous activity	112 (43.8)	71 (54.2)	67 (41.4)	46 (55.4)
	(2) Ambulatory and capable of self-care	13 (5.1)	4 (3.1)	11 (6.8)	3 (3.6)
	(3) Capable of only limited self-care	0	0	0	0
	(4) Completely disabled	0	0	0	0
	Missing	0	1 (0.8)	0	0
Baseline pain (BPI-SF worst pain [Item 3]) score	0 to <2	125 (48.8)	57 (43.5)	83 (51.2)	37 (44.6)
	2 to 3	31 (12.1)	13 (9.9)	17 (10.5)	9 (10.8)
	>3	93 (36.3)	56 (42.7)	56 (34.6)	34 (41.0)
	Missing	7 (2.7)	5 (3.8)	6 (3.7)	3 (3.6)
Baseline PSA (µg/L)	Median	68.220	106.490	62.180	112.920
	Min, Max	0.20, 7240.74	1.85, 7115.00	0.20, 7240.74	1.85, 7115.00
Baseline Hb (g/L)	n	256	130	162	83
	Mean (std)	122.3 (12.96)	120.7 (13.89)	122.6 (12.87)	122.5 (13.95)

Baseline alkaline phosphatase (U/L)	n	256	130	162	83
	Mean (std)	163.3 (192.43)	170.7 (183.49)	172.2 (201.75)	182.7 (203.14)
Baseline lactate dehydrogenase (U/L)	n	252	127	160	80
	Mean (std)	258.2 (224.61)	261.4 (169.39)	268.0 (254.07)	267.3 (185.02)
Patient positive by F1 CDx test	Yes	248 (96.9)	128 (97.7)	157 (96.9)	83 (100.0)
	No	8 (3.1)	3 (2.3)	5 (3.1)	0
Patient positive by Myriad germline test	Yes	43 (16.8)	19 (14.5)	43 (26.5)	19 (22.9)
	No	213 (83.2)	112 (85.5)	119 (73.5)	64 (77.1)
Measurable disease at baseline[C]	Yes	149 (58.2)	72 (55.0)	95 (58.6)	46 (55.4)
	No	107 (41.8)	59 (45.0)	67 (41.4)	37 (44.6)
Received prior taxane therapy[C]	Yes	170 (66.4)	84 (64.1)	106 (65.4)	52 (62.7)
	No	86 (33.6)	47 (35.9)	56 (34.6)	31 (37.3)
Personal history of second malignancy apart from prostate cancer	Yes	24 (9.4)	13 (9.9)	14 (8.6)	10 (12.0)
	No	232 (90.6)	118 (90.1)	148 (91.4)	73 (88.0)
Family history of prostate cancer	Yes	56 (21.9)	23 (17.6)	33 (20.4)	16 (19.3)
	No	200 (78.1)	108 (82.4)	129 (79.6)	67 (80.7)
Family history of other cancers	Yes	130 (50.8)	61 (46.6)	88 (54.3)	40 (48.2)
	No	126 (49.2)	70 (52.4)	74 (45.7)	43 (51.8)

- n refers to the number of patients with non-missing data.
- As per investigator assessment.
- Derived from electronic case report data.

bd Twice daily; BPI-SF Brief Pain Inventory Short Form; CRPC Castration-resistant prostate cancer; CSR Clinical Study Report; DCO Data cut-off; ECOG Eastern Cooperative Oncology Group; FAS Full Analysis Set; Hb Haemoglobin; mCRPC Metastatic castration-resistant prostate cancer; Max Maximum; Min Minimum; NHA New hormonal agent; PS Performance status; PSA Prostate-specific antigen; std standard deviation.

Previous treatments

Table 18. Previous disease-related treatment modalities - Cohort A+B and Cohort A (FAS) (DCO 04 June 2019)

	Cohort A+B		Cohort A	
	Olaparib 300 mg bd (N=256)	**Investigators choice of NHA (N=131)**	**Olaparib 300 mg bd (N=162)**	**Investigators choice of NHA (N=83)**

Patients with any previous treatment modalities	256 (100)	131 (100)	162 (100)	83 (100)
Immunotherapy	18 (7.0)	11 (8.4)	13 (8.0)	7 (8.4)
Hormonal therapy	256 (100)	131 (100)	162 (100)	83 (100)
Prior NHA	251 (98) [a]	131 (100)	160 (98.8)[a]	83 (100)
Enzalutamide	103 (40.2)	54 (41.2)	67 (41.4)	40 (48.2)
Abiraterone	97 (37.9)	54 (41.2)	61 (37.7)	29 (34.9)
Enzalutamide and abiraterone	51 (19.9)	23 (17.6)	32 (19.8)	14 (16.9)
Local therapy with curative intent for prostate cancer[b]	105 (41.0)	57 (43.5)	71 (43.8)	31 (37.3)
Radical prostatectomy	70 (27.3)	29 (22.1)	51 (31.5)	16 (19.3)
Definitive radiotherapy on prostate	0	0	0	0
Taxane chemotherapy	170 (66.4)	84 (64.1)	106 (65.4)	52 (62.7)
Platinum chemotherapy[c]	1 (0.4)	0	0	0
Taxane treatment at mCRPC	147 (57.4)	73 (55.7)	91 (56.2)	43 (51.8)
Prior docetaxel	95 (37.1)	48 (36.6)	60 (37.0)	24 (28.9)
Prior cabazitaxel	13 (5.1)	2 (1.5)	5 (3.1)	1 (1.2)
Prior docetaxel and cabazitaxel	39 (15.2)	23 (17.6)	26 (16.0)	18 (21.7)
No taxane treatment at mCRPC	109 (42.6)	58 (44.3)	71 (43.8)	40 (48.2)
Radiotherapy (any)	173 (67.6)	85 (64.9)	102 (63.0)	55 (66.3)
Other	72 (28.1)	45 (34.4)	42 (25.9)	25 (30.1)

a. All patients met the inclusion criteria for prior NHA treatment, however for 2 patients, the data on prior NHA treatment was not present in the eCRF at database lock.

b. Local therapy with curative intent for prostate cancer categories were not mutually exclusive.
c. Prior platinum-based chemotherapy for prostate cancer was an exclusion criterion in this study. Patients could be counted in >1 previous disease-related modality.

bd twice daily; eCRF electronic case report form; FAS full analysis set; NHA new hormonal agent.

Data derived from Table 14.1.6.1 and Table 14.1.8.1.

Patients with BRCA1m/BRCA2m

Median age was 68 years and 67 years in the olaparib and comparator arms, respectively. Prior therapy in the olaparib arm was 71% taxane, 41% enzalutamide, 37% abiraterone acetate and 20% both enzalutamide and abiraterone acetate. Prior therapy in the comparator arm was 60% taxane, 50% enzalutamide, 36% abiraterone acetate and 14% both enzalutamide and abiraterone acetate. Fifty-eight percent (58%) of patients in the olaparib arm and 55% in the comparator arm had measurable disease at study entry. The proportion of patients with bone, lymph node, respiratory and liver metastases was 89%, 62%, 23% and 12%, respectively in the olaparib arm and 86%, 71%, 16% and 17%, respectively in the comparator arm. Most patients in both treatment arms had an ECOG of 0 or 1 (93%). Baseline pain scores (BPI-SF worst pain) were 0-<2 (52%), 2-3 (10%) or >3 (34%) in the olaparib arm and 0-<2 (45%), 2-3 (7%) or >3 (45%) in the comparator arm. Median baseline PSA was 57.48 µg/L in the olaparib arm and 103.95 µg/L in the comparator.

Numbers analysed

Table 19. Analysis sets (Cohort A)

	Number of patients		
	Olaparib 300 mg bd (N=162)	**Investigators choice of NHA (N=83)**	**Total (N=245)**
Patients randomised	162	83	245
Patients included in FAS	162	83	245
Patients included in EFR analysis set (BICR)	84	43	127
Patients included in EFR analysis set (investigator)	95	46	141
Patients included in SAS	162	83	245
Patients excluded from SAS[a]	0	0	0
Did not receive treatment	0	0	0
Patients included in PK analysis set[b]	34	0	34
Patients excluded from PK analysis set[a, b]	128	83	211
Did not receive treatment	0	0	0
No post-dose analysable plasma sample	11	0	11
Major protocol deviations	0	0	0
No PK sample available	117	0	117
Patients included in safety switch analysis set	0	50	50

a) An individual patient could have been excluded for more than 1 reason.

b) Per protocol, PK samples were only collected for a subset of patients in the olaparib arm and therefore, no patients in the investigators choice of NHA arm were included in the PK analysis set.

bd twice daily; BICR blinded independent central review; EFR evaluable for response; FAS full analysis set; NHA new hormonal agent; PK pharmacokinetic; SAS safety analysis set.

Data derived from Table 14.1.3.1.

Table 20. Analysis sets (Cohort A+B)

	Number of patients		
	Olaparib 300 mg bd (N=256)	**Investigators choice of NHA (N=131)**	**Total (N=387)**
Patients randomised	256	131	387
Patients included in FAS	256	131	387
Patients included in EFR analysis set (BICR)	138	67	205
Patients included in EFR analysis set (investigator)	149	72	221
Patients included in SAS	256	130	386
Patients excluded from SAS[a]	0	1	1
Did not receive treatment	0	1	1
Patients included in PK analysis set[b]	60	0	60
Patients excluded from PK analysis set[a, b]	196	131	327
Did not receive treatment	0	0	0
No post-dose analysable plasma sample	19	0	19
Major protocol deviations	0	0	0
No PK sample available	177	0	177
Patients included in safety switch analysis set	0	72	72

a) An individual patient could have been excluded for more than 1 reason.

b) Per protocol, PK samples were only collected for a subset of patients in the olaparib arm and therefore, no patients in the investigators choice of NHA arm were included in the PK analysis set.

bd twice daily; BICR blinded independent central review; EFR evaluable for response; FAS full analysis set; NHA new hormonal agent; PK pharmacokinetic; SAS safety analysis set.

Data derived from Table 14.1.3.1.

HRR testing results

- **Screening part 1**

Overall, 4425 patients were screened for inclusion into PROfound. Samples from 4069 patients were received at Foundation Medicine and 356 screened patients did not supply a sample. Of the 4069 patients who supplied a sample, 4047 patients were eligible for testing and were tested for their tHRR status at Foundation Medicine for the PROfound study and 22 patients were ineligible for testing.

The 4047 patients tested at FMI include 12 (0.3%) patients (who had a prior FoundationOne test that was confirmed by CLIA HRR CTA testing or data re-analysis and 4035 (99.7%) patients who were prospectively tested using the CLIA HRR CTA.

Out of these 4035 patients:

- 2780 patients (68.9%) had a valid CLIA HRR CTA test result.

- 767 patients were reported as having a mutation detected in one or more of the HRR gene panel members. A total of **380 prospectively tested tHRRm patients** were randomised onto the PROfound study and 387 patients were screen failed for non-testing related reasons. Overall, 27.6% (767/2780) successfully tested patients were determined as tHRRm.
- 2013 patients were reported as having no qualifying mutation detected in all of the 15 HRR gene panel members and as a result were screen failed for PROfound

- 1255 patients were reported as a failed CLIA HRR CTA test. Reasons for failures were split into 3 categories: pathology review, DNA extraction and Post DNA extraction (sequencing workflow including data interpretation). Some of the patients failed due to more than one reason. The primary reasons for failures among the 1255 patients reported as FAIL were as follows: Note: some patients supplied more than one sample and the multiple supplied samples failed for different reasons, these patients are summarised in a separate category:
  - 277 (22.1 %) patients failed due to not meeting pathology review criteria.
  - 533 (42.5%) patients failed DNA extraction failure criteria.
  - 280 (22.3 %) patients failed post DNA extraction criteria.
  - 165 (13.1%) patients failed for more than one of the categories above.
- In addition to patients who failed testing, 315 patients were initially reported as failed by the CLIA HRR CTA test but subsequently had another tissue sample tested which was successful. The reasons for reported failure of the first test was were as follows
  - 100 (31.7%)8%) out of these 315 patients failed due to not meeting pathology review criteria.
  - 119 (37.8%) patients failed DNA extraction failure criteria.
  - 81 (25.7%) patients failed post DNA extraction criteria.
  - 15 (4.8%) patients failed for more than one of the categories above.

Overall, 4035 samples from 4425 screened patients were prospectively tested in PROfound. The prospective sample **testing success rate was 68.9%** (2780/4035).

In total, **387** patients were randomised using either a prospectively generated CLIA HRR CTA tHRRm test result (n = 380, 98.2%) or a confirmed FoundationOne tHRRm test result (n = 7, 1.8%).

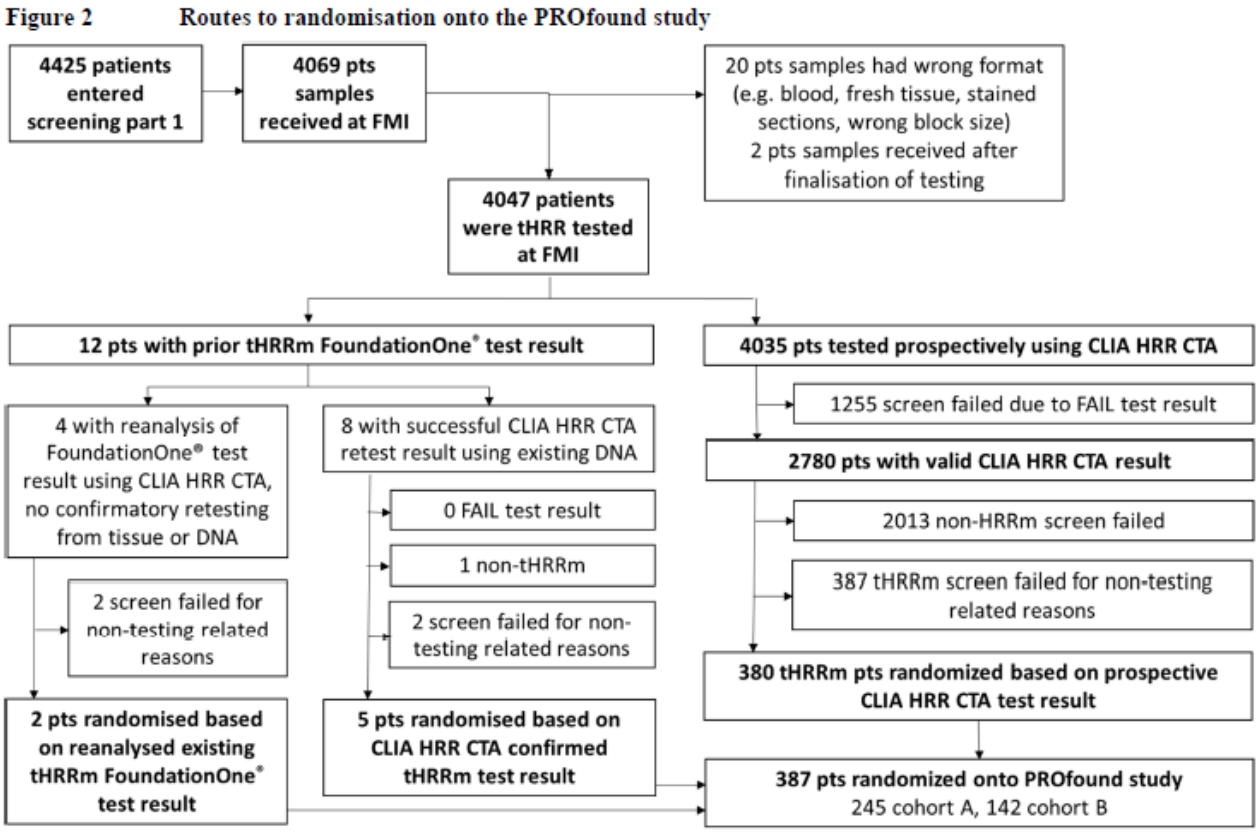


Figure 10: Routes to randomisation onto the PROfound study

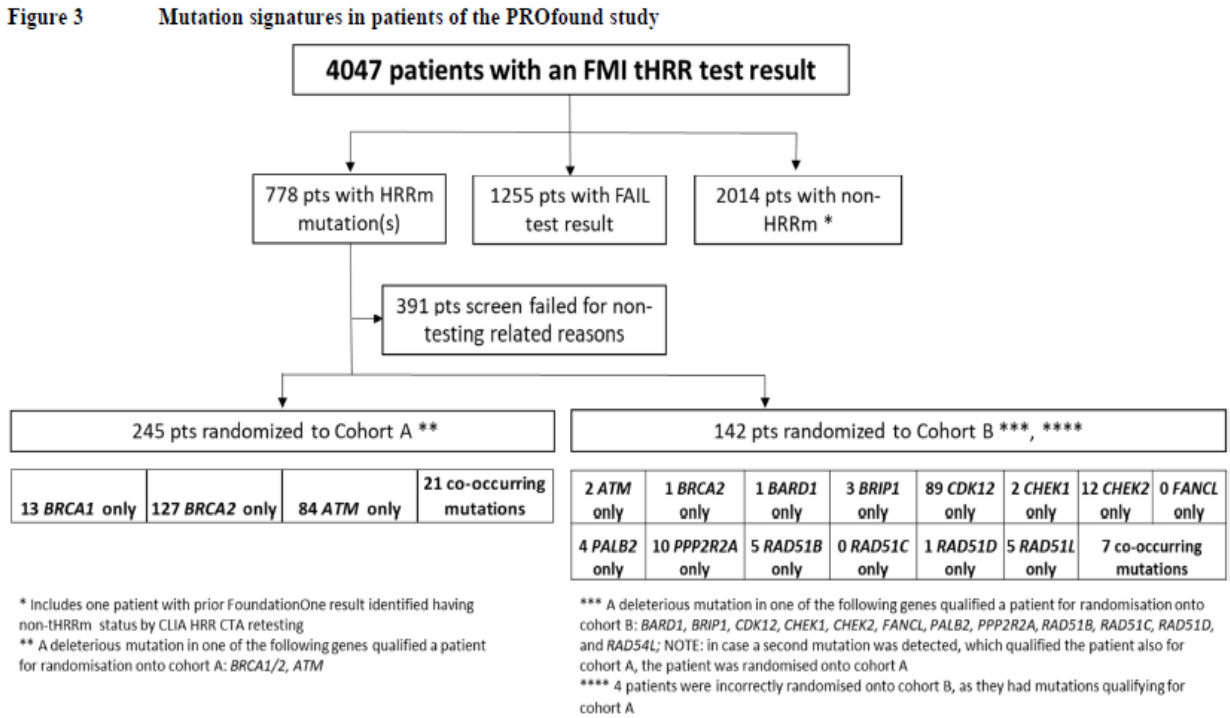


Figure 11: Mutation signatures in patients of the PROfound study

Four patients were incorrectly assigned to Cohort B (1 BRCA2 [olaparib], 1 BRCA2+CDK12 (investigators choice of NHA) and 2 ATM [both olaparib]).

Of the 224 patients in Cohort A with a single mutation, approximately two thirds of patients had a BRCA1 or BRCA2 mutation alone and one third of patients had an ATM mutation alone. Of the 135 patients in Cohort B with a single mutation, two thirds of patients had a CDK12 mutation alone. The remaining one third of patients had a single mutation in 1 of 9 HRR genes (BARD1, BRIP1, CHEK1, CHEK2, PALB2, PPP2R2A, RAD51B, RAD51D and RAD54L). No patients in Cohort B had a FANCL or RAD51C mutation alone.

A total of 21 patients in Cohort A and 7 patients in Cohort B had co-occurring mutations.

Table 21. Patients with single HRR gene mutations (FAS)

Gene	Number (%) of patients								
	Cohort A			Cohort B			Cohort A+B		
	Olaparib 300 mg bd (N=148)	Investigators choice of NHA (N=76)	Total (N=224)	Olaparib 300 mg bd (N=91)	Investigators choice of NHA (N=44)	Total (N=135)	Olaparib 300 mg bd (N=239)	Investigators choice of NHA (N=120)	Total (N=359)
BRCA1	8 (5.4)	5 (6.6)	13 (5.8)	0	0	0	8 (3.3)	5 (4.2)	13 (3.6)
BRCA2	80 (54.1)	47 (61.8)	127 (56.7)	1 (1.1)	0	1 (0.7)	81 (33.9)	47 (39.2)	128 (35.7)
ATM	60 (40.5)	24 (31.6)	84 (37.5)	2 (2.2)	0	2 (1.5)	62 (25.9)	24 (20.0)	86 (24.0)
BARD1	0	0	0	0	1 (2.3)	1 (0.7)	0	1 (0.8)	1 (0.3)
BRIP1	0	0	0	2 (2.2)	1 (2.3)	3 (2.2)	2 (0.8)	1 (0.8)	3 (0.8)
CDK12	0	0	0	61 (67.0)	28 (63.6)	89 (65.9)	61 (25.5)	28 (23.3)	89 (24.8)
CHEK1	0	0	0	1 (1.1)	1 (2.3)	2 (1.5)	1 (0.4)	1 (0.8)	2 (0.6)
CHEK2	0	0	0	7 (7.7)	5 (11.4)	12 (8.9)	7 (2.9)	5 (4.2)	12 (3.3)
FANCL	0	0	0	0	0	0	0	0	0
PALB2	0	0	0	3 (3.3)	1 (2.3)	4 (3.0)	3 (1.3)	1 (0.8)	4 (1.1)
PPP2R2A	0	0	0	6 (6.6)	4 (9.1)	10 (7.4)	6 (2.5)	4 (3.3)	10 (2.8)
RAD51B	0	0	0	4 (4.4)	1 (2.3)	5 (3.7)	4 (1.7)	1 (0.8)	5 (1.4)
RAD51C	0	0	0	0	0	0	0	0	0

Only patients with a single HRR gene mutation were included.

ATM ataxia telangiectasia mutated; BARD1 BRCA1 associated ring domain protein; bd twice daily; BRCA breast cancer susceptibility gene; BRIP1 BRCA1 interacting protein C-terminal helicase 1; CDK12 cyclin-dependent kinase 12; CHEK1 checkpoint kinase 1; CHEK2 checkpoint kinase 2; FANCL FA complementation group; FAS full analysis set; HRR homologous recombination repair; NHA new hormonal agent; PALB2 partner and localizer of BRCA2; PPP2R2A protein phosphatase 2 regulatory subunit B alpha; RAD51B RAD51 paralog B; RAD51C RAD51 paralog C; RAD51D RAD51 paralog D; RAD54L RAD54 like.

Table 22. Patients with HRR gene co-mutations (FAS)

Gene	Number (%) of patients								
	Cohort A			Cohort B			Cohort A+B		
	Olaparib 300 mg bd (N=14)	Investigators choice of NHA (N=7)	Total (N=21)	Olaparib 300 mg bd (N=3)	Investigators choice of NHA (N=4)	Total (N=7)	Olaparib 300 mg bd (N=17)	Investigators choice of NHA (N=11)	Total (N=28)
BRCA1 and ATM	1 (7.1)	0	1 (4.8)	0	0	0	1 (5.9)	0	1 (3.6)
BRCA1 and *RAD54L*	1 (7.1)	0	1 (4.8)	0	0	0	1 (5.9)	0	1 (3.6)
BRCA2 and *CDK12*	2 (14.3)	2 (28.6)	4 (19.0)	0	1 (25.0)	1 (14.3)	2 (11.8)	3 (27.3)	5 (17.9)
BRCA2 and *ATM*	2 (14.3)	0	2 (9.5)	0	0	0	2 (11.8)	0	2 (7.1)
BRCA2 and *PPP2R2A*	1 (7.1)	2 (28.6)	3 (14.3)	0	0	0	1 (5.9)	2 (18.2)	3 (10.7)
BRCA2 and *CHEK2*	2 (14.3)	0	2 (9.5)	0	0	0	2 (11.8)	0	2 (7.1)
BRCA2 and *BARD1*	2 (14.3)	0	2 (9.5)	0	0	0	2 (11.8)	0	2 (7.1)
BRCA2 and *CDK12* and *CHEK2*	1 (7.1)	0	1 (4.8)	0	0	0	1 (5.9)	0	1 (3.6)
BRCA2 and *CHEK2* and *RAD51D*	1 (7.1)	0	1 (4.8)	0	0	0	1 (5.9)	0	1 (3.6)
BRCA2 and *RAD51B*	0	1 (14.3)	1 (4.8)	0	0	0	0	1 (9.1)	1 (3.6)
ATM and *PPP2R2A*	0	1 (14.3)	1 (4.8)	0	0	0	0	1 (9.1)	1 (3.6)
ATM and *CHEK2*	0	1 (14.3)	1 (4.8)	0	0	0	0	1 (9.1)	1 (3.6)
ATM and *RAD51B*	1 (7.1)	0	1 (4.8)	0	0	0	1 (5.9)	0	1 (3.6)
CDK12 and *PALB2*	0	0	0	1 (33.3)	1 (25.0)	2 (28.6)	1 (5.9)	1 (9.1)	2 (7.1)

CDK12 and *BARD1*	0	0	0	1 (33.3)	0	1 (14.3)	1 (5.9)	0	1 (3.6)
CDK12 and *CHEK1*	0	0	0	1 (33.3)	0	1 (14.3)	1 (5.9)	0	1 (3.6)
PALB2 and *BRIP1*	0	0	0	0	1 (25.0)	1 (14.3)	0	1 (9.1)	1 (3.6)
PALB2 and *PPP2R2A*	0	0	0	0	1 (25.0)	1 (14.3)	0	1 (9.1)	1 (3.6)

Only patients with at least 2 HRR gene mutations were included. Rows are mutually exclusive.
ATM ataxia telangiectasia mutated; *BARD1 BRCA1* associated ring domain protein; bd twice daily; *BRCA* breast cancer susceptibility gene; *BRIP1 BRCA1* interacting protein C-terminal helicase 1; *CDK12* cyclin-dependent kinase 12; *CHEK1* checkpoint kinase 1; *CHEK2* checkpoint kinase 2; *FANCL* FA complementation group; FAS full analysis set; HRR homologous recombination repair; NHA new hormonal agent; *PALB2* partner and localizer of *BRCA2*; *PPP2R2A* protein phosphatase 2 regulatory subunit B alpha; *RAD51B RAD51* paralog B; *RAD51C RAD51* paralog C; *RAD51D RAD51* paralog D; *RAD54L RAD54* like.

- **Screening part 2**
    - *Confirmed FMI F1CDx Subgroup*

Out of **387 patients randomised** based on the CLIA HRR CTA QC criteria and rules, application of the FoundationOneCDx QC criteria resulted in **6 patients (1.6%)** not passing QC criteria as they did not meet the minimum tissue volume requirements (≥0.6mm^3). Furthermore, **an additional 2 patients** were randomised solely on a prior FoundationOne result available without CLIA HRR CTA confirmatory results from tissue or DNA. Overall, therefore, there were **379 (97.9 %) patients** who had a result which would be considered as valid by applying the FoundationOneCDx QC criteria and 8 patients excluded due to low tissue volume (n=6) or due to not having a CLIA HRR CTA result (n=2).

For 379 patients with valid test results according to the FoundationOneCDx QC criteria a further **3 patients were excluded** from the confirmed FMI F1CDx subgroup as they had a BRCA mutation which was included in the curated mutation list for CLIA HRR CTA, but not included in the curated mutation list for FoundationOneCDx FDA approved CDx BRCA rules.

In total, **376/387 (97.2%)** randomised patients were considered as tHRRm according to the FoundationOneCDx QC and mutation classification rules. These patients comprise the Confirmed FMI F1CDx tHRRm subgroup. These 376 patients are assigned as follows:

- 240 patients in Cohort A
- 136 patients in Cohort B

    - *Confirmed Myriad gBRCAm subgroup*

Subjects confirmed to have a qualifying HRR gene mutation, were required to submit a blood sample for germline HRR gene analysis after successfully passing screening part 2. Of the 387 randomised patients, 354 patients had a blood sample available for testing.

As germline diagnostic development was not planned at the outset of PROfound, the main study consent did not include consent for development of a germline diagnostic, only germline testing was consented in the main study consent. To facilitate use of germline HRR gene data for companion diagnostic development, patients had to sign an optional consent for future medical research which did permit diagnostic development activities. Germline HRR testing to support companion diagnostic development, in patients who provided optional consent for future medical research, was performed at Myriad using the BRACAnalysis CDx and tested for BRCA1 and BRCA2 mutations only.

Out of the 288 patients who were germline tested and successfully reported at Myriad, a total of 62 patients were reported as carrying a deleterious or suspected deleterious germline mutation in BRCA1 and/or BRCA2 (61 Deleterious, 1 Suspected Deleterious). All gBRCAm patients were in Cohort A.

Of the tBRCAm patients tested for their gBRCA status, 61/114 carried a deleterious or suspected deleterious germline mutation according to Myriad's classification. Within the 174 patients who were non-tBRCAm, 1 patient was reported as gBRCAm. This patient was randomised into Cohort A on the basis of an ATM mutation detected by prospective testing using the CLIA HRR CTA.

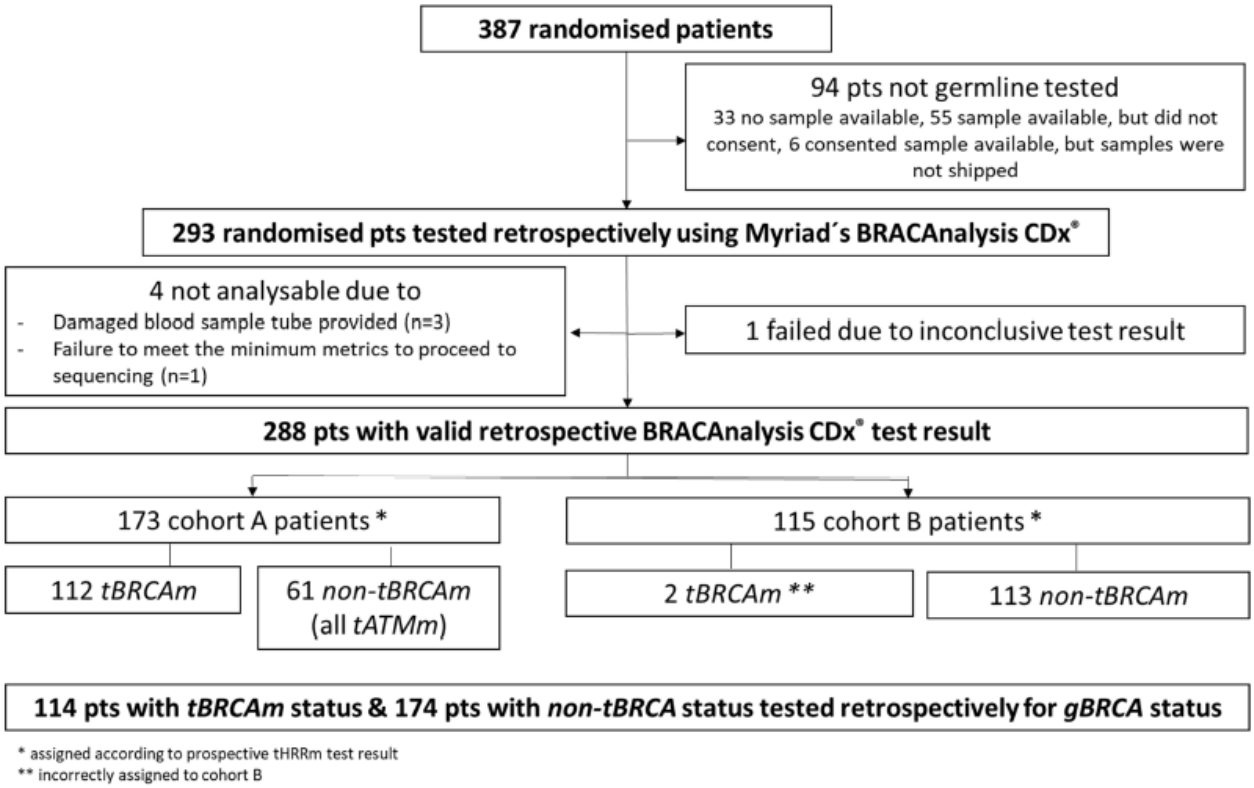


Figure 12: Retrospective gBRCA testing of patients randomised onto the PROfound study

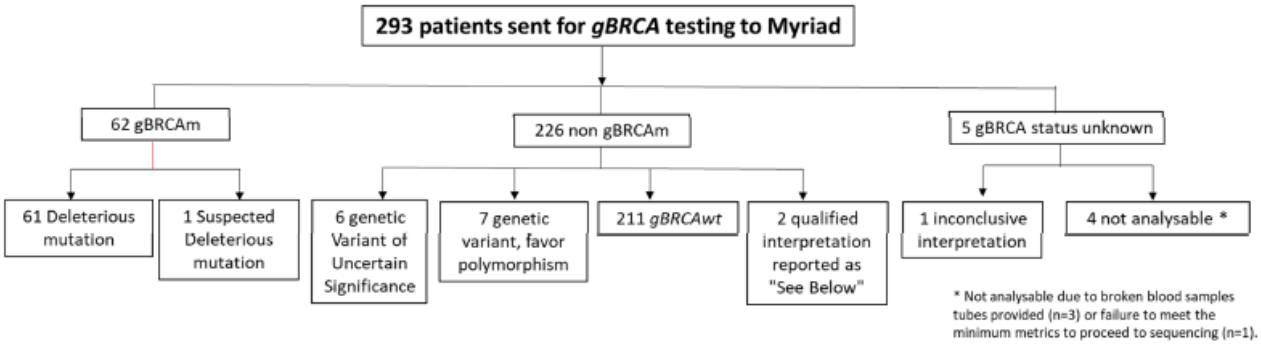


Figure 13: Overall mutation status in Myriad gBRCA tested patients

Overall, patients with BRCA1m, BRCA2m detected in their tumours were patients enrolled on the basis of prospective central testing, with the exception of 3 patients enrolled using a local test result. Of the 160 patients with a BRCA1 or BRCA2 mutation in PROfound, 114 patients were retrospectively tested to determine if the identified BRCA1/2 mutation was germline or somatic in origin. Within these patients, 63 BRCA1/2 mutations were identified in the germline blood sample and hence were determined to be germline in origin. The remaining 51 patients did not have a tumour detected BRCA1/2 mutation identified in the germline blood sample and hence the BRCA1/2 mutations are determined to be somatic in origin. For the remaining 46 patients, somatic or germline origin is unknown.

Outcomes and estimation

- **Primary endpoint: rPFS by BICR (cohort A)**

The DCO for the analysis of rPFS (4 June 2019) took place when 174 progression events had occurred (71% maturity) in Cohort A, approximately 26 months after the first patient was randomised.

The progression status based on BICR at the time of rPFS analysis is presented below.

Table 23. Progression status based on BICR assessments at the time of rPFS analysis (FAS; Cohort A) (DCO 04 June 2019)

Progression status	Type of event	Number (%) of patients	
		Olaparib 300 mg bd (N=162)	Investigators choice of NHA (N=83)
Progression[a]	Total	106 (65.4)	68 (81.9)
	RECIST progression only	51 (31.5)	50 (60.2)
	Bone scan PCWG-3 criteria progression only	34 (21.0)	11 (13.3)
	RECIST and bone scan PCWG-3 progression[b]	6 (3.7)	1 (1.2)
	Death in the absence of progression	15 (9.3)	6 (7.2)
No progression	Total	56	15 (18.1)
	Censored progression[c]	1 (0.6)	0
	Censored death[d]	6 (3.7)	2
	Progression free at time of analysis[e]	40 (24.7)	9 (10.8)
	Lost to follow-up[f]	0	0
	Withdrawn consent[f]	9 (5.6)	4
	Discontinued study[f]	0	0
	No post-baseline	0	0

a) Progression, as assessed by BICR, was defined by RECIST 1.1 and/or PCWG-3 or death (by any cause in the absence of progression) regardless of whether the patient withdrew from randomised therapy or received another anticancer therapy prior to progression.

b) Defined as RECIST and PCWG-3 progression at the same visit.

c) RECIST or bone scan PCWG-3 progression event occurred after 2 or more missed visits.

d) Includes patients who die after 2 or more missed visits.

e) Includes patients not known to have progressed at the time of analysis, but are ongoing study and at risk for future progression.

f) No progression at the last RECIST or bone scan assessment.

Table 24. Summary of primary analysis of rPFS by BICR and sensitivity analysis (FAS; Cohort A) (DCO 04 June 2019)

	Olaparib 300 mg bd (N=162)	Investigators choice of NHA (N=83)
Primary analysis (BICR assessment)		
n (%) of events[a]	106 (65.4)	68 (81.9)
Treatment effect		
Median rPFS (95% CI) [months]	7.39 (6.24, 9.33)	3.55 (1.91, 3.71)
HR (95% CI)[b]	0.34 (0.25, 0.47)	
2-sided p-value[c]	<0.0001	
rPFS at 6 months (%)	59.76	22.63
rPFS at 12 months (%)	28.11	9.40
Sensitivity analysis		
Investigator's assessment		
n (%) of events[a]	95 (58.6)	66 (79.5)
Treatment effect		
Median rPFS (95% CI) [months]	9.79 (8.74, 12.65)	3.55 (1.87, 3.71)
HR (95% CI)[b]	0.24 (0.17, 0.34)	
2-sided p-value[c]	<0.0001	
rPFS at 6 months (%)	70.49	24.49
rPFS at 12 months (%)	42.39	2.76
Evaluation time bias[d]		
n (%) of events[a]	106 (65.4)	68 (81.9)
Treatment effect		
Median rPFS [months]	6.57	2.63
HR (95% CI)[b]	0.35 (0.25, 0.48)	
2-sided p-value[c]	<0.0001	
Attrition bias[e]		
n (%) of events[a]	106 (65.4)	66 (79.5)
Treatment effect		
Median rPFS [months]	7.39	3.52
HR (95% CI)[b]	0.34 (0.25, 0.47)	
2-sided p-value[c]	<0.0001	
Unequivocal clinical progression in addition to rPFS[f]		
n (%) of events[a]	111 (68.5)	69 (83.1)
Treatment effect		
Median rPFS [months]	7.39	3.52
HR (95% CI)[b]	0.35(0.26, 0.49)	
2-sided p-value[c]	<0.0001	
Revised confirmation criteria for bone scan[g]		
n (%) of events[a]	108 (66.7)	68 (81.9)

Treatment effect		
Median rPFS [months]	7.39	3.55
HR (95% CI)[b]	0.35 (0.26, 0.49)	
2-sided p-value[c]	<0.0001	
Censoring patients with subsequent therapy or discontinuation of study drug[e]		
n (%) of events[a]	88 (54.3)	58 (69.9)
Treatment effect		
Median rPFS [months]	9.07	3.55
HR (95% CI)[b]	0.32(0.23, 0.46)	
2-sided p-value[c]	<0.0001	

a) Progression, as assessed by BICR, was defined by RECIST 1.1 and/or PCWG-3 or death (by any cause in the absence of progression) regardless of whether the patient withdrew from randomised therapy or received another anticancer therapy prior to progression.

b) The HR and CI were calculated using a Cox proportional hazards model adjusted for the variables selected in the primary pooling strategy (prior taxane use and measurable disease in Cohort A). The Efron approach was used for handling ties. An HR <1 favours olaparib 300 mg bd.

c) The analysis was performed using the log-rank test stratified by the variables selected in the primary pooling strategy (prior taxane use and measurable disease in Cohort A) using the Breslow method for handling ties.

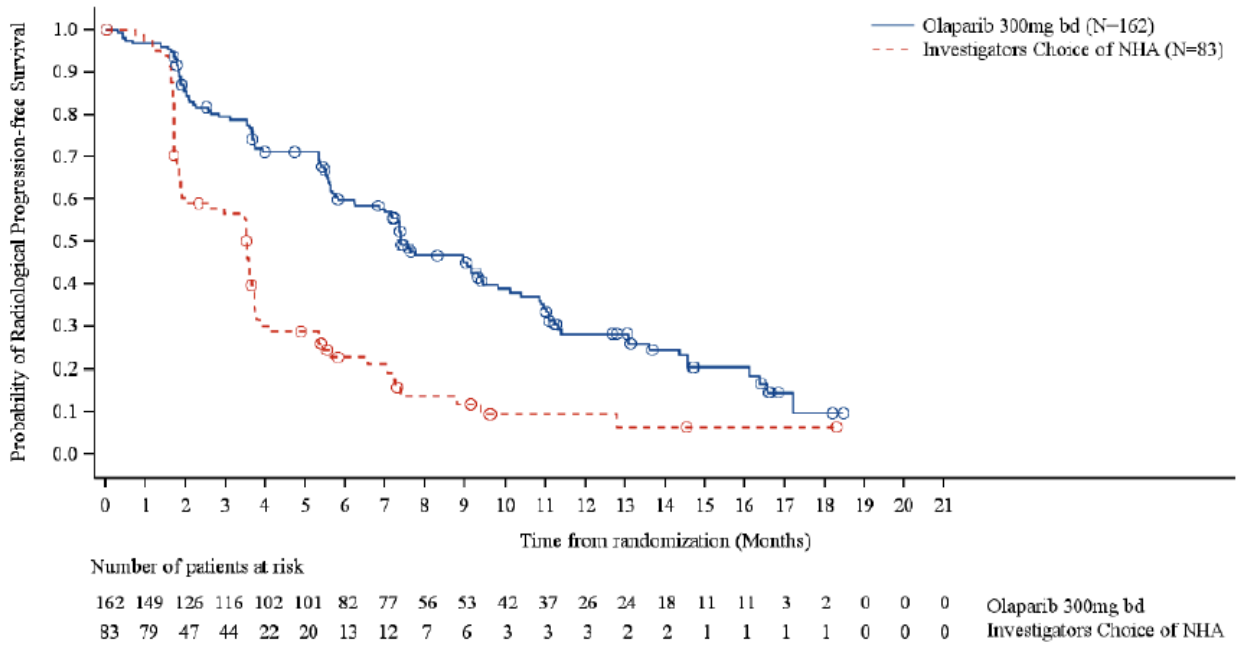
d) The midpoint between the time of progression and the previous evaluable assessment (RECIST or PCWG-3) was used in this analysis. Values resulting in non-integer values were rounded down.

e) Progression used the actual rPFS event times of patients who progressed or died in the absence of progression following 2, or more, not evaluable tumour assessments. In addition, patients taking subsequent therapy prior to progression or death were censored at their last evaluable assessment.

f) Unequivocal progression was included as an event.

g) Revised confirmation criteria where bone progression accompanied by unequivocal clinical progression did not require a confirmatory bone scan.

bd twice daily; BICR blinded independent central review; CI confidence interval; FAS full analysis set; HR hazard ratio; NHA new hormonal agent; PCWG-3 Prostate Cancer Working Group 3; RECIST Response Evaluation Criteria in Solid Tumours; rPFS radiological progression-free survival.



A circle indicates a censored observation. Progression, as assessed by BICR, was defined by RECIST 1.1 and/or PCWG-3 or death (by any cause in the absence of progression) regardless of whether the patient withdrew from randomised therapy or received another anticancer therapy prior to progression. bd twice daily; BICR blinded independent central review; FAS full analysis set; NHA new hormonal agent; PCWG-3 Prostate Cancer Working Group 3; RECIST Response Evaluation Criteria in Solid Tumours; rPFS radiological progression-free survival. Data derived from Figure 14.2.1.2.4.

Figure 14: rPFS based on BICR, Kaplan-Meier plot (FAS; Cohort A) (DCO 04 June 2019)

Table 25. Summary of rPFS by BICR in Cohort A (FAS and FMI F1CDx subset) (DCO 04 June 2019)

	FAS		FMI F1CDx subset[a]	
	Olaparib 300 mg bd	**Investigator choice of NHA**	**Olaparib 300 mg bd**	**Investigators choice of NHA**
rPFS by BICR (maturity 71%)				
Number of events/total number of patients (%)[b]	106/162 (65.4)	68/83 (81.9)	101/157 (64.3)	68/83 (81.9)
Median rPFS (95% CI) [months]	7.39 (6.24, 9.33)	3.55 (1.91, 3.71)	7.39 (6.87, 9.33)	3.55 (1.91, 3.71)
HR (95% CI)[c]	0.34 (0.25, 0.47)		0.33 (0.24, 0.46)	
p-value (2-sided)[d]	<0.0001		<0.0001	

[a] Note that all p-values for the FMI F1CDx subset are nominal.
[b] Progression, as assessed by BICR, was defined by RECIST 1.1 and PCWG-3 or death (by any cause in the absence of progression) regardless of whether the patient
withdrew from randomised therapy or received another anticancer therapy prior to progression.
[c] The HR and CI were calculated using a Cox proportional hazards model adjusted for prior taxane use and measurable disease. The Efron approach was used for handling
ties. An HR <1 favours olaparib 300 mg bd.
[d] The analysis was performed using the log-rank test stratified by prior taxane use and measurable disease using the Breslow method for handling ties.

Key secondary endpoints

- **<u>Radiological ORR (Cohort A)</u>**

Table 26. Confirmed radiological objective response rate, logistic regression based on BICR (EFR; Cohort A) (DCO 04 June 2019)

Treatment group	**N**	**Number (%) of patients with response[a]**	**Comparison between groups**		
			Odds ratio	**95% CI[b]**	**2-sided p-value[c]**
Olaparib 300 mg bd	84	28 (33.3)	20.86	4.18, 379.18	<0.0001
Investigators choice of NHA	43	1 (2.3)			

a) Radiological objective response rate determined based on BICR assessed RECIST 1.1 and bone scan data (using all scans regardless of whether they were scheduled or not) in patients with measurable disease. Response required confirmation. Radiological objective response rate compared using logistic regression (PROC GENMOD) adjusting for previous taxane use as a covariate.

b) CI calculated using profile likelihood method.

c) Where the number of patients with a response was ≥5, a 1-sided p-value was calculated based on twice the change in log-likelihood resulting from the addition of the treatment factor to the model that contains the specified covariates. Where the

number of patients with a response was <5, the 2-sided p-value was calculated based on the mid p-value modification of the Fisher's exact test.

An odds ratio >1 favours olaparib.

bd twice daily; BICR blinded independent central review; CI confidence interval; EFR evaluable for response; NHA new hormonal agent; RECIST Response Evaluation Criteria in Solid Tumours.

In the olaparib arm of Cohort A, 27 patients (32.1%) achieved a confirmed PR and 1 patient (1.2%) achieved a confirmed CR.

In the investigators choice of NHA arm, only 1 patient (2.3%) achieved a confirmed PR.

Stable disease (SD) was observed in 45.2% of patients in the olaparib arm and 53.5% of patients in the investigators choice of NHA arm.

- **rPFS by BICR (Cohort A+B)**

Table 27. Summary of analysis of rPFS based on BICR in Cohort A+B (FAS; FAS, FMI F1CDx subset and Myriad gBRCAm subset) (DCO 04 June 2019)

	FAS		FMI F1CDx subset[a]		Myriad *gBRCAm* subset[a]	
	Olaparib 300 mg bd	Investigators choice of NHA	Olaparib 300 mg bd	Investigators choice of NHA	Olaparib 300 mg bd	Investigators choice of NHA
rPFS by BICR (maturity 72%)						
Number of events/total number of patients (%)[b]	180/256 (70.3)	99/131 (75.6)	172/248 (69.4)	96/128 (75.0)	25/43 (58.1)	17/19 (89.5)
Median rPFS (95% CI) [months]	5.82 (5.52, 7.36)	3.52 (2.20, 3.65)	6.21 (5.52, 7.36)	3.52 (2.10, 3.65)	10.12 (7.59, 13.08)	1.87 (1.71, 5.32)
HR (95% CI)[c]	0.49 (0.38, 0.63)		0.49 (0.38, 0.63)		0.08 (0.03, 0.18)	
p-value (2-sided)[d]	<0.0001		<0.0001		<0.0001	

- **Time to pain progression (based on BPI-SF worst pain [Item 3] and opiate use; Cohort A)**

Table 28. Summary of analysis of time to pain progression (FAS; Cohort A) (DCO 04 June 2019)

	Olaparib 300 mg bd (N=162)	Investigators choice of NHA (N=83)
n (%) of events[a]	21 (13.0)	14 (16.9)
Treatment effect		
Median TTPP (95% CI) [months]	NC	9.92

HR (95% CI)[b]	0.44 (0.22, 0.91)	
2-sided p-value[c]	0.0192	
No pain progression at 6 months (%)	84.09	67.14
No pain progression at 12 months (%)	76.48	43.08

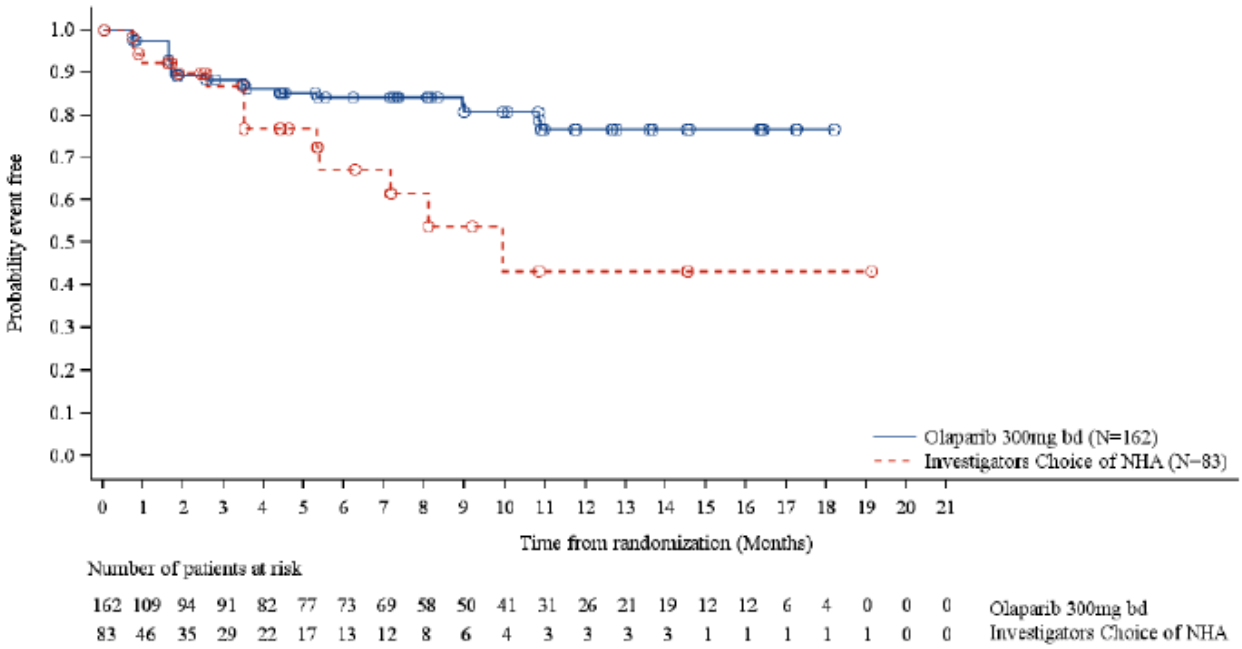
a) TTPP defined as time from randomisation to time point at which worsening in pain is observed for asymptomatic patients and symptomatic patients at baseline. Analgesic use defined by AQA score included in the definition. Pain was defined using BPI-SF worst pain (Item 3).

b) The HR and CI were calculated using a Cox proportional hazards model adjusted for the variables selected in the primary pooling strategy (no variables in Cohort A). The Efron approach was used for handling ties. An HR <1 favours olaparib 300 mg bd.

c) The analysis was performed using the log-rank test stratified by the variables selected in the primary pooling strategy (no variables in Cohort A) using the Breslow method for handling ties.

AQA Analgesic Quantification Algorithm; bd twice daily; BPI-SF Brief Pain Inventory – Short Form; CI confidence interval; FAS full analysis set; HR hazard ratio; NC not calculable; NHA new hormonal agent; TTPP time to pain progression.

Data derived from Table 14.2.3.1.



A circle indicates a censored observation. TTPP defined as time from randomisation to time point at which worsening in pain is observed for asymptomatic patients and symptomatic patients at baseline. Analgesic use defined by AQA score included in the definition. Pain was defined using BPI-SF worst pain (Item 3).

AQA Analgesic Quantification Algorithm; bd twice daily; BPI-SF Brief Pain Inventory – Short Form; FAS full analysis set; NHA new hormonal agent; TTPP time to pain progression.

Data derived from Figure 14.2.3.13.

Figure 15: Time to pain progression, Kaplan Meier plot (FAS; cohort A) (DCO 04 June 2019)

- **Overall survival (Cohort A)**

The interim OS data were 38% mature (93 events out of 245 patients). At the time of the DCO of 4 June 2019, 56.8% of olaparib-treated patients and 48.2% of investigators choice of NHA-treated patients were alive and in survival follow-up. The level of statistical significance for this interim analysis is at a two-sided alpha of 0.010. Final OS analysis was planned to be conducted at approximately 60% maturity in Cohort A with a level of statistical significance for the final OS analysis at a two-sided alpha of 0.047. The observed final OS analysis **p-value in Cohort A was 0.0175.** The final OS data were 60.4% mature (148 events out of 245 patients). At the time of the DCO, **30.2% of olaparib-treated patients** and

25.3% of investigators choice of NHA-treated patients were known to be alive and were in survival follow-up.

Table 29. Summary of overall survival at the time of final analysis (FAS; Cohort A) (DCO 20 March 2020)

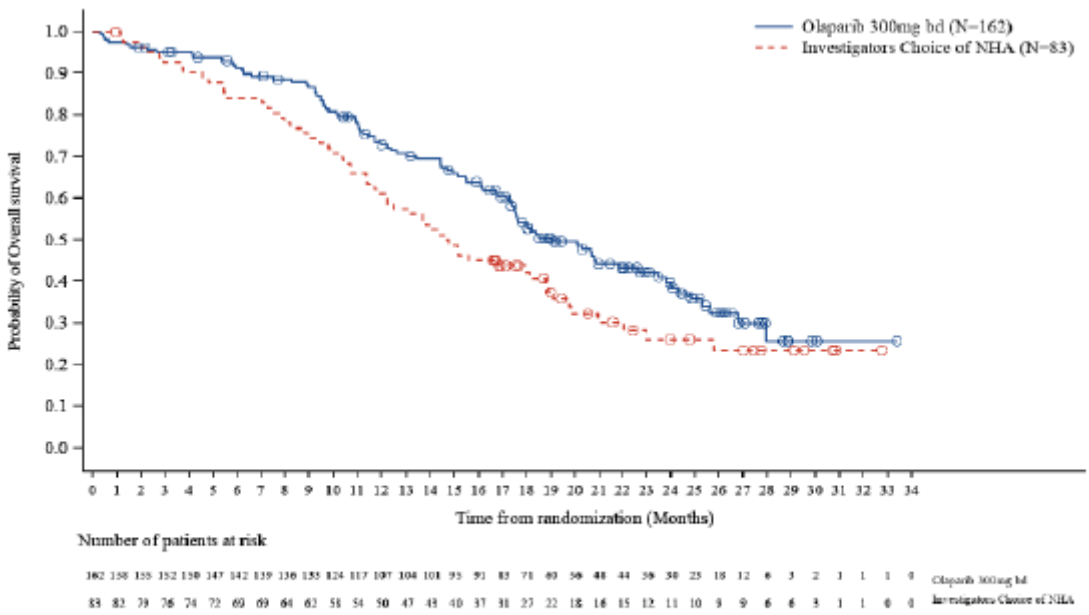
	Olaparib 300 mg bd (N=162)	Investigators choice of NHA (N=83)
n (%) of deaths	91 (56.2)	57 (68.7)
Median OS (95% CI) [months][a]	19.09 (17.35, 23.43)	14.69 (11.93, 18.79)
HR (95% CI)[b]	0.69 (0.50, 0.97)	
2-sided p-value[c]	0.0175	
OS at 6 months (%)[a]	91.21	84.15
OS at 12 months (%)[a]	72.81	60.98

[a] Calculated using the Kaplan-Meier technique.

[b] The HR and CI were calculated using a Cox proportional hazards model adjusted for the variables selected in the primary pooling strategy (prior taxane use and measurable disease in Cohort A). The Efron approach was used for handling ties. An HR <1 favours olaparib 300 mg bd.

[c] The analysis was performed using the log-rank test stratified by the variables selected in the primary pooling strategy (prior taxane use and measurable disease in Cohort A) using the Breslow method for handling ties.

bd = twice daily; CI = confidence interval; FAS = full analysis set; HR = hazard ratio; NHA = new hormonal agent; OS = overall survival.



A circle indicates a censored observation.
bd = twice daily; FAS = full analysis set; NHA = new hormonal agent.
Data derived from Figure 14.2.4.4, PROfound CSR Addendum, Module 5.3.5.1.

Figure 16: Overall survival, Kaplan-Meier plot (FAS; Cohort A) (DCO 20 March 2020)

Other secondary variables

- ***Cohort A***

Table 30. Cohort A: Summary of secondary efficacy outcome variables (FAS) (DCO 04 June 2019)

	FAS	
	Olaparib 300 mg bd	**Investigators choice of NHA**
DoR (patients with confirmed objective response [EFR set])		
N	28	1
Median (95% CI) [months][h]	5.88 (5.52, 9.03)	7.39 (NC, NC)
Time to onset of response (patients with confirmed objective response [EFR set])		
Median (95% CI) [months][i]	3.15 (1.91, 3.81)	2.04 (NC, NC)
Confirmed ORR of soft tissue (EFR set)		
Number of objective responders/total number of patients with measurable disease	30/84 (35.7)	1/43 (2.3)
Odds ratio (95% CI)[f]	23.26 (4.67, 422.50)	
p-value (2-sided)[g]	<0.0001	
PFS2 (FAS)		
Number of events/total number of patients (%)	61/162 (37.7)	44/83 (53.0)
Median PFS2 (95% CI) [months][m]	17.22 (12.71, 18.30)	10.64 (9.13, 11.24)
HR (95% CI)[c]	0.53 (0.36, 0.79)	
p-value (2-sided) [nominal][n]	0.0003	
Time to first SSRE (FAS)		
Number of events/total number of patients (%)	25/162 (15.4)	19/83 (22.9)
Median (95% CI) [months]	NC (NC, NC)	NC (NC, NC)
HR (95% CI)[o]	0.37 (0.20, 0.70)	
p-value (2-sided) [nominal][d]	0.0013	
Time to opiate use for cancer related pain (FAS)		
Number of events/total number of patients (%)	42/113 (37.2)	29/58 (50.0)
Median (95% CI) [months]	17.97 (12.68, NC)	7.52 (3.22, NC)
HR (95% CI)[l]	0.61 (0.38, 0.99)	
p-value (2-sided) [nominal][d]	0.0443	
PSA_{50} response (FAS)		
Number of patients with confirmed response (n)[p]	66	6
Confirmed response (%) [95% CI][p]	40.7 (33.10, 48.73)	7.2 (2.70, 15.07)
CTC conversion		
Number of patients with CTC conversion (n)[q]	29	5
CTC conversion (%) [95% CI][r]	17.9 (12.33, 24.69)	6.0 (1.98, 13.50)

c The HR and CI were calculated using a Cox proportional hazards model adjusted for prior taxane use and measurable disease. The Efron approach was used for handling ties. An HR <1 favours olaparib 300 mg bd.

d The 2-sided p-values were calculated using the log-rank test stratified by the same variables selected in the primary pooling strategy for each cohort, using the Breslow method for handling ties.
e Radiological ORR determined based on BICR assessed RECIST 1.1 and bone scan data (using all scans regardless of whether they were scheduled or not) in patients with measurable disease by BICR. Response required confirmation. Radiological objective response rate compared using logistic regression (PROC GENMOD) adjusting for previous taxane use as a covariate.
f CI calculated using profile likelihood method. An odds ratio >1 favours olaparib 300 mg bd.
g Where the number of patients with a response was ≥5, a 1-sided p-value was calculated based on twice the change in log-likelihood resulting from the addition of the treatment factor to the model that contains the specified covariates. Where the number of patients with a response was <5, the 2-sided p-value was calculated based on the mid p-value modification of the Fisher's exact test.
h DoR is the time from the first documentation of CR/PR until the date of radiological progression by RECIST 1.1 or PCWG-3 as assessed by BICR, or death in the absence of disease progression. If a patient does not progress following a response, then their rPFS censoring date was used as the date at which the patient was censored for DoR. Includes patients who had measurable disease at baseline and had a confirmed response (CR or PR). Calculated using the Kaplan Meier method.
i Distribution-free CI.
j ORR determined based on BICR assessed RECIST 1.1 (using all scans regardless of whether they were scheduled or not) in patients with measurable disease by BICR. Response required confirmation. ORR compared using logistic regression (PROC GENMOD) adjusted for previous taxane use as a covariate.
k TTPP defined as time from randomisation to time point at which worsening in pain is observed for asymptomatic patients and symptomatic patients at baseline. Analgesic use included in the definition. Pain was defined using BPI-SF worst pain (Item 3).
l The HR and CI were calculated using a Cox proportional hazards model adjusted for the variables selected in the primary pooling strategy (no variables in Cohort A). The Efron approach was used for handling ties. An HR <1 favours olaparib 300 mg bd.
m Calculated using the Kaplan-Meier technique.
n The 2-sided p-values were calculated using the log-rank rest stratified by prior taxane and measurable disease
o The HR and CI were calculated using a Cox proportional hazards model adjusted for the variables selected in the primary pooling strategy (prior taxane use in Cohort A). The Efron approach was used for handling ties. An HR <1 favours olaparib 300 mg bd.
p Confirmed response defined as a reduction in PSA level of 50% or more on 2 consecutive occasions at least 3 weeks apart compared with baseline. Patients may have more than one confirmed response but will be counted one for this response rate.
q CTC conversion defined as the proportion of patients achieving a decline in the number of CTCs from ≥5 cells/7.5 mL at baseline to <5 cells/7.5 mL at any visit post baseline. All patients in the FAS were included, regardless of whether or not they had a baseline CTC measurement. Of note, patients with a CTC count at baseline of <5 cells/7.5 mL were counted as not having CTC conversion.
r CIs calculated using Clopper-Pearson exact method for binomial proportion.
Note: In PROfound, in order to strongly control the Type I error at 5% 2-sided, an MTP was employed across the primary endpoint (rPFS [Cohort A]) and key secondary endpoints (confirmed ORR [Cohort A], rPFS [Cohort A+B], TTPP [Cohort A] and OS [Cohort A]). All other variables that were tested (time to first SSRE, time to opiate use for cancer related pain, confirmed ORR for soft tissue, PFS2, time to pain severity progression and time to deterioration in FACT-P) were at a 2-sided significance level of 5% but not adjusted for multiplicity. In the FMI F1CDx subset and Myriad gBRCAm subset all variables (rPFS, confirmed ORR, TTPP and OS) were not adjusted for multiplicity. Twenty-one patients in Cohort A had a co-occurring mutation.
AQA Analgesic Quantification Algorithm; bd Twice daily; BPI-SF Brief Pain Inventory-Short Form; BICR Blinded independent central review; BRCA Breast cancer susceptibility gene; CDx Companion diagnostic; CI Confidence interval; CR Complete response; CSR Clinical Study Report; CTC Circulating tumour cells; DCO Data cut-off;
DoR Duration of response; EFR Evaluable for response; FACT-P Functional Assessment of Cancer Therapy - Prostate Cancer; FAS Full analysis set; FMI Foundation Medicine Inc.; gBRCAm Germline BRCA mutated; HR Hazard ratio; MTP Multiple testing procedure; NA Not applicable; NC Not calculable; NHA New hormonal agent; PFS2 Time from randomisation to second progression or death; PSA Prostate specific antigen; PR Partial response; PSA50 A ≥50% decline in PSA from baseline; RECIST Response Evaluation Criteria in Solid Tumors; SSRE Symptomatic skeletal-related event; TTPP Time to pain progression.

- ***HRQoL in Cohort A and Cohort A+B***

All PRO questionnaires were administered via an ePRO device. Patients were asked to complete the BPI-SF and the Analgesic Log daily for 7 consecutive days every 4 weeks from the date of randomisation until 24 weeks post discontinuation of randomised study treatment. FACT-P was administered at baseline and every 8 weeks until study treatment discontinuation and every 8 weeks thereafter for 24 weeks.

Table 31. Summary of pain severity and pain interference data (BPI-SF) – Cohort A and Cohort A+B (FAS) (DCO 04 June 2019)

	Cohort A		Cohort A+B	
	Olaparib 300 mg bd	**Investigators choice**	**Olaparib 300 mg bd**	**Investigators choice of**
Time to pain severity progression (BPI-SF pain severity subscale/domain)				
Number of events/total number of patients (%)[a]	16/162 (9.9)	9/83 (10.8)	24/256 (9.4)	11/131 (8.4)
Median (95% CI) [months]	NC (NC, NC)	NC (NC, NC)	NC (NC, NC)	NC (NC, NC)
HR (95% CI)[b]	0.56 (0.25, 1.34)		0.71 (0.35, 1.54)	
p-value (2-sided) [nominal][c]	0.1669		0.4112	
Pain palliation (BPI-SF worst pain [Item 3])				
Number of responders/total number of patients baseline (%)[d]	8/40 (20.0)	5/26 (19.2)	15/68 (22.1)	6/41 (14.6)
Odds ratio (95% CI)	1.05 (0.31, 3.88)		1.65 (0.61, 5.00)	
p-value (2-sided) [nominal][e]	0.9387		0.3337	
Pain interference score (BPI-SF pain interference subscale/domain) - overall adjusted mean change from baseline				
N	122	61	200	99
Overall adjusted mean change from baseline (std)[f]	-0.17 (0.128)	0.67 (0.198)	-0.03 (0.108)	0.72 (0.168)
Estimated mean difference (95% CI)	-0.85 (-1.31, -0.39)		-0.75 (-1.14, -0.36)	
p-value (2-sided) [nominal]	0.0004		0.0002	

a. Time to pain severity progression defined as time from randomisation to time point at which worsening in pain is observed for asymptomatic patients and symptomatic patients at baseline. Analgesic use included in the definition. Pain is defined using BPI-SF pain severity subscale. Overall pain severity score is calculated for each patient/visit as the mean of the individual non-missing items (worst, least, average, right now) of the BPI-SF.

b. The HR and CI were calculated using a Cox Proportional Hazards model adjusted for the variables in the primary pooling strategy (no variables in Cohort A and measurable disease in Cohort A+B). The Efron approach was used for handling ties. An HR <1 favours olaparib 300 mg bd.

c. The analysis was performed using the log-rank test stratified by the variables in the primary pooling strategy (no variables in Cohort A and measurable disease in Cohort A+B) using the Breslow method for handling ties.

d. Pain palliation defined for patients with a BPI-SF 'worse pain' item 3 score ≥4 points at baseline and was assessed as the proportion of patients with a decrease of ≥ 2 points in BPI-SF item 3 score at 12 weeks, confirmed at least 2 weeks later, without a ≥1 point increase (or ≥2 increase if starting value was 0) in AQA analgesic score. Pain palliation compared using logistic regression (PROC GENMOD) adjusting for the variables selected in the primary pooling strategy: no variables (Cohort A), no variables (Cohort A+B). An odds ratio > 1 favours olaparib 300 mg bd. CI calculated using profile likelihood method. An odds ratio >1 favours olaparib 300 mg bd.

e. Where the number of patients with a response was <5, the 2-sided p-value was calculated based on the mid p-value modification of the Fisher's exact test.

Table 32. Mixed Model of Repeated Measures - mean change from baseline in FACT-P scores (HRQoL, functioning and prostate cancer symptoms) – Cohort A and Cohort A+B (FAS) (DCO 04 June 2019)

		Cohort A		Cohort A+B	
		Olaparib 300 mg	Investigators	Olaparib 300	Investigators choice
		(N=162)	(N=83)	(N=256)	(N=131)
FACT-P total	Number of patients	95	44	162	74
	Overall adjusted mean change from baseline (std)	-6.23 (1.728)	-12.44 (2.568)	-8.01 (1.437)	-14.67 (2.244)
	Estimated mean difference (95% CI)	6.21 (0.12, 12.30)		6.67 (1.50, 11.83)	
	p-value (2-sided) [nominal]	0.0456		0.0116	
FACT-G total	Number of patients	95	44	162	74
	Overall adjusted mean change from baseline (std)	-5.94 (1.286)	-9.74 (1.912)	-6.99 (1.053)	-10.31 (1.644)
	Estimated mean difference	3.80 (-0.74, 8.34)		3.33 (-0.46, 7.11)	
	p-value (2-sided) [nominal]	0.0998		0.0847	
TOI	Number of patients	95	44	162	74
	Overall adjusted mean change from baseline (std)	-3.77 (1.341)	-9.13 (1.997)	-5.05 (1.072)	-12.21 (1.690)
	Estimated mean difference (95% CI)	5.35 (0.62, 10.08)		7.16 (3.29, 11.04)	
	p-value (2-sided) [nominal]	0.0270		0.0003	
PWB	Number of patients	9	44	1	74
	Overall adjusted mean change from baseline (std)	-2.00 (0.532)	-3.50 (0.794)	-2.10 (0.414)	-4.30 (0.652)
	Estimated mean difference (95% CI)	1.50 (-0.39, 3.38)		2.20 (0.70, 3.70)	
	p-value (2-sided) [nominal]	0.1185		0.0042	
FWB	Number of	9	44	1	74
	Overall adjusted mean change from baseline (std)	-1.53 (0.467)	-3.06 (0.685)	-1.94 (0.358)	-3.53 (0.568)
	Estimated mean difference (95%	1.54 (-0.09, 3.17)		1.59 (0.29, 2.89)	
	p-value (2-sided)	0.0646		0.0171	
PCS	Number of	9	44	1	74
	Overall adjusted mean change from baseline (std)	-0.28 (0.543)	-2.62 (0.815)	-0.99 (0.453)	-4.32 (0.722)
	Estimated mean difference (95% CI)	2.34 (0.42, 4.27)		3.33 (1.68, 4.98)	
	p-value (2-sided)	0.0174		<0.0001	
	Number of	9	44	1	74

FAPSI-6	Overall adjusted mean change from baseline (std)	0.03 (0.408)	-1.92 (0.611)	-0.54 (0.341)	-2.92 (0.545)
	Estimated mean difference (95% CI)	1.95 (0.50, 3.40)		2.38 (1.13, 3.63)	
	p-value (2-sided) [nominal]	0.0086		0.0002	

Twenty-one patients in Cohort A and 28 patients in Cohort A+B had a co-occurring mutation.

The analysis was performed using a MMRM with treatment, visit, treatment by visit interaction, baseline FACT-P total score and baseline score by visit interaction, with prior taxane use and measurable disease included as fixed effects. The treatment by visit interaction remains in the model regardless of significance. An unstructured covariance matrix is used to model the within-patient error. The Kenward-Roger approximation is used to estimate degrees of freedom.

FACT-P Total score change from baseline values can be a minimum of -156 and a maximum of 156. TOI score change from baseline values can be a minimum of -104 and a maximum of 104. FWB and PWB score change from baseline values can be a minimum of -28 and a maximum of 28. PCS score change from baseline values can be a minimum of -48 and a maximum of 48. FAPSI-6 score change from baseline values can be a minimum of -24 and a maximum of 24. FACT-G Total score is the sum of PWB, SWB, EWB and FWB.

FACT-G Functional Assessment of Cancer Therapy – General; FACT-P Functional Assessment of Cancer Therapy – Prostate Cancer; FAPSI-6 FACT Advanced Prostate Symptom Index 6; FAS Full analysis set; FWB Functional well-being; HR Hazard ratio; HRQoL Health-related quality of life;; PCS Prostate cancer subscale; PWB Physical well-being; TOI Trial Outcome Index.

Ancillary analyses

- ***Co-occurring HRR mutations***

Co-occurring HRR mutations are defined as HRR alterations occurring in at least 2 different HRR genes in a patient. Proportion of co-occurring HRR mutations in PROfound randomised HRRm patients was 7.2% (28/387), which was consistent with the total proportion of co-occurring HRR mutations in all PROfound screened mCRPC population with a positive HRRm at 7.6% (59/778), which represents the largest clinical trial mCRPC dataset to date.

- ***rPFS based on BICR (Cohort A)***

Table 33: rPFS based on BICR, Cox proportional hazards subgroup analysis (FAS) Cohort A (n=245)

Subgroup	Treatment Group	N	Number (%) of patient with events[a]	Median (months)	Median 95% CI	Comparison between groups: Hazard ratio	Comparison between groups: 95% CI
All patients [b]	Olaparib 300mg bd	162	106 (65.4)	7.39	6.24, 9.33	0.34	0.25, 0.47
	Investigators choice of NHA	83	68 (81.9)	3.55	1.91, 3.71		
Previous taxane use [c]	Olaparib 300mg bd	106	72 (67.9)	7.39	5.82, 9.43	0.28	0.19, 0.41
	Investigators choice of NHA	52	47 (90.4)	1.94	1.71, 3.52		
No previous taxane use [c]	Olaparib 300mg bd	56	34 (60.7)	7.39	5.52, 11.07	0.55	0.32, 0.97
	Investigators choice of NHA	31	21 (67.7)	4.07	3.61, 6.57		

Table 34: Concordance between investigator and blinded independent central reviews of rPFS (FAS; Cohort A) (DCO 04 June 2019)

Concordance status	Type of concordance	Number (%) of patients: Olaparib 300 mg bd (N=162)	Number (%) of patients: Investigators choice of NHA (N=83)
Concordant	Total	139 (85.8)	71 (85.5)
	Concordant rPFS event[a]	89 (54.9)	61 (73.5)
	BICR more than 6 weeks earlier	33 (20.4)	11 (13.3)
	Within 6 weeks	49 (30.2)	39 (47.0)
	BICR more than 6 weeks later	7 (4.3)	11 (13.3)
	Concordant no rPFS event	50 (30.9)	10 (12.0)
Discordant	Total	23 (14.2)	12 (14.5)
	rPFS event by BICR but not by investigator	17 (10.5)	7 (8.4)
	rPFS event by investigator but not by BICR	6 (3.7)	5 (6.0)
BICR concordance rate when investigator declared an rPFS event (%)[b]		93.7	92.4
BICR concordance rate when investigator did not declare an rPFS event (%)[c]		74.6	58.8

[a] Patients with an rPFS event (including death) in the rPFS time to event analysis based on BICR and based on investigator assessment.

[b] Concordant rPFS event/(concordant rPFS event+rPFS by investigator but not by BICR)

[c] Concordant no rPFS event/(concordant no rPFS event+rPFS by BICR but not by investigator)

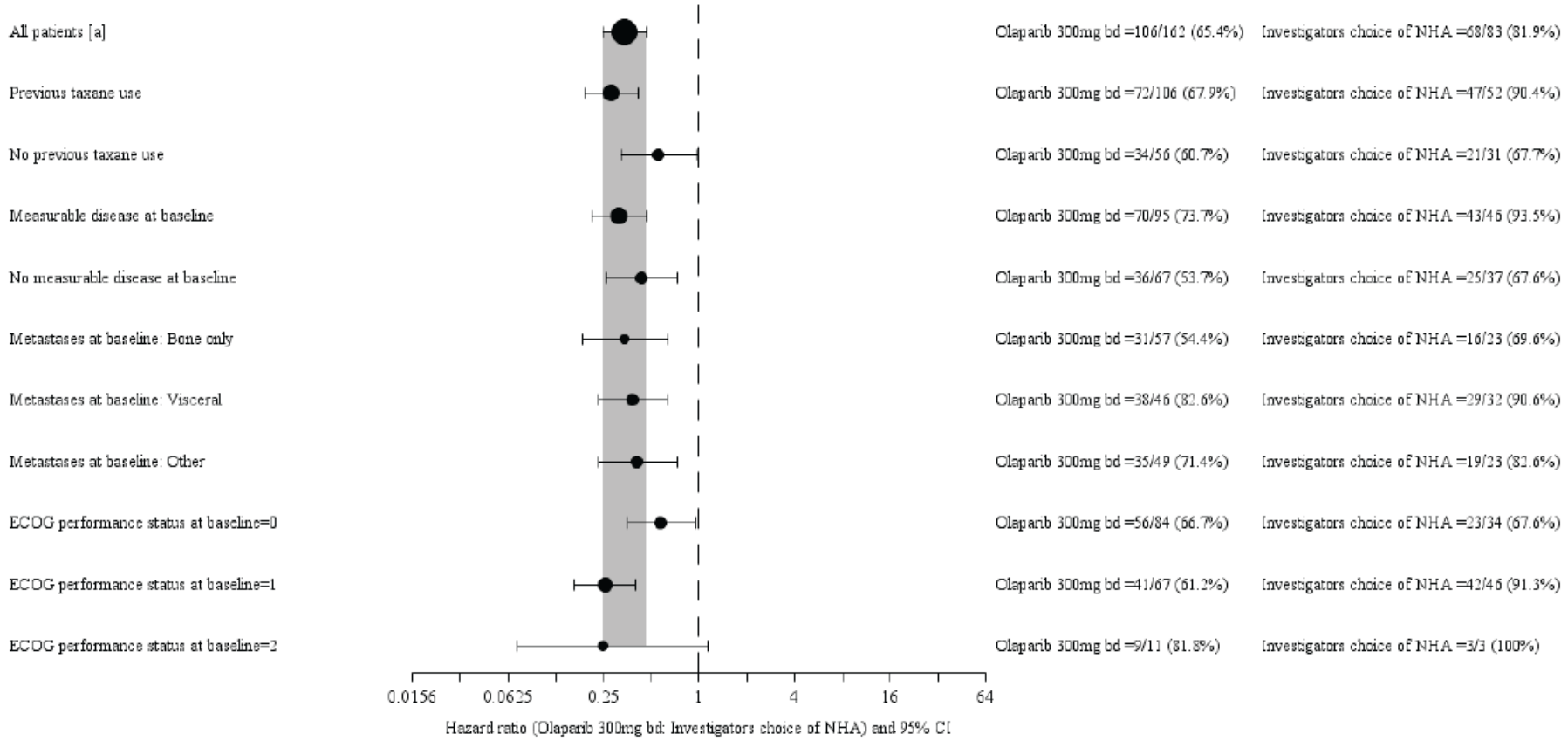
bd twice daily; BICR blinded independent central review; FAS full analysis set; NHA new hormonal agent; rPFS radiological progression-free survival.

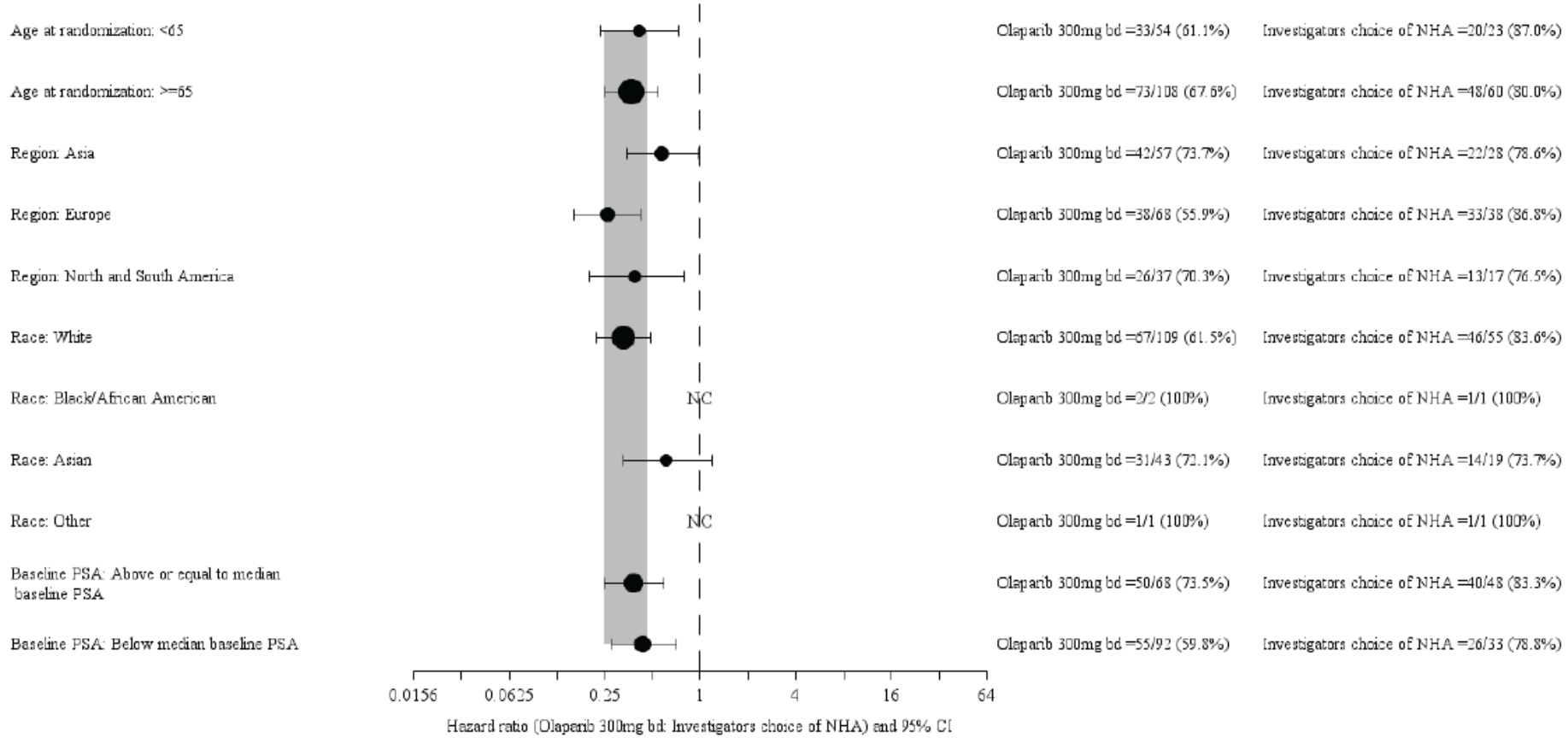
Data derived from Table 14.2.10.1.

- ***Subgroup analyses of rPFS in Cohort A***

Analyses for the primary endpoint (rPFS by BICR in Cohort A) for 8 pre-specified subgroups were conducted to assess the consistency of treatment effect across potential or expected prognostic factors. The global interaction test was not statistically significant at the 10% level (p=0.4760)

Cohort A (N=245)





a The analysis performed included the stratification factors selected in the primary pooling strategy as covariates.
Progression, as assessed by BICR, was defined using RECIST 1.1 and/or PCWG-3 or death (by any cause in the absence of progression) regardless of whether the patient withdrew from randomised therapy or received another anti-cancer therapy.
The analysis was performed using a Cox proportional hazards model that contains a term for treatment, factor and treatment by factor interaction.
Size of circle is proportional to the number of events. Grey band represents the 95% CI for the overall (all patients) HR. An HR <1 favours olaparib 300 mg bd.
Subgroup categories with fewer than 5 events across both treatment groups are not presented.
Median PSA used in this analysis was derived from Cohort A+B.
bd twice daily; BICR blinded independent central review; CI confidence interval; ECOG Eastern Cooperative Oncology Group; FAS full analysis set;
HR hazard ratio; NHA new hormonal agent; PCWG-3 Prostate Cancer Working Group 3; RECIST Response Evaluation Criteria in Solid Tumours;
rPFS radiological progression-free survival; PSA prostate specific antigen.
Data derived from Figure 14.2.1.4.2.

Figure 17: Forest plot of Subgroup analyses of rPFS in Cohort A

- ***Subgroup analyses by gene mutation (Cohort A+B)***

Table 35. Summary of rPFS, OS and SSRE by gene subgroup (FAS)

	Number of events/total number of patients (%)			Median (95% CI) [months]	
	Olaparib 300 mg bd	**Investigators choice of NHA**	**HR (95% CI)**	**Olaparib 300 mg bd**	**Investigators choice of NHA**
rPFS (BICR)[a] (DCO 04 June 2019)					
Overall Cohort A+B[b]	180/256 (70.3)	99/131 (75.6)	0.49 (0.38, 0.63)	5.82 (5.52, 7.36)	3.52 (2.20, 3.65)
BRCA1 and/or *BRCA2*[c]	62/102 (60.8)	51/58 (87.9)	0.22 (0.15, 0.32)	9.79 (7.62, 11.30)	2.96 (1.81, 3.55)
BRCA1 and/or *BRCA2* and/or *ATM*[c]	108/165 (65.5)	69/84 (82.1)	0.38 (0.28, 0.52)	7.39 (6.87, 9.33)	3.52 (1.87, 3.65)
Tail B genes[d]	30/39 (76.9)	16/24 (66.7)	1.00 (0.55, 1.88)	3.91 (2.00, 7.20)	3.71 (1.87, 5.75)
Any single HRR mutation[e]	169/239 (70.7)	91/120 (75.8)	0.53 (0.41, 0.69)	6.08 (5.52, 7.36)	3.52 (1.97, 3.71)
BRCA1[e]	7/8 (87.5)	5/5 (100)	0.41 (0.13, 1.39)	2.07 (1.38, 5.52)	1.84 (1.71, 3.71)
BRCA2[e]	47/81 (58.0)	40/47 (85.1)	0.21 (0.13, 0.32)	10.84 (9.17, 13.08)	3.48 (1.74, 3.65)
ATM[e]	46/62 (74.2)	17/24 (70.8)	1.04 (0.61, 1.87)	5.36 (3.61, 6.21)	4.70 (1.84, 7.26)
CDK12[e]	47/61 (77.0)	18/28 (64.3)	0.74 (0.44, 1.31)	5.09 (3.61, 5.52)	2.20 (1.71, 4.83)
PALB2[e]	1/3 (33.3)	0/1 (0.0)	NC (NC, NC)	NC (NC, NC)	NC (NC, NC)
RAD51B[e]	3/4 (75.0)	1/1 (100)	NC (NC, NC)	10.89 (1.61, 14.75)	1.77 (NC, NC)
RAD51D[e]	1/1 (100)	0	NC (NC, NC)	1.91 (NC, NC)	NC (NC, NC)
CHEK1[e]	1/1 (100)	1/1 (100)	NC (NC, NC)	1.84 (NC, NC)	3.71 (NC, NC)
CHEK2[e]	6/7 (85.7)	3/5 (60.0)	0.87 (0.23, 4.13)	5.59 (1.64, 11.99)	3.35 (1.38, NC)
RAD54L[e]	3/3 (100)	2/2 (100)	0.33 (0.05, 2.54)	7.20 (3.71, 7.39)	2.41 (1.81, 3.02)
PPP2R2A[e]	5/6 (83.3)	2/4 (50.0)	6.61 (1.41, 46.41)	2.69 (1.77, 3.91)	NC (NC, NC)
BRIP1[e]	2/2 (100)	1/1 (100)	NC (NC, NC)	3.56 (1.71, 5.42)	1.68 (NC, NC)
BARD1[e]	0	1/1 (100)	NC (NC, NC)	NC (NC, NC)	5.75 (NC, NC)
OS[f] (DCO 20 March 2020)					
Overall Cohort A+B[b]	160/256 (62.5)	88/131 (67.2)	0.79 (0.61, 1.03)	17.31 (15.47, 18.63)	14.00 (11.47, 17.08)
BRCA1 and/or *BRCA2*	53/102 (52.0)	41/58 (70.7)	0.63 (0.42, 0.95)	20.11 (17.35, 26.81)	14.44 (10.71, 18.89)
BRCA1 and/or *BRCA2* and/or *ATM*	93/165 (56.4)	58/84 (69.0)	0.70 (0.51, 0.98)	19.09 (17.35, 23.43)	14.62 (11.93, 18.79)
Non-*BRCA* mutation	107/154 (69.5)	47/73 (64.4)	0.95 (0.68, 1.34)	15.80 (13.86, 17.31)	13.34 (11.17, 17.74)

Non-*BRCA*, non-*PPP2R2A* mutations	102/148 (68.9)	45/69 (65.2)	0.82 (0.58, 1.18)	15.87 (14.06, 18.00)	12.22 (10.38, 17.08)
BRCA1 [c]	5/8 (62.5)	5/5 (100)	0.42 (0.12, 1.53)	11.70 (1.38, NC)	9.40 (5.45, 14.62)
BRCA2 [c]	39/81 (48.1)	32/47 (68.1)	0.59 (0.37, 0.95)	24.84 (17.35, NC)	15.15 (10.71, 19.75)
ATM [c]	39/62 (62.9)	15/24 (62.5)	0.93 (0.53, 1.75)	18.00 (14.42, 23.43)	15.57 (12.12, 22.01)
CDK12 [c]	47/61 (77.0)	18/28 (64.3)	0.97 (0.57, 1.71)	14.06 (11.14, 15.87)	11.47 (7.82, 17.74)
PALB2 [c]	2/3 (66.7)	1/1 (100)	NC (NC, NC)	16.43 (14.36, NC)	6.93 (NC, NC)
RAD51B [c]	2/4 (50.0)	1/1 (100)	NC (NC, NC)	NC (NC, NC)	3.58 (NC, NC)
RAD51D [c]	1/1 (100)	0	NC (NC, NC)	16.72 (NC, NC)	NC (NC, NC)
CHEK1 [c]	1/1 (100)	0/1 (0)	NC (NC, NC)	10.41 (NC, NC)	NC (NC, NC)
CHEK2 [c]	4/7 (57.1)	3/5 (60.0)	0.87 (0.19, 4.44)	16.56 (6.47, NC)	17.08 (3.35, NC)
RAD54L [c]	2/3 (66.7)	2/2 (100)	NC (NC, NC)	19.32 (9.00, 19.32)	5.70 (3.02, 8.38)
PPP2R2A [c]	5/6 (83.3)	2/4 (50.0)	5.11 (1.10, 35.73)	8.08 (3.78, NC)	NC (NC, NC)
BRIP1 [c]	1/2 (50.0)	1/1 (100)	NC (NC, NC)	NC (NC, NC)	9.69 (NC, NC)
BARD1 [c]	0	1/1 (100)	NC (NC, NC)	NC (NC, NC)	5.75 (NC, NC)
SSRE[g] (DCO 04 June 2019)					
Overall Cohort A+B[h]	41/256 (16.0)	25/131 (19.1)	0.485 (0.291, 0.821)	NC (NC, NC)	NC (8.18, NC)
BRCA1 and/or *BRCA2*[c]	14/102 (13.7)	12/58 (20.7)	0.289 (0.130, 0.650)	NC (NC, NC)	NC (NC, NC)
BRCA1 and/or *BRCA2* and/or *ATM* [c]	25/165 (15.2)	19/84 (22.6)	0.356 (0.193, 0.666)	NC (NC, NC)	NC (NC, NC)
Tail B genes[d]	5/39 (12.8)	2/24 (8.3)	1.223 (0.263, 8.542)	NC (NC, NC)	NC (NC, NC)
Any single HRR mutation	39/239 (16.3)	23/120 (19.2)	0.513 (0.305, 0.882)	NC (NC, NC)	NC (NC, NC)
BRCA1[e]	0/8 (0)	2/5 (40.0)	NC (NC, NC)	NC (NC, NC)	NC (NC, NC)
BRCA2 [e]	12/81 (14.8)	9/47 (19.1)	0.323 (0.134, 0.807)	NC (NC, NC)	NC (NC, NC)
ATM [e]	11/62 (17.7)	6/24 (25.0)	0.558 (0.211, 1.626)	NC (NC, NC)	8.57 (7.23, NC)
CDK12 [e]	12/61 (19.7)	5/28 (17.9)	0.728 (0.268, 2.301)	10.15 (9.59, NC)	8.18 (8.18, NC)
PALB2 [e]	0/3 (0)	0/1 (0)	NC (NC, NC)	NC (NC, NC)	NC (NC, NC)
RAD51B [e]	0/4 (0)	0/1 (0)	NC (NC, NC)	NC (NC, NC)	NC (NC, NC)
RAD51D [e]	0/1 (0)	0	NC (NC, NC)	NC (NC, NC)	NC (NC, NC)
CHEK1 [e]	0/1 (0)	0/1 (0)	NC (NC, NC)	NC (NC, NC)	NC (NC, NC)
CHEK2 [e]	1/7 (14.3)	0/5 (0)	NC (NC, NC)	NC (NC, NC)	NC (NC, NC)
RAD54L [e]	1/3 (33.3)	1/2 (50.0)	NC (NC, NC)	NC (NC, NC)	1.18 (NC, NC)
PPP2R2A [e]	2/6 (33.3)	0/4 (0)	NC (NC, NC)	4.53 (0.82, NC)	NC (NC, NC)
BRIP1 [e]	0/2 (0)	0/1 (0)	NC (NC, NC)	NC (NC, NC)	NC (NC, NC)
BARD1 [e]	0	0/1 (0)	NC (NC, NC)	NC (NC, NC)	NC (NC, NC)

a) Progression, as assessed by BICR, was defined by RECIST 1.1 and/or PCWG-3 or death (by any cause in the absence of progression) regardless of whether the patient withdrew from randomised therapy or received another anti-cancer therapy prior to progression. The analysis was performed using a Cox proportional hazards model that contains a term for treatment, factor and treatment by factor interaction. CI calculated using profile likelihood method. Subgroups with fewer than 5 events across both treatment groups do not have HRs and CIs presented.

b) The analysis performed included the stratification factors selected in the primary pooling strategy as covariates.

c) Analyses are based on patients with single and co-mutations.

d) Includes patients with the following mutations: *BARD1* and/or *BRIP1* and/or *CHEK1* and/or *CHEK2* and/or *FANCL* and/or *PALB2* and/or *PPP2R2A* and/or *RAD51B* and/or*RAD51C* and/or *RAD51D* and/or *RAD54L*.

e) Gene subgroup analysis is based on patients with a single HRR mutation.

f) Median OS and its CI were calculated using the Kaplan-Meier technique. The HR and its CI were calculated using a Cox Proportional Hazards model, adjusting for prior taxane and measurable disease as covariates, with the Efron approach being used for handling ties.

g) Time to first SSRE data are from a post hoc exploratory analysis for Cohort A+B.

h) The HR and CI were calculated using a Cox Proportional Hazards model adjusted for the variables selected in the primary pooling strategy: prior taxane. The Efron approach was used for handling ties.

An HR <1 favours olaparib 300 mg bd.
No patients in Cohort B had *FANCL* or *RAD51C* mutations.

If there were less than 5 events across both treatment arms in a subgroup then descriptive statistics were provided instead.

ATM Ataxia telangiectasia mutated; bd Twice daily; BICR Blinded independent central review; BRCA Breast cancer susceptibility gene; CI Confidence interval;
CSR Clinical Study Report; DCO Data cut-off; FAS Full analysis set; HR Hazard ratio; HRR Homologous recombination repair; NC Not calculated; NHA New hormonal agent; OS Overall survival; PCWG-3 Prostate Cancer Working Group 3; RECIST Response Evaluation Criteria in Solid Tumours; rPFS Radiological progression-free survival; SSRE Symptomatic skeletal-related event.

- ***ATM gene subgroup***

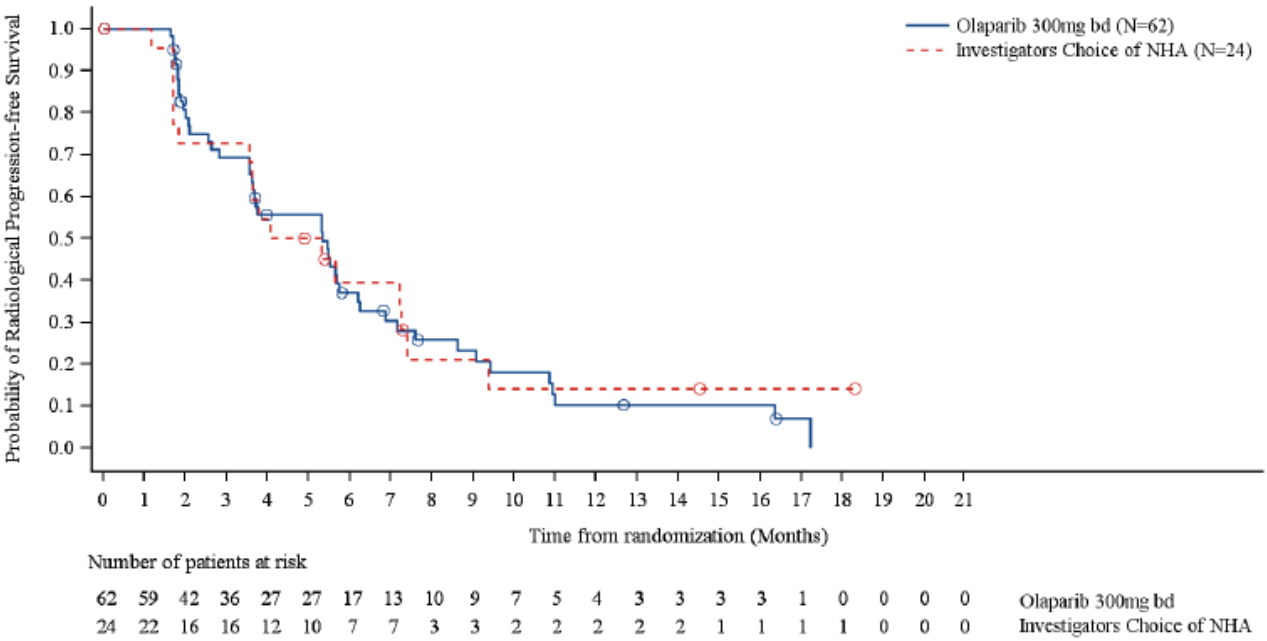


Figure 18: ATM gene subgroup: Kaplan-Meier plot of rPFS (by BICR)

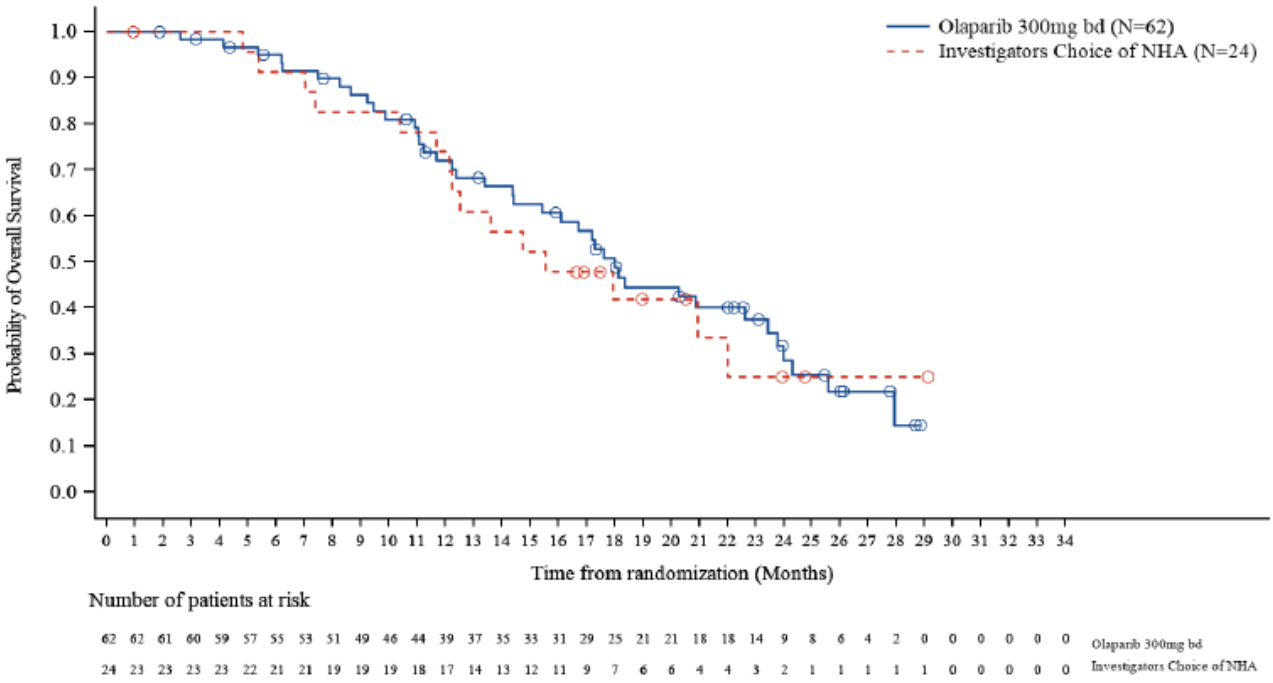


Figure 19: ATM gene subgroup: Kaplan-Meier plot of OS

- ***BRCA1/2 genes subgroup***

There was a statistically significant improvement in BICR assessed rPFS for olaparib vs the investigators choice of NHA arm in BRCA1/2m patients (with single mutations in BRCA1/2 genes and co-mutations with other HRR-related genes, see tables 21, 22, 35). The final analysis of OS showed a nominally statistically significant improvement in OS in BRCA1/2m patients randomised to Lynparza vs comparator.

Table 36: BRCA1/2 gene subgroup: Summary of rPFS, OS and SSRE by gene subgroup (Full Analysis Set)

	Number of events/total number of patients (%)			**Median (95% CI) [months]**	
	Olaparib 300 mg bd	**Investigators choice of NHA**	**HR (95% CI)**	**Olaparib 300 mg bd**	**Investigators choice of NHA**
rPFS (BICR) - DCO 04 June 2019					
BRCA1 and/or *BRCA2*	62/102 (61)	51/58 (88)	0.22 (0.15, 0.32)	9.8 (7.6, 11.3)	3.0 (1.8, 3.6)
OS DCO - 20 March 2020					
BRCA1 and/or *BRCA2*	53/102 (52)	41/58 (71)	0.63 (0.42, 0.95)	20.1 (17.4, 26.8)	14.4 (10.7, 18.9)
***SSRE* -** DCO 04 June 2019					
BRCA1 and/or *BRCA2*	14/102 (13.7)	12/58 (20.7)	0.29 (0.13, 0.65)	NC (NC, NC)	NC (NC, NC)

Table 37: BRCA1/2 gene subgroup: Summary of confirmed ORR (Evaluable for Response Set DCO 04 June 2019)

	Number (%) of patients with a response/total number of patients		
	Olaparib 300 mg bd	**Investigators choice of NHA**	**Odds ratio (95% CI)**
Confirmed ORR by BICR - DCO 04 June 2019			
BRCA1 and/or *BRCA2*	25/57 (44.0)	0/33 (0)	NC (NC, NC)

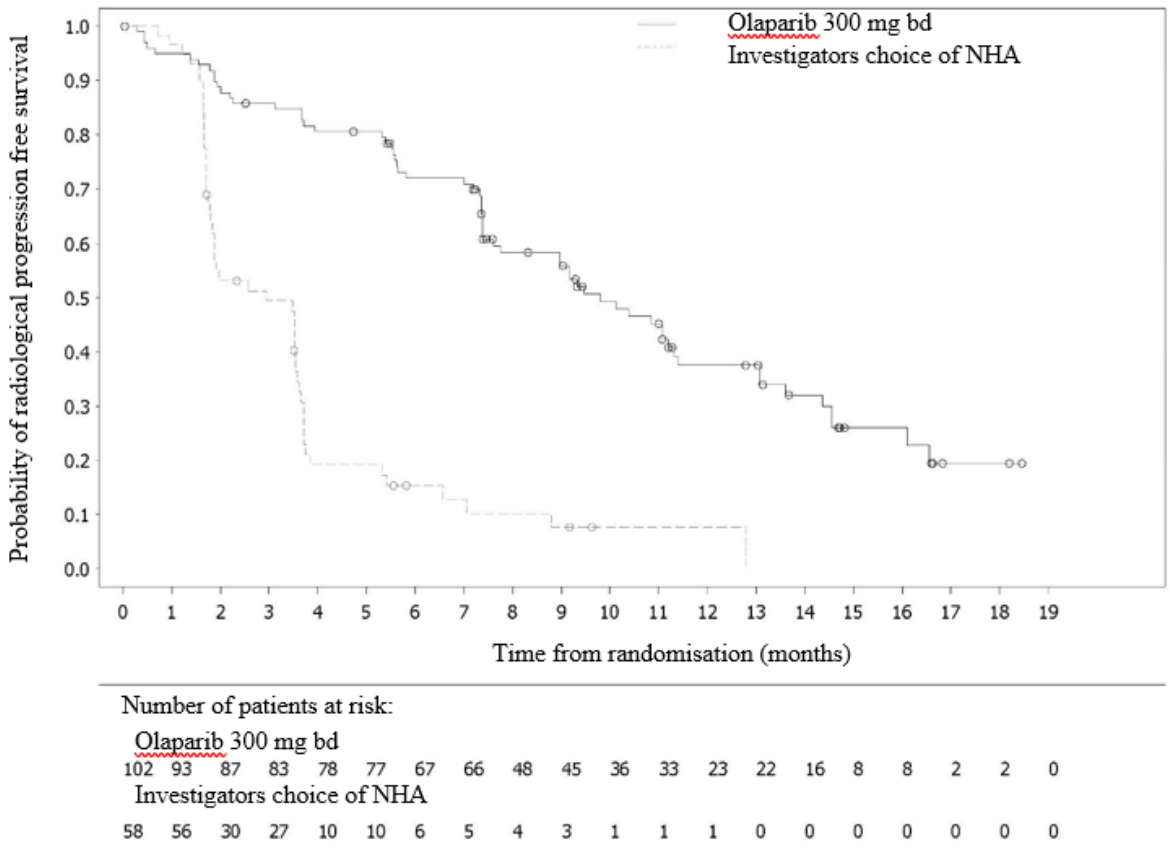


Figure 20: BRCA1/2m patients: Kaplan-Meier plot of rPFS (by BICR)

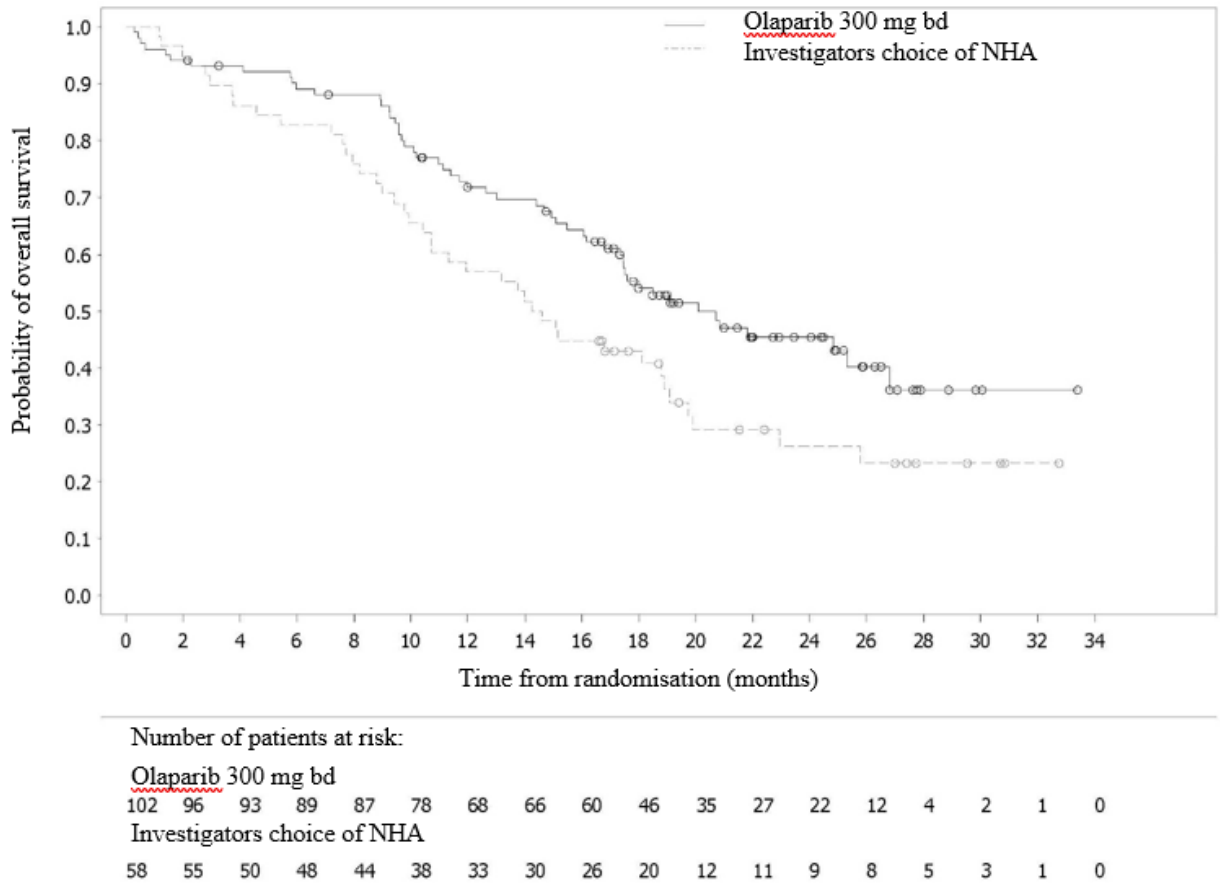


Figure 21: *BRCA1/2*m patients: Kaplan-Meier plot of OS

- ***Exploratory analysis for BRCAm patients by gBRCAm vs sBRCAm***

A post hoc exploratory subgroup analysis of rPFS, confirmed ORR, TTPP, OS, PSA_{50} response and CTC conversion rate was conducted in patients with either germline or somatic single BRCA mutations in Cohort A, patients with co-mutations in BRCA1/2 and other HRR genes were excluded from these analyses.

Table 38. Exploratory analyses: efficacy in *gBRCAm* vs *sBRCAm* patients in Cohort A

Cohort A (patients with a single *BRCA* mutation)	***gBRCAm* subset**		***sBRCAm* subset**	
	Olaparib 300 mg bd	**Investigators choice of NHA**	**Olaparib 300 mg bd**	**Investigators choice of NHA**
rPFS (FAS)				
Number of events/total number of patients (%)[a]	22/40 (55.0)	16/18 (88.9)	14/24 (58.3)	15/16 (93.8)
Median (months)[b]	10.84	1.86	11.07	2.27
HR (95% CI)[c]	0.127 (0.058, 0.272)		0.166 (0.064, 0.407)	
p-value (2-sided)[d]	<0.0001		<0.0001	
Confirmed ORR (EFR set)				
Number of objective responders/total number of patients with measurable disease at baseline (%)[e]	9/18 (50.0)	0/12 (0)	6/13 (46.2)	0/8 (0)
Odds ratio (95% CI)[f,g]	NC (NC, NC)		NC (NC, NC)	
p-value (2-sided)[h]	0.0023*		0.0297*	
TTPP (FAS; based on BPI-SF worst pain [Item 3])				
Number of events/total number of patients (%)[i]	6/40 (15.0)	5/18 (27.8)	1/24 (4.2)	2/16 (12.5)
Median (months)[b]	NC	5.32	NC	5.39
HR (95% CI)[c]	0.298 (0.082, 1.077)		NC (NC, NC)	
p-value (2-sided)[d]	0.0458		NC	
OS (FAS)				
Number of events/total number of patients (%)[j]	8/40 (20.0)	9/18 (50.0)	8/24 (33.3)	6/16 (37.5)
Median (months)[b]	NC	16.76	18.50	18.89
HR (95% CI)[c]	0.457 (0.171, 1.198)		0.847 (0.293, 2.587)	
p-value (2-sided)[d]	0.0997		0.7603	
PSA_{50} response (FAS)				
Number of patients with confirmed response/number of evaluable patients[k,l]	27/40	0/16	15/20	0/15

Confirmed response (%) [95% CI][l,m]	67.5 (50.87, 81.43)	NC (NC, NC)	75.0 (50.90, 91.34)	NC (NC, NC)
CTC conversion rate (FAS)				
Number of patients with CTC conversion/number of evaluable patients[n,o]	7/12	2/7	3/6	2/5
CTC conversion (%) [95% CI][m,o]	58.3 (27.67, 84.83)	28.6 (3.67, 70.96)	50.0 (11.81, 88.19)	40.0 (5.27, 85.34)

[a] rPFS is defined as time from randomisation until date of RECIST/PCWG-3 progression or death. Progression-free includes patients who have not progressed or died. Based on BICR assessment of radiological scans (RECIST/PCWG-3).
[b] Calculated using Kaplan-Meier technique.
[c] Estimated from Cox proportional hazards model, unadjusted.
[d] Determined using log-rank test, unadjusted.
[e] Radiological objective response based on BICR assessed RECIST and bone scan data. Response (PR/CR) requires confirmation.
[f] Logistic regression performed adjusting for previous taxane as a covariate (using proc genmod). An odds ratio >1 favours olaparib 300 mg bd
[g] CI calculated using profile likelihood method.
[h] p-values use the likelihood ratio test method. Where there was an insufficient number of responders, a 2 sided p-value was calculated based on the mid p-value modification of Fisher's exact test, indicated by *.
[i] TTPP defined as time from randomisation to time point at which worsening in pain is observed for asymptomatic patients and symptomatic patients at baseline. Pain is defined using BPI-SF Item 3 (worst pain).
[j] OS is defined as time from randomisation until date of death.
[k] An evaluable patient was a patient with a valid baseline and post-baseline PSA measurement.
[l] Confirmed response defined as a reduction in PSA level of 50% or more on 2 consecutive occasions at least 3 weeks apart compared with baseline. Patients may have had more than 1 confirmed response but will be counted once for this response rate.
[m] CIs calculated using Clopper-Pearson exact method for binomial proportion.
[n] Evaluable patients = patients with ≥5 cells/7.5 mL at baseline and at least one valid post-baseline CTC count measurement.
[o] CTC conversion defined as the proportion of patients achieving a decline in the number of CTC counts from ≥5 cells/7.5 mL at baseline to <5 cells/7.5 mL at any visit post baseline.
BICR Blinded independent central review; BPI-SF Brief Pain Inventory – Short Form; *BRCA* Breast cancer susceptibility gene; CTC Circulating tumour cells; CI Confidence interval; EFR Evaluable for response; FAS Full analysis set; *gBRCAm* germline *BRCA* mutated; HR Hazard ratio; NC Not calculable; ORR Objective response rate; OS Overall survival; PCWG-3 Prostate Cancer Working Group 3; PSA Prostate specific antigen; RECIST Response Evaluation Criteria in Solid Tumors; rPFS Radiological progression-free survival; *sBRCAm* somatic *BRCA* mutated; TTPP Time to pain progression.
Data derived from Tables 1894.1.1, 1894.1.2, 1894.2.1, 1894.3.1, 1894.3.2, 1894.4.1, 1894.4.2, 1919.1.1, 1919.1.2, 1919.2.1, 1919.2.2, Module 5.3.5.3.

- ***Exploratory analysis in <u>non-BRCA1/2 Patients</u>***

Post-hoc subgroup analysis excluding patients with any BRCA mutation, including those with co-occurring mutations in BRCA1 or BRCA2 plus another gene, was performed for rPFS and OS.

Table 39: rPFS (BICR) Cohort A+B Analysis, Excluding Patients with Any BRCA Mutation (FAS)

	Olaparib 300 mg bd (N=154)	Investigators choice of NHA (N=73)
n (%) of events[a]	118 (76.6)	48 (65.8)
Treatment effect		
Median rPFS (95% CI) [months][b]	5.29 (3.68, 5.49)	3.71 (2.79, 5.42)
HR (95% CI)[c]	0.944 (0.678, 1.337)	
2-sided p-value[d]	0.6551	
Progression free at 6 months (%)[b]	33.72	30.63
Progression free at 12 months (%)[b]	10.40	19.09

[a] Progression, as assessed by BICR, was defined by RECIST 1.1 and/or PCWG-3 or death (by any cause in the absence of progression) regardless of whether the patient withdrew from randomised therapy or received another anticancer therapy prior to progression.

[b] Calculated using the Kaplan-Meier technique.

[c] The HR and CI were calculated using a Cox proportional hazards model adjusted for the variables selected in the primary pooling strategy (prior taxane use and measurable disease in Cohort A+B). The Efron approach was used for handling ties. An HR <1 favours olaparib 300 mg bd.

[d] The analysis was performed using the log-rank test stratified by the variables selected in the primary pooling strategy (prior taxane use and measurable disease in Cohort A+B) using the Breslow method for handling ties.

bd = twice daily; BICR = blinded independent central review; *BRCA* = breast cancer susceptibility gene; CI = confidence interval; FAS = Full Analysis Set; HR = hazard ratio; NHA = new hormonal agent; PCWG-3 = Prostate Cancer Working Group 3; RECIST = Response Evaluation Criteria in Solid Tumours; rPFS = radiological progression-free survival.

Data derived from IEMT Table 2047.1

Summary of bone agents

A summary of bone agents in patients with bone metastases at baseline is presented below. The term 'bone agents' includes all patients treated before randomisation and during the PROfound study with the agents listed in Table 40.

Table 40: Summary of Bone Agents (Full Analysis Set; Patients with Bone Metastases at Baseline); Cohort A and Cohort A+B

	Cohort A			Cohort A+B		
	Olaparib 300 mg bd (N=127)	**Inv Choice of NHA (N=67)**	**Total (N=194)**	**Olaparib 300 mg bd (N=204)**	**Inv Choice of NHA (N=104)**	**Total (N=308)**
Number of patients with bone agents prior to randomisation						
Any	64 (50.4)	42 (62.7)	106 (54.6)	109 (53.4)	62 (59.6)	171 (55.5)
Alendronate sodium	1 (0.8)	2 (3.0)	3 (1.5)	2 (1.0)	2 (1.9)	4 (1.3)
Denosumab	29 (22.8)	16 (23.9)	45 (23.2)	52 (25.5)	24 (23.1)	76 (24.7)
Palliative radiotherapy	39 (30.7)	26 (38.8)	65 (33.5)	60 (29.4)	35 (33.7)	95 (30.8)

Table 40: Summary of Bone Agents (Full Analysis Set; Patients with Bone Metastases at Baseline); Cohort A and Cohort A+B

	Cohort A			Cohort A+B		
	Olaparib 300 mg bd (N=127)	**Inv Choice of NHA (N=67)**	**Total (N=194)**	**Olaparib 300 mg bd (N=204)**	**Inv Choice of NHA (N=104)**	**Total (N=308)**
Radium RA223 dichloride	7 (5.5)	6 (9.0)	13 (6.7)	13 (6.4)	9 (8.7)	22 (7.1)
Zoledronic acid	7 (5.5)	7 (10.4)	14 (7.2)	15 (7.4)	13 (12.5)	28 (9.1)
Number of patients with bone agents during study						
Any	47 (37.0)	36 (53.7)	83 (42.8)	83 (40.7)	51 (49.0)	134 (43.5)
Alendronate sodium	1 (0.8)	2 (3.0)	3 (1.5)	2 (1.0)	2 (1.9)	4 (1.3)
Denosumab	25 (19.7)	15 (22.4)	40 (20.6)	49 (24.0)	23 (22.1)	72 (23.4)
Palliative radiotherapy	22 (17.3)	16 (23.9)	38 (19.6)	33 (16.2)	19 (18.3)	52 (16.9)
Zoledronic acid	4 (3.1)	7 (10.4)	11 (5.7)	11 (5.4)	12 (11.5)	23 (7.5)

- bd = twice daily; Inv = investigator; NHA = new hormonal agent.
- Source: IEMT Table 2272.1.

Eligibility criterion number 8 of the PROfound study permitted concomitant use of bone-targeted therapy with bisphosphonates or denosumab provided patients had been on a stable regimen for at least 4 weeks prior to entering the study.

Subsequent therapies

Table 41. Subsequent anticancer therapies in Cohort A (Full analysis set)

Cohort A (N=245)

	Number (%) of patients		
Anticancer therapy [a]	Olaparib 300mg bd (N=162)	Investigators choice of NHA (N=83)	Total (N=245)
Patients with any post-discontinuation anticancer therapy	47 (29.0)	57 (68.7)	104 (42.4)
Immunotherapy	2 (1.2)	0	2 (0.8)
Pembrolizumab	2 (1.2)	0	2 (0.8)
Hormonal therapy	19 (11.7)	5 (6.0)	24 (9.8)
Abiraterone	7 (4.3)	2 (2.4)	9 (3.7)
Abiraterone Acetate	3 (1.9)	0	3 (1.2)
Enzalutamide	8 (4.9)	1 (1.2)	9 (3.7)
Ethinylestradiol	1 (0.6)	1 (1.2)	2 (0.8)
Goserelin	1 (0.6)	0	1 (0.4)
Leuprorelin Acetate	0	1 (1.2)	1 (0.4)

Cohort A (N=245)

Anticancer therapy [a]	Number (%) of patients Olaparib 300mg bd (N=162)	Investigators choice of NHA (N=83)	Total (N=245)
Taxane Chemotherapy	26 (16.0)	10 (12.0)	36 (14.7)
Cabazitaxel	13 (8.0)	6 (7.2)	19 (7.8)
Docetaxel	14 (8.6)	6 (7.2)	20 (8.2)
Paclitaxel	1 (0.6)	0	1 (0.4)
Platinum Chemotherapy	6 (3.7)	1 (1.2)	7 (2.9)
Carboplatin	6 (3.7)	1 (1.2)	7 (2.9)
PARP Inhibitor	3 (1.9)	51 (61.4)	54 (22.0)
Olaparib	3 (1.9)	51 (61.4)	54 (22.0)
Other	12 (7.4)	2 (2.4)	14 (5.7)

Impact of Subsequent Olaparib

In order to assess the impact of olaparib as a subsequent therapy in a high proportion of NHA patients, cross-over adjusted analyses have been performed using the pre--specified sensitivity OS analysis (RPSFTM). This included patients from the investigators choice of NHA arm who were eligible to receive olaparib (i.e., had BICR confirmed progression).

At the DCO 20 March 2020, 56 patients (67.5%) in the NHA arm of Cohort A received olaparib as a subsequent therapy and 30 patients (62.5%) in the NHA arm of Cohort B received olaparib as a subsequent therapy. Thus, in total 86 patients (65.6%) in the NHA arm (Cohort A+B) received olaparib as a subsequent therapy.

Table 42 Effect of Treatment Switching on OS by Cohort at the Final DCO (RPSFTM); DCO 20 March 2020

	Hazard Ratio (95% Confidence Interval) [a]		
	Cohort A	**Cohort B**	**Cohort A+B**
FAS	0.69 (0.50, 0.97)	0.96 (0.63, 1.49)	0.79 (0.61, 1.03)
FAS - Treatment switch adjusted (re-censoring)	0.42 (0.19, 0.91)	0.83 (0.11, 5.98)	0.55 (0.29, 1.06)

[d] The hazard ratio and CI were calculated using a Cox Proportional Hazards model, adjusting for prior taxane and measurable disease (Cohort A), prior taxane (Cohort B), prior taxane and measurable disease (Cohort A+B) as covariates, with the Efron approach being used for handling ties. A hazard ratio <1 favours olaparib 300 mg bd.

DCO = data cut-off; FAS = full analysis set; OS = overall survival; RPSFTM = Rank Preserving Structural Failure Time Model.

Source: Table 14.2.4.1 and Table 14.2.4.46, PROfound CSR addendum, Module 5.3.5.1.

Subgroup analyses according to NHA treatment

In PROfound, there were a total of 131 patients randomised to the investigator's choice of NHA arm and 130 of these patients received treatment (63 abiraterone, 67 enzalutamide). Forty-seven out of the 130 patients were in Cohort B (17 abiraterone, 30 enzalutamide). In Cohort B, the median rPFS was 3.32 months (95% CI 1.77, 5.42) for patients on abiraterone and 3.65 months (95% CI 1.77, NC) for patients on enzalutamide. The rPFS HR for patients on olaparib compared to abiraterone was 0.83 (95% CI 0.46, 1.64) and 0.94 (95% 0.56, 1.65) for patients on enzalutamide.

In Cohort B, the median OS for patients on abiraterone was 10.78 months (95% CI 6.93, 16.16) and 17.02 months (95% CI 7.82, NC) for patients on enzalutamide. The OS HR for patients on olaparib compared to abiraterone was 0.75 (95% CI 0.38, 1.65) and 0.77 (95% 0.43, 1.48) for patients on enzalutamide.

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 43. Summary of Efficacy for PROfound trial

Title: A Phase III, Open Label, Randomized Study to Assess the Efficacy and Safety of Olaparib (Lynparza™) Versus Enzalutamide or Abiraterone Acetate in Men with Metastatic Castration-Resistant Prostate Cancer who have failed prior treatment with a New Hormonal Agent and Have HRR Gene Mutations			
Study identifier	Study Code - D081DC00007 (PROfound) EudraCT Number - 2016-000300-28		
Design	Phase III, randomised, open-label, Investigators choice of NHA controlled, multicentre Patients were divided into two cohorts based on HRR gene mutation status: - Cohort A: mutations in either BRCA1, BRCA2 or ATM - Cohort B: mutations among 12 other genes involved in the HRR pathway (BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, or RAD54L)		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Olaparib		300 mg (2 x 150 mg tablets) orally bd
	Investigator's choice of NHA		- Abiraterone acetate: 1000 mg once daily in combination with 5 mg prednisone (or prednisolone) orally bd Or - Enzalutamide: 160 mg orally once daily
Endpoints and definitions	Primary endpoint	rPFS by BICR	The time from randomisation until the date of objective radiological disease progression or death (by any cause in the absence of disease progression) regardless of whether the patient withdrew from randomised therapy or received another anticancer therapy prior to disease progression. Objective progression is assessed according to RECIST v1.1 in soft tissue and PCWG-3 in bone.
	Secondary endpoints	ORR by BICR	Number of patients with a CR and PR according to the BICR assessed by RECIST 1.1 and PCWG-3 divided by the number of patients in the treatment group with measurable disease at baseline.
		TTPP based on BPI-SF worst pain and opiate analgesic use	Time from the date of randomisation to the time point at which worsening in pain was observed for asymptomatic patients and symptomatic patients (at baseline)
		OS	Time from the date of randomisation until death due to any cause.

		PFS2	Time from the date of randomisation to the earliest of the investigator-assessed progression events (subsequent to that used for the primary variable of rPFS) or death
Database lock	04 June 2019 and final OS analysis 20 March 2020		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	**Full analysis set (FAS):** all randomised patients **Patients evaluable for response (EFS):** a subset of the FAS population who had measurable disease at baseline as per the RECIST 1.1 criteria (the EFR analysis set) for the analysis of ORR, DoR and BoR		
Descriptive statistics and estimate variability	**Treatment group in Cohort A**	**Olaparib**	**Investigators choice of NHA**
	Number of subject	**162**	**83**
	Median rPFS (months)	7.39	3.55
	95% CI	6.24, 9.33	1.91, 3.71
	ORR (nb of objective responders/total number of patients with measurable disease)	28/84 (33.3%)	1/43 (2.3%)
	95% CI	NA	NA
	Median TTPP (months)	NC	9.92
	95% CI	NC, NC	5.39, NC
	Median OS (months) (60.4% mature)	19.09	14.69
	95% CI	17.35, 23.43	11.93, 18.79
	Median PFS2 (months)	17.22	10.64
	95% CI	12.71, 18.30	9.13, 11.24
	Treatment group in BRCA1/2-mutated mCRPC	**Olaparib**	**Investigators choice of NHA**
	Number of subject	**102**	**58**
	Median rPFS[a] by BIRC (months) (71% maturity)	9.8	3.0
	95% CI	(7.6, 11.3)	(1.8, 3.6)

	ORR[a] (nb of objective responders/total number of patients with measurable disease)	25/57 (44%)	0/33 (0)
	95% CI	NA	NA
	Median OS^ (months)	20.1	14.4
	95% CI	(17.4, 26.8)	(10.7, 18.9)
Effect estimate per comparison		Comparison groups	Olaparib vs NHA
	Primary endpoint rPFS in Cohort A (71% maturity)	Hazard ratio	0.34
		95% CI	0.25, 0.47
		2 sided P-value	<0.0001
	Key secondary endpoint ORR in Cohort A (46% maturity)	Comparison groups	Olaparib vs NHA
		Odds ratio	20.86
		95% CI	4.18, 379.18
		2 sided P-value	<0.0001
	rPFS[a] by BIRC in BRCA1/2m mCRPC	Comparison groups	Olaparib vs NHA
		Hazard ratio	0.22
		95% CI	0.15, 0.32
	Key secondary endpoint TTPP in Cohort A (49.4% maturity)	Comparison groups	Olaparib vs NHA
		Hazard ratio	0.44
		95% CI	0.22, 0.91
		2 sided P-value	0.0192
	Key secondary endpoint OS in Cohort A (60.4% maturity)	Comparison groups	Olaparib vs NHA
		Hazard ratio	0.69
		95% CI	0.50, 0.97
		2 sided P-value	0.0175
	OS[a] in BRCA1/2m mCRPC*	Comparison groups	Olaparib vs NHA
		Hazard ratio	0.63
		95% CI	0.42, 0.95
	Confirmed ORR by BICR[a]	Comparison groups	Olaparib vs NHA
		Odds ratio	NC
		95% CI	NC, NC
Notes	The statistical MTP was performed for rPFS in cohort A, ORR in cohort A, rPFS in cohort A+B, TTPP in cohort A and OS in cohort A. * The HR and CI were calculated using a Cox proportional hazards model that contains terms for treatment, factor and treatment by factor interaction. [a] Not controlled for multiplicity		

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The claimed indication was for Lynparza, tablet formulation, in monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) and homologous recombination repair (HRR) gene mutations (germline and/ or somatic) who have progressed following a prior new hormonal agent (NHA). Patients must have confirmation of a HRR gene mutation before Lynparza treatment is initiated.

The current application is based on the results of the pivotal study PROfound. This was a Phase III, randomised, open-label, multicentre trial to assess the efficacy and safety of olaparib monotherapy in patients with mCRPC that have qualifying HRR gene mutations that were predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function) who have failed prior treatment with a NHA. Treatment was continued until objective radiological disease progression or until patients were unable to tolerate study treatment. Once patients receiving investigators choice of NHA were determined to have objective radiological progression by a BICR, or by investigator assessment if after the date of DCO for the primary analysis, they were eligible to switch to treatment with olaparib. This cross-over strategy may bring a confounding impact on OS and PFS2 as well as the safety profile. Furthermore, it should be noted that patients also had the possibility to access PARP inhibitor outside of this study (off-label use, other clinical trials).

Randomization was stratified based on prior receipt of taxane chemotherapy (yes vs no) and presence of measurable disease at baseline (yes vs no). The stratification based on taxane chemotherapy would avoid heterogeneous population due to variability in the prior use of docetaxel and/or cabazitaxel as raised in the CHMP Scientific Advice, which was agreed. The other stratification by measurable disease was agreed since ORR, DoR and BoR are assessed in subset of the FAS population who had measurable disease at baseline.

Patients with mutations in BRCA1, BRCA2 or ATM were randomised in Cohort A (irrespective of co-occurring mutations in one of the 12 other HRR genes), whereas patients with mutations among other genes involved in the HRR pathway were randomised in Cohort B.

The MAH focused on 15 pre-specified HRR genes with a biological rationale for loss of function to predict sensitivity to olaparib. Between 24% to 30% of mCRPCs have loss of function mutations in genes involved in HRR of DNA damage response (DDR) and BRCA2 mutations are the most common mutations among genes involved in HR repair in advanced prostate cancer patients. Although the role of the selected gene mutations in the HRR pathway is acknowledged, the clinical benefit of a PARP inhibitor on the non-BRCA mutations remains unknown. For other HRR genes and particular mutations within those, there is no or only limited clinical data available to support a possible benefit of olaparib or another PARP inhibitor in prostate cancer patients. The applicant provided updated preclinical data on PARPi sensitivity for ATM, CDK12 and PPP2R2PA and literature data from additional studies in prostate cancer and other cancers with other PARPi (data not shown). Emerging preclinical data that became available after submission has shown weak evidence of PPP2R2A as an HRR gene that may confer sensitivity to a PARP inhibitor. Regarding ATM, the applicant provided preclinical data on ATM loss in prostate cancer cell lines

leading to sensitisation to olaparib treatments *in vitro*, but no *in vivo* pharmacological data or clinical evidence that could confirm the biological plausibility.

A scientific advice (SA) was sought in July 2016 for a pivotal study targeting BRCA1/2 or ATM mutated mCRPC patients only. Changes in the design of the pivotal study were noted compared to the proposal in the CHMP SA. A double-blind design was initially planned but has been changed to an open-label study due to the absence of feasibility to get a matching placebo for enzalutamide. A BICR was therefore set. The other change to the SA was the use of the comparators enzalutamide and abiraterone acetate for both Cohorts A and B. The initially planned use of placebo was not endorsed and the subsequently proposed use of enzalutamide re-challenge was questioned at the time of SA. Since the efficacy of enzalutamide and abiraterone could be considered similar, the use of these two comparators was preferred to re-challenge with the same agent. The inclusion of patients previously treated with NHAs and taxanes was endorsed at the time of SA. The main efficacy endpoints have been maintained, with a primary endpoint of rPFS being based only on cohort A population whereas the study also aimed to assess the efficacy and safety of olaparib monotherapy in a broader target population (patients with mCRPC that have qualifying HRR gene mutations). Therefore, the design of PROfound study was considered not adapted to the large claimed indication encompassing patient population with alterations in any of the 15 HRR genes.

PROfound study included metastatic CRPC patients with HRRm, except patients with brain metastases. Patients with disease spread limited to regional pelvic lymph nodes or local recurrence were not eligible. The qualifying HRR gene mutation were to be detected in tumour tissue; no germline DNA nor ctDNA were used in prospective HRR testing. Patients should have progressed with prior NHA for the treatment of metastatic prostate cancer and/or CRPC, taking into account that abiraterone acetate is indicated in mCRPC and metastatic hormone sensitive prostate cancer (HSPC) whereas enzalutamide is indicated in non-metastatic CRPC and mCRPC. Patients having prior platinum-based chemotherapy for prostate cancer were excluded.

Having a tumour qualifying mutation in one of 15 HRR genes was a requirement to entry in this study. The determination of the mutation status was a key component for BRCA1, BRCA2 and ATM mutations (either as single mutations among HRR genes or concomitantly with mutations in such genes) that were qualifying for inclusion in Cohort A for the primary efficacy analysis. The randomisation of patients was based on tumour HRRm prospectively determined by an investigational HRR clinical trial assay conducted in CLIA laboratory at FMI based on FoundationOne CDx specifications which was not yet approved by FDA at the time of the initiation of the study. Patients with a prior FoundationOne test result could also be screened with a confirmatory CLIA HRR CTA result.

A second screening was done on the randomised tHRRm patients for the determination of two subgroups: a confirmed FMI F1CDx subgroup including patients with tHRRm results from CLIA HRR CTA matching with FoundationOne CDx quality control criteria and classification rules, and a confirmed Myriad gBRCAm subgroup including patients with a germline BRCA1/2 mutation based on the use of a retrospective BRCAnalysis CDx test. The other germline HRR mutations were not tested.

The selected dose of olaparib for this study was the approved commercial tablet dose (300 mg BID) with the 100 mg strength tablet which is considered acceptable. The selected doses of abiraterone acetate (1000 mg) with 5 mg prednisone (or prednisolone) administered orally bd and enzalutamide (160 mg) were in line with the marketing authorisation.

The primary endpoint was rPFS by BICR in Cohort A. The choice of rPFS by BICR as primary endpoint instead of OS was acceptable despite the poor prognosis of mCRPC. As raised in the sought CHMP SA, although OS would be the preferred primary endpoint, the feasibility challenges for powering the trial in a relatively small biomarker-selected patient population were acknowledged, as well as the possibility to the patients from NHA arm to switch to olaparib that could confound OS. The assessment by BICR was also

agreed since the study had open-label design. Sensitivity analysis were planned in the SAP as follows: assessment of possible evaluation time bias, attrition bias, ascertainment bias (discrepancies between BICR and investigator's assessment), use of unequivocal clinical progression, confirmation of bone progression and censoring patients with subsequent therapy.

The comparisons between olaparib and NHA arms for all other secondary endpoints (time to first SSRE, DoR, time to opiate use, PSA_{50} response, CTC conversion rate, PFS2 and HRQoL) in this study were not confirmatory since no multiplicity adjustment plan was set up.

Overall, the study primary objective reflected a study designed to evaluate efficacy of olaparib in mCRPC subjects with BRCA1, BRCA2 or ATM mutations only. The study was designed to provide at least 95% power to demonstrate a statistically significant difference in rPFS at a 2-sided alpha level of 5% assuming a true treatment effect was indicated by a hazard ratio (HR) of 0.53 in Cohort A.

The study was planned to enrol approximately 240 patients in Cohort A and 100 patients in Cohort B. The number of patients enrolled in Cohort B was not driven by a formal sample size calculation but was determined by the enrolment period for Cohort A. Ultimately 142 patients were enrolled in Cohort B.

Important protocol deviations (IPD) occurred more frequently in cohort B compared to cohort A, respectively 12.0% vs 5.3%. Nevertheless, IPD were balanced between the treatment arms in each cohort: 4.9% olaparib vs 6.0% NHA in cohort A, 12.8% olaparib vs 10.4% NHA in cohort B, 7.8% olaparib vs 7.6% NHA in cohort A+B. Considering the IPD was beyond the pre-defined 10% threshold regardless of the treatment arms, two relevant rPFS 'deviation bias' sensitivity analyses by excluding the patients with IPD were conducted in Cohort B and their results were consistent with the primary Cohort B FAS analysis (data not shown).

Efficacy data and additional analyses

Baseline data

The median age in cohorts A+B was 69.0 years old in both arms, which is slightly younger than the literature observations of a median age of ≥70 years for unselected mCRPC patients who received enzalutamide, abiraterone or docetaxel following progression on a prior enzalutamide or abiraterone (Azad et al 2015, de Bono et al 2018, Khalaf et al 2018, Loriot et al 2013, Mezynski et al 2012, Vogelzang et al 2015). Nevertheless it is reported in the literature a relative increase in risk of prostate cancer in men <65 years ranges from 1.8-fold to 3.8-fold for gBRCA1m carriers (Leongamornlert et al 2012, Thompson and Easton 2002) and from 2.5-fold to 8.6-fold for gBRCA2m carriers (Breast Cancer Linkage Consortium 1999, Gallagher et al 2010, Kote-Jarai et al 2011, van Asperen et al 2005) compared to non-carriers. More subjects ≥65 years old were randomized in NHA arm compared to olaparib arm, respectively 72.3% vs 66.7% in cohort A, 77.1% vs 70.2% in Cohort B and 74.0% vs 68.0% in Cohort A+B.

Differences between the two arms were noticed for the median baseline PSA which was higher in NHA arm compared to olaparib arm (106.490 µg/L vs 68.2 µg/L respectively in cohorts A+B). The applicant provided the results of sensitivity analyses for rPFS (BICR) and OS to assess the impact of baseline PSA imbalances between the arms (data not shown). Overall, the adjusted rPFS and OS were consistent with the values from the primary model. Also baseline pain score was higher in NHA arm compared to olaparib arm.

The histology (mostly adenocarcinoma), the ECOG PS at baseline (0-1) and total Gleason Score at diagnosis (7-9) were globally balanced between the treatment groups and the cohorts.

Median time from CRPC and mCRPC diagnosis to randomisation was similar among the olaparib arm and NHA arm: 24.8 months vs 23.7 months respectively for median time from CRPC to randomisation in cohorts A+B; 23.3 months vs 21.9 months respectively for median time from mCRPC to randomisation in cohort A+B. The time from randomisation to CRPC diagnosis was generally similar than time from randomisation to mCRPC diagnosis.

Bone was the most common site of distant metastasis in mCRPC patients at baseline. According to the inclusion criteria, the patients with confirmed bone metastatic lesions were also eligible and allowed to continue the use of bisphosphonates or denosumab (for bone disease) before or even during the study. In general, the proportions of the patients with bone metastases receiving bone agents before or during the study were similar and their baseline characteristics were well balanced between two treatment groups (data not shown).The MAH provided subgroup analysis in Cohort A and Cohort A+Bby bone agents taken as per the eligibility criteria in the study. The subgroup analyses for rPFS (BICR) and final OS by bone agents taken showed for both Cohort A and Cohort A+B consistent results across subgroups regardless of whether or not bone agents were taken during study and/or prior to randomisation (data not shown). Overall, the provided results did not suggest a clinically relevant (confounding, moderating or mediating) role of bone agents.

The sites of disease baseline were presented together (prostate and other metastatic locations), therefore the distinction between the extent of disease was unclear. Demographics and baseline characteristics were generally well balanced between the olaparib and comparator arms in patients with *BRCA1/2* mutations.

Regarding the previous treatment-related disease, about two-third of randomized subjects received prior taxane (66.4% in olaparib arm and 64.1% in NHA arm in cohort A+B). Of those subjects, most of them received taxane treatment at mCRPC and were balanced between the treatment arms and cohort: in cohort A+B, a total of 147/256 (57.4%) subjects received taxane at mCRPC in olaparib arm and 73/131 (55.7%) subjects received taxane at mCRPC in NHA arm.

Subjects received both enzalutamide and abiraterone in about 20% in olaparib arm and 17.6% in NHA arm in cohort A+B. The subjects receiving prior abiraterone were well balanced with patients with prior enzalutamide in both arms and cohorts: overall, 40.6% of patients received prior enzalutamide, 39.0% of patients received prior abiraterone.

The inclusion criteria indicated that patients must have progressed on prior NHA for metastatic prostate cancer and/or CRPC. Most of the subjects in cohort A+B had progressed on NHA at mCRPC (98.0%), and most of them received at least 2 lines of treatment (58.8%). These rates were balanced between cohort A and cohort B and among the treatment groups. The treatment sequencing was heterogenous among the subjects, resulting in the absence of optimal recommended sequencing for mCRPC. The MAH confirmed that all subjects included in the study received and progressed on prior NHA either in the metastatic setting or in an earlier disease setting.

In Cohort A+B, 35.2% patients in the olaparib arm and 63.4% patients in the investigators choice of NHA arm received subsequent anticancer therapies, including PARP inhibitor, hormonal therapy/taxane chemotherapy. In the summary of the number of patients remaining on treatment at 6, 12, and 18 months after randomisation, almost half of the patients in the comparator arm switched to olaparib after the disease progression (data not shown).

HRR testing results

Of the 4047 patients that were primarily screened and tested for HRR mutations, there were 4035 patients who were prospectively tested using the CLIA HRR CTA, of which 31.1% (1255/4035) patients failed due to fail test results. Mutations detections were done on either archival tissue or *de novo* tissue. According to the MAH, the reasons of this fail test results were pathology review, DNA extraction and Post DNA

extraction. The use of archival tumoral tissue for the mutation detection may increase the percentage of failure since the quantity of tissue can be low.

Of the 2780 subjects with valid CTA results, 767 (27.6%) subjects were tested tHRRm, which was in line with the prevalence of the loss of function mutations in genes involved in HRR of DNA damage response in mCRPCs estimated between 24% to 30% (Abida et al 2017, Armenia et al 2018, Chung et al 2019, Mateo et al 2015, Robinson et al 2015). Overall, 387/4047 (9.5%) subjects that were tested at FMI were tHRRm and randomized in the study.

Among 4047 patients with an FMI tHRR test result, 778 patients had HRRm mutations. Among these, 391 patients screen failed for non-testing related reasons. Most of the non-testing relating reasons for screen fail were related to inclusion criteria not fulfilled, i.e. normal organ or bone marrow function (19.9%), qualifying HRR mutation in tumour tissue (9.0%) and radiographic progression at study entry while on ADT (7.2%). For 35 of the 391 patients having valid tHRR test result and that screen failed, the reason of not meeting inclusion criterion 9 (confirmation of the presence of an eligible HRR gene mutation) remains unknown.

Overall the mutations in HRR were well balanced between the arms olaparib and NHA. Single BRCA2 mutation occurred with the higher prevalence among the randomized subjects (37.5%).

Single ATM and CDK12 mutations were the second most frequent mutations (24.0% and 24.8% respectively), then single BRCA1 mutation (3.6%). This single mutation occurrence seems in line with the prevalence from the literature. In PROfound, 28/387 (7.23%) subjects harboured co-occurring HRR mutations. A comparative table of the co-occurring HRR mutations in PROfound study was provided. The FMI dataset used for the comparison was generated on a similar sequencing platform as PROfound at FMI while it would have been more adequate to compare the PROfound data with external data from literature. However, it is understood that it is challenging due to differences of elaboration of the datasets (different sequencing platforms and sample preparation, only somatic mutations reported in some datasets). Overall the comparison provided shows similar rate of co-occurring HRR mutation compared to patients screened and patients with HRRm.

Since exploratory endpoints were added in a protocol amendment to compare the effect of olaparib vs NHA in subjects harbouring a qualifying mutation as detected by ctDNA analysis, the comparison of HRR gene mutation status between tumour DNA and plasma derived ctDNA results and the rPFS analysis with mutation identified by ctDNA were provided (data not shown). The overall percent agreements between the CLIA HRR CTA tissue test result and F1 Liquid CDx test result for analysis of plasma ctDNA was consistent among the assessed mutations, i.e. for BRCA1m, BRCA2m and ATMm, respectively 98.2%, 93.7% and 91.3%. The rPFS by BICR for Cohort A with mutation identified by ctDNA was similar to the FAS.The MAH is recommended to provide updated results of the ctDNA analyses specifically for BRCA1/2 mutations from PROfound and other studies with olaparib in prostate cancer patients (recommendation).

Primary endpoint

PROfound study met its primary endpoint with the demonstration of a statistically significant improvement in rPFS in cohort A as assessed by BICR for olaparib compared to investigators choice NHA. At DCO (04 June 2019), 174 progression events had occurred (71% maturity) in Cohort A with a higher proportion on the NHA arm than the olaparib arm (81.9% NHA vs 65.4% olaparib, respectively), approximately 26 months after the first patient was randomised.

The difference in median rPFS by BIRC between olaparib vs NHA was 3.8 months in favour of olaparib (HR = 0.34, 95% IC 0.25-0.47, p<0.0001). The median rPFS was 7.39 months in olaparib arm vs 3.55 months in investigators choice of NHA arm. Progression events occurred in 65.4% of subjects in olaparib arm vs 81.9% of subjects in investigators choice of NHA arm. Similar rPFS results were obtained between the FAS and FMI F1CDx subset. Overall the sensitivity analysis of rPFS in cohort A were concordant with

the primary analysis. However, the pre-defined potential prognostic factors did not include other important prognostic factors such as the previous primary malignancy(ies), previous/concurrent administration of bisphosphonates or denosumab, duration of previous NHA response, the previous treatment with both enzalutamide and abiraterone.

Nearly 10% of enrolled patients had a secondary malignancy. In cohort A and A+B, treatment benefit favouring olaparib was shown in the subgroup analysis for the patients with a personal history of secondary malignancies, but this was not observed in cohort B. The minimum interval between previous other malignancies and the randomisation date varied from 2 to 4 years among some enrolled patients, which seems contradictory to the exclusion criteria 6 (exclusion of patients with other malignancy 5 years before the study enrolment).

In the sensitivity analysis**,** the discordance between investigator and BICR based radiological disease progression was reported in nearly 14% patients of Cohort A.

A slight imbalance in the distribution of the patients previously administrated with abiraterone and enzalutamide was observed between the olaparib and the comparator arm in Cohort B and in the Myriad gBRCAm subset. In cohort B, there was no significant difference on median rPFS and OS between the abiraterone or enzalutamide-treated and olaparib-treated patients indicating the impact on clinical efficacy caused by the imbalanced choice of abiraterone or enzalutamide might be limited. In Myriad gBRCAm subset (cohort A+B), median rPFS of the olaparib treated patients was superior to that of either abiraterone or enzalutamide treated patients. These results are in line with the clinical outcomes from the primary analyses. However, there was no similar improvement in median OS observed among olaparib treated patients in Myriad gBRCAm subset probably due to the immaturity of the OS data and some other potential imbalanced factors.

In addition, the applicant also performed a subgroup analysis on patients who previously received both enzalutamide and abiraterone in case of the potential influence on the efficacy caused by the overlapping resistance mechanism (data not shown). Olaparib improved rPFS (BICR) and OS among mCRPC patients compared to investigators choice of NHA, consistently with the primary analysis results.

Key secondary endpoints

The key secondary endpoints were multiplicity controlled. There was a statistically significant improvement in confirmed radiological ORR by BICR for patients in Cohort A with measurable disease at baseline in the olaparib arm compared with the investigators choice of NHA arm (33.3% vs 2.3%), with an odds ratio of 20.86 (95%CI 4.28-379.18, p<0.0001). Most of the subjects that reached an objective response in olaparib arm achieved a partial response (27 of 28 subjects). Only one subject reached an objective response in NHA arm (PR).

A statistically significant improvement in rPFS by BICR in Cohort A+B was also shown in the olaparib arm compared with the investigators choice of NHA arm. The KM plot shows a separation of the curves in favour of olaparib; this separation started at approximately 2 months (coinciding with the first planned tumour assessment). The median rPFS was 5.82 months in olaparib arm vs 3.52 months in investigators choice arm, and the median progression-free interval was 2.3 months (HR = 0.49, 95% CI 0.38-0.63, p<0.0001). Results in FMI F1CDx subset were consistent with FAS. Since the median rPFS in olaparib arm was lower in cohort A+B than in cohort A only (7.39 months) and taking into account that more subjects were randomized in cohort A than cohort B, it is questionable how much the results in cohorts A+B were driven by the rPFS in cohort A and, especially, by BRCAm patients. Moreover, results in Myriad gBRCAm subset showed a better improvement of rPFS with olaparib compared to NHA with a median progression-free interval of 8.25 months.

The median TTPP based on BPI-SF worst pain [Item 3] and opiate use has not been reached in olaparib arm in cohort A. Nevertheless, there was a statistically significant delay in TTPP in the olaparib arm

compared with the investigators choice of NHA arm (HR: 0.44; p=0.0192). The KM plot showed a separation of the 2 curves at approximately 3.5 months after randomization.

The initially submitted OS data were immature (38% mature; 93/245 events) at the time of DCO (4 June 2019). The MAH provided the final OS analysis (DCO 20 March 2020; 60.4% mature; 148 events out of 245 patients in Cohort A). There was a statistically significant improvement in OS in Cohort A with a HR of 0.69 (95%CI 0.50, 0.97; p=0.0175) and a median OS improvement of 4.4 months compared to NHA. The OS at 12 months was 73.07% in olaparib arm vs 56.94% in NHA arm and at the time of DCO, 56.8% of olaparib-treated patients and 48.2% of investigators choice of NHA-treated patients were alive and in survival follow-up. The KM plots showed a separation of the curves at approximately 3 months after randomisation. Moreover, approximately 80% of subjects with a BICR confirmed progression in the investigators choice of NHA arm crossed-over to olaparib arm, which could lead to confounded results. A sensitivity analysis to adjust the impact of olaparib has been performed and the results were still in favour to olaparib arm with HR of 0.42 (95% CI 0.19, 0.91).

Overall the PROfound study met its primary endpoint and key secondary endpoints that were multiplicity controlled.

Other secondary endpoints

The other efficacy endpoints in Cohort A, Cohort A+B and Cohort B were not adjusted for multiplicity.

For the other efficacy endpoints in Cohort A, there was a favourable trend for olaparib compared to NHA except for the median duration of response (DoR) which was longer in NHA arm (7.39 months, 95% CI NC, NC) compared to olaparib arm (5.88 months, 95% CI 5.52, 9.03), taking into account that DoR was based on a single subject with a confirmed response in NHA arm. There was a favourable trend in PFS2 (assessed by the investigators) for the olaparib arm (median PFS2 = 17.22 months, 95% CI 12.71, 18.30) compared to the investigators choice of NHA arm (median PFS2 = 10.64, 95%CI 9.13, 11.24) as demonstrated by an improvement in median PFS 2 of 6.6 months in Cohort A, with the switch from NHA arm to olaparib that could have confounded the PFS 2. PSA_{50} results should be interpreted with caution since imbalances in PSA baseline were noted between the 2 arms.

For the other efficacy endpoints in Cohort A+B, a favourable trend in efficacy endpoints was shown with olaparib compared to NHA. The results were consistent with the Cohort A for interim and final OS, DoR, time to opiate use and CTC conversion but the efficacy improvement is less important in Cohort A+B compared to Cohort A for rPFS, ORR, PFS2, PSA_{50}.

All of PRO results showed that compared with the investigator's choice of NHA, no statistically significant or clinically meaningful difference or at least a favouring trend on QOL were observed after olaparib treatment among some HRR-mutated mCRPC patients. In most cases, the concordance of these PRO results between Cohort A and Cohort A+B reinforced the positive effect of the olaparib over NHAs. However, the results in BRCAm population is not considered robust for inclusion in the SmPC.

Subgroup analysis

Subgroup analysis of rPFS in cohort A did not reveal an obvious differential benefit across most of the pre-defined subgroups compared with the overall population. In Asian population rPFS was less favourable to olaparib compared to the White population. A larger effect in terms of rPFS was noted for olaparib compared to NHA in subjects with prior taxane than in subjects without prior taxane (respectively HR = 0.28 [95% CI 0.19, 0.41] vs HR = 0.55 [95% CI 0.32, 0.97]).

Subgroup analysis per gene mutation were conducted in Cohort A+B, considering mutations in single gene and co-mutations. In patients with tBRCA2m, there was a clear improvement of rPFS for olaparib compared to NHA (median rPFS in olaparib 10.84 months vs 3.48 months in NHA) with a median progression-free interval of 7.36 months and HR = 0.21 (95% CI = 0.13, 0.32), an OS improvement with median OS of

24.84 months in olaparib arm vs 15.15 months in NHA arm (HR = 0.59, 95% CI 0.37, 0.95) and an ORR higher in olaparib arm compared to NHA arm (respectively 55.8% vs 0).

In BRCA1 and/or BRCA2 subgroup, there was an improvement of median rPFS with olaparib (9.79 months, 95% CI 7.62, 11.30) compared to NHA (2.96 months, 95% CI 1.81, 3.55) with HR of 0.22 (95% CI 0.15, 0.32).

A numerical improvement of rPFS and OS was shown with olaparib for BRCA1 subgroup but the very low number of patients leads to limitation for any conclusion.

No difference of median rPFS between olaparib (5.36 months, 95% CI 3.61, 6.21) compared to NHA (4.70 months, 95% CI 1.84, 7.26) in ATM subgroup was shown with HR = 1.04 (95% CI 0.61-1.87) and a very limited improvement of median OS was observed (18.00 months in olaparib arm vs 15.57 months in NHA arm) with HR=0.93 (95% CI 0.53, 1.75).

Since BRCA2 mutation was the most frequently reported HRR mutation among the mCRPC subjects (128/359 in single mutation and 17/28 in co-occurring mutations) and the efficacy results in this subgroup demonstrates a clear benefit of olaparib vs NHA, the efficacy results in Cohort A might likely be driven by results in BRCA2m. Although the number of patients with BRCA1 mutations was lower, based on biological rationale and overall available data, results in patients with BRCA2 mutations could be extrapolated to patients with BRCA1 mutations.

In accordance with the EMA Guideline on the investigation of subgroups in confirmatory clinical trials (EMA/CHMP/539146/2013), the inconsistency of BRCA1/2m and ATMm subgroups among the trial was further discussed. In all trials investigating the effect of PARP inhibitors and exploring subsets of mutations possibly predictive of sensitivity to these drugs, activity and benefit size were more pronounced in the BRCAm groups as opposed to other groups. Grouping ATMm patients with BRCAm ones and not the other mutations appears *a posteriori* questionable: outcomes in ATMm patients were similar to those observed in cohort B and contrast with the undisputable benefit in BRCAm patients.

Regarding the 12 other HRR mutations from cohort B, the low number of subjects in each gene subgroup cannot allow to draw any conclusion on a potential benefit of olaparib compared to NHA. The CDK12 subgroup is comparable to ATM subgroup in terms of number of subjects and efficacy results trend to a more favourable effect of olaparib in CDK12 compared to ATM.

Overall, the efficacy results by gene subgroups show that BRCA2m subjects were the best responders to olaparib compared to NHA and likely drove the efficacy results among the Cohort A and Cohort A+B. Although the number of subjects in each subgroup was low, no difference in efficacy of olaparib compared to NHA was shown in the ATMm subgroup. Moreover the efficacy results in non-BRCAm patients showed no difference of olaparib arm with the comparator, i.e. for rPFS, HR = 0.94 (95%CI 0.68-1.34) with a median rPFS improvement of 1.58 months and for final OS, HR = 0.95 (95%CI 0.68-1.34) with a median OS improvement of 2.46 months. The exploratory analysis for BRCAm patients by gBRCAm vs sBRCAm showed that median rPFS in gBRCAm and sBRCAm were consistent in subjects with a single mutation across the Cohort A. A favourable trend for olaparib was shown for the other efficacy endpoints for both gBRACm and sBRCAm, however these results were limited by the low number of subjects. A total of 19 subjects harboured BRCA1/2 co-occurring mutations. The exclusion of co-occurring mutations from the efficacy analysis for BRCAm patients by gBRCAm vs sBRCAm was justified by the applicant to enable evaluation of the contribution of each individual HRR mutation to clinical outcomes, which is agreed.

Subgroup analysis in Cohort B excluding patients with BRCA1, BRCA2 or ATM mutation (a total of 4 subjects incorrectly assigned in Cohort B) showed a rPFS that was less favourable to olaparib compared to the primary analysis in Cohort B, respectively HR = 0.942 (95% CI 0.619, 1.469) vs HR = 0.88 (95%CI 0.58, 1.36). The other efficacy results were consistent with the primary analysis of cohort B with a similar small numerical improvement of OS (HR=0.749, 95% CI 0.452, 1.270) and no improvement of TTPP nor ORR.

The treatment benefit observed when the 4 other patients with a BRCA2 or ATM mutation were included in Cohort A was consistent with the primary analyses of Cohort A. The rPFS in cohort B may have been slightly driven by the subjects with BRCA1, BRCA2 or ATM mutation.

Supportive efficacy data was provided by Study 42, an open-label, non-randomised, non-comparative study assessing efficacy and the safety of olaparib in advanced cancer who have confirmed a genetic BRCA1/ BRCA2 mutation, including prostate cancer (data not shown). The efficacy results are based on a low number of subjects with advanced prostate cancer (N=8) with a gBRCA mutation, therefore it remains challenging to interpret them for the support of an indication including a broader panel of HRR mutations.

At the time of PROfound study initiation, only abiraterone and enzalutamide were approved among new hormonal agents (NHAs) or next-generation anti-androgen therapies. However, other NHAs have been approved for the treatment of prostate cancer. Given the mechanism of action of NHAs that either block the biosynthesis of androgens (i.e., abiraterone) or prevent the androgens from stimulating prostate cancer cells by blockade to the androgen receptors on prostate cancer cells (e.g. enzalutamide), it was considered reasonable to extrapolate the results obtained with prior use of enzalutamide to other medicines of the same class as being mechanistically and therapeutically similar. Patients with BRCAm who failed either abiraterone or enzalutamide received appear to derive similar clinical benefit from olaparib treatment.

2.4.3. Conclusions on the clinical efficacy

PROfound study met its primary endpoint rPFS by BICR in Cohort A, which was supported by the key secondary endpoints (statistically improvement of confirmed ORR, TTPP and final OS in Cohort A). The subgroup gene analysis showed that the benefit of olaparib is higher in the subgroup with BRCA1/2 mutations compared to the other HRR gene mutations, which may drive the efficacy in Cohort A. In particular, no difference in efficacy of olaparib compared to NHA was shown in the ATM subgroup.

The efficacy results in Cohort A+B also showed an improvement of rPFS, ORR and final OS with olaparib but these results are likely driven by efficacy in Cohort A and especially in patients with BRCAm since the results in Cohort B have not demonstrated a benefit of olaparib compared to NHA.

A benefit of olaparib compared to NHA is shown in patients with BRCA1/2m but has not been demonstrated in Cohort B and ATM subgroup. Moreover, the efficacy results in non-BRCAm patients showed no difference between olaparib arm and the comparator.

2.5. Clinical safety

Introduction

Across the entire clinical program, as of 15 June 2019, approximately 11919 patients are estimated to have received treatment with olaparib. The focus of this application is the PROfound study, where olaparib 300 mg bd or investigators choice of NHA was given as a treatment for mCRPC patients with HRRm who have failed prior treatment with an NHA.

Supportive safety data, for olaparib 300 mg bd as a monotherapy, are provided by a pool of 1585 patients who were intended to receive this dose and received olaparib in AstraZeneca-sponsored studies, as indicated in Table 44.

Table 44: Number of patients in the 300mg bd pool (DCO 4 June 2019)

Study/pooled dataset	Number of patients intended for the 300mg bd cohort

	and received olaparib (all tumour types)
Total exposed	**1585**
PROfound: Phase III mCRPC patients with a HRRm who have failed prior treatment with an NHA.	256
POLO: Phase III gBRCAm metastatic pancreatic adenocarcinoma patients whose disease has not progressed on first-line platinum-based chemotherapy	91
SOLO3: Phase III gBRCAm ≥third line ovarian cancer patients	178
SOLO1: Phase III FIGO Stage III-IV ovarian cancer SOLO1 China cohort	260 40
SOLO2: Phase III platinum-sensitive serous ovarian cancer SOLO2: China cohorta	195 22
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 4: Phase I Food interaction & QT	57
Study 6: Phase I Renal impairment study	43
Study 7: Phase I CYP3A4 inhibition and QT	56
Study 8: Phase I CYP induction	19
Study D081CC00001: Phase I anti-hormonal PK study	69
Study D081BC00001: Phase I Japan Monotherapy study	19
D0816C00005: Phase I hepatic impairment study	31
D081BC00002: China PK study	20

Patient exposure

Overall extent of exposure: PROfound

All of the 256 patients randomised to the olaparib arm in PROfound study received study treatment; 1 patient in the investigators' choice of NHA arm did not receive treatment. The PROfound SAS consisted of 386 patients (256 who received olaparib and 130 who received investigators choice of NHA).

As shown in Table 45, a higher proportion of olaparib-treated patients received treatment for a period of at least 3 months compared with the investigators choice of NHA arm. The number of patients still on treatment began to diverge between arms after 2 months (in favour of olaparib).

Table 45: PROfound overall extent of exposure

Month (approximate)	Number (%) of patients	
	Olaparib 300 mg bd (N=256)	Investigators choice of NHA (N=130)
≥Day 1	256 (100)	130 (100)
≥1 month (30.4 days)	247 (96.5)	123 (94.6)
≥2 months (60.9 days)	228 (89.1)	100 (76.9)
≥3 months (91.3 days)	214 (83.6)	78 (60.0)
≥6 months (182.6 days)	158 (61.7)	39 (30.0)
≥9 months (273.9 days)	100 (39.1)	14 (10.8)
≥12 months (365.3 days)	52 (20.3)	5 (3.8)
≥18 months (547.9 days)	10 (3.9)	1 (0.8)

As shown in Table 46, the median total treatment duration in the olaparib arm (7.5 months), was approximately 1.9 times longer than in the investigators choice of NHA (3.9 months), consistent with the delayed time to disease progression or death. Actual treatment duration was similar to total treatment duration suggesting short treatment interruptions.

Table 46: Duration of olaparib/investigators choice of NHA

Treatment duration (days)	Olaparib 300 mg bd (N=256)	Investigators choice of NHA (N=130)
Total treatment duration[a]		
Mean (std)	242.8 (147.68)	146.3 (106.54)
Median	227.0	119.5
Minimum; Maximum	1; 692	17; 596
Total treatment days	62145	19018
Actual treatment duration[b]		
Mean (std)	229.6 (140.73)	143.7 (105.68)
Median	214.5	119.0
Minimum; Maximum	1; 589	17; 596
Total treatment days	58776	18683

In general, toxicity observed during the course of the study could be managed by dose interruptions and reductions; reduction to 250 mg bd as a first step and further reduction to 200 mg bd as a second step, with no dose re-escalations allowed. These interruptions and reductions included single missed or forgotten doses.

In both arms, AE was the most common reason for dose interruption (90 [35.2%] olaparib-treated patients versus 11 [8.5%] investigators choice of NHA-treated patients), dose reductions (59 [23.0%] olaparib-treated patients versus 6 [4.6%] investigators choice of NHA-treated patients) and dose modifications (99 [38.7%] olaparib-treated patients versus 13 [10.0%] investigators choice of NHA-treated patients).

Median relative dose intensity (percentage of the actual dose delivered relative to the intended dose through to treatment discontinuation) and percentage intended dose (percentage of the actual dose delivered relative to the intended dose through progression) were similar and were >98% in both treatment arms, suggesting that most patients were treated through to progression and dose modifications had a small impact on dose intensity.

An assessment of mean daily dose over time throughout PROfound (Table 47) showed that the majority of patients in the olaparib treatment arm (55.8% to 82.8%, dependent on time period) received between 500 and 600 mg/day.

Table 47: PROfound: Total daily dose of olaparib by time period (Cohort A+B)

Mean olaparib total daily dose (mg)	Number (%) of patients by time period				
	Up to 3 months (N=256)	>3 to ≤6 months (N=214)	>6 to ≤9 months (N=158)	>9 to ≤12 months (N=100)	>12 months (N=52)
>600 to ≤700	0	1 (0.5)	0	0	0
>500 to ≤600	212 (82.8)	151 (70.6)	107 (67.7)	63 (63.0)	29 (55.8)
>400 to ≤500	32 (12.5)	37 (17.3)	26 (16.5)	15 (15.0)	10 (19.2)
≤400	12 (4.7)	25 (11.7)	25 (15.8)	22 (22.0)	13 (25.0)

Overall extend of exposure: Olaparib 300 mg bd pool

The median total treatment duration in the 300 mg bd pool was 266.0 days (approximately 8.7 months).

Table 48: Overall extent of exposure in the 300 mg bd pool

Treatment period	Number (%) of patients
	Olaparib 300 mg bd (N=1585)
≥0	1585 (100)
≥1 week	1570 (99.1)
≥1 month	1495 (94.3)
≥3 months	1246 (78.6)
≥6 months	977 (61.6)
≥12 months	599 (37.8)
≥18 months	417 (26.3)
≥24 months	285 (18.0)
≥36 months	22 (1.4)
≥48 months	6 (0.5)

Demographics

Demographic and disease characteristics of patients in PROfound are summarised in **Table 16** and **Table 17**.

In the FAS, demographic and baseline characteristics were generally well balanced between treatment groups, in line with expectations and representative of the proposed indication. The majority of patients were White, and one quarter of patients were Asian (27.1%). There were no noteworthy differences in age, race and ethnicity between the treatment groups. The median age of patients in PROfound (69.0 years in both treatment arms) was slightly younger than the median age of ≥70 years for unselected mCRPC patients who received enzalutamide, abiraterone or docetaxel following progression on a prior NHA (enzalutamide or abiraterone; see Azad et al 2015, de Bono et al 2018, Khalaf et al 2018, Loriot et al 2013, Mezynski et al 2012, Vogelzang et al 2015).

The demographics and baseline characteristics of the Myriad gBRCAm subset (n=62 patients) and the FMI F1CDx subset (n=376 patients) were similar to the FAS (n=387 patients).

Comparison with olaparib 300mg bd pool

Demographic data have not been pooled, as the group of studies contributing to the 300 mg bd pooled dataset have different patient populations of varying stages of disease. Summaries of the key demographic and baseline patient characteristics for the 15 studies contributing to the pooled dataset are provided in Table 49. The data in this table are for all patients in these studies and not just those in the olaparib 300 mg bd tablet dose cohorts. The majority of patients in the 300 mg bd pool had either ovarian, fallopian tube or primary peritoneal cancer (818/1585 [51.6%] patients), breast cancer (268/1585 [16.9%] patients) or prostate cancer (267/1585 [16.8%] patients). Patients with other advanced solid tumours, including colon/colorectal (n=23 patients) or pancreatic (n=103 patients) cancers were also treated in these studies. Patients were generally heavily pre-treated with anticancer therapies.

Table 49: Key demographic and baseline characteristics by study: studies in olaparib 300 mg bd pool

Study Number of Subjects randomised/ treated	Age/sex/race	Performance status	Tumour type	Prior anticancer treatment	Gene mutation status
D081DC00007 (PROfound) N=387/386 (256 in the pooled dataset)	47 to 91 years (mean age 68.6 years) All Male 248 (64.1%) White, 105 (27.1%) Asian, 8 (2.1%) Black or African American, 3 (0.8%) Other and 23 (5.9%) Missing	ECOG PS ≤2 186 (48.1%) PS0 183 (47.3%) PS1 17 (4.4%) PS2 (data was missing for 1 patient)	HRRm metastatic castration-resistant prostate cancer	All pre-treated	All HRRm
D081FC00001 (POLO) N=154/151 (91 in the pooled dataset)	36 to 84 years (mean age 57.5 years) 70 (45.5%) Female 84 (54.5%) Male 141 (91.6%) White, 6 (3.9%) Asian, 5 (3.2%) Black, African American and 2 (1.3%) Other	ECOG PS ≤1 103 (66.9%) PS0 48 (31.2%) PS1 (data were missing for 3 patients)	Metastatic pancreatic adenocarcinoma	All pre-treated Median number of prior chemotherapies for metastatic disease was 1.0	All *gBRCAm*
D0816C00010 (SOLO3) N=266/254 (178 in the pooled dataset)	39 to 79 years (mean age 58.5 years) All Female 148 (83.1%) White, 24 (13.5%) Asian, 6 (3.4%) Black, African American and Other	ECOG PS ≤2 198 (74.4%) PS0 67 (25.2%) PS1 1 (0.4%) PS2	Advanced (FIGO Stage III-IV) Ovarian Cancer	All pre-treated Median number of prior chemotherapies was 3.0	All *gBRCAm*
SOLO1 N=391/390 (260 n the pooled dataset)	29 to 84 years (mean age 53.5 years) All Female 320 (81.8%) White, 59 (15.1%) Asian, 12 (3.1%) Black, African American and Other	ECOG PS ≤1 305 (78.0%) PS0 85 (21.7%) PS1	Advanced (FIGO Stage III-IV) Ovarian Cancer	All pre-treated Median number of prior chemotherapies was 1.0	389 *gBRCAm* 2 *sBRCAm*
SOLO1 China cohort N=64/64 (44[3] in the pooled dataset)	33 to 67 years (mean age 51.0 years) All Female 64 (100%) Asian.	ECOG PS ≤1 33 (51.6%) PS0 31 (48.4%) PS1	Advanced (FIGO Stage III-IV) Ovarian Cancer	All pre-treated Median number of prior chemotherapies was 1.0	All *gBRCAm*
OlympiAD N=302/296 (205 in the pooled dataset)	22 to 76 years (mean age 45.3 years) 295 (97.7%) Female, 7 (2.3%) Male 197 (65.2%) White, 94 (31.1%) Asian, 11 (3.6%) Black, African American and Other	ECOG PS ≤1 210 (69.5%) PS0 92 (30.5%) PS1	Metastatic breast cancer	All pre-treated Median number of prior chemotherapies was 1.0	All *gBRCAm*

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

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

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

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

Adverse events

Overview of AE

The number and proportion of patients who had at least one AE in any category in PROfound are summarised in Table 50.

Table 50: PROfound: Number (%) of patients who had at least 1 AE in any category (Cohort A+B SAS)

AE category	Number (%) of patients*	
	Olaparib 300 mg bd (N=256)	Investigators choice of NHA (N=130)
Any AE	244 (95.3)	114 (87.7)
Any AE of CTCAE Grade 3 or higher	130 (50.8)	49 (37.7)
Any AE with outcome = death	10 (3.9)	5 (3.8)
Any SAE (including events with outcome = death)	91 (35.5)	36 (27.7)
Any AE leading to discontinuation of study treatment	46 (18.0)	11 (8.5)
Any AE leading to dose reduction of study treatment	57 (22.3)	5 (3.8)
Any AE leading to interruption of study treatment	115 (44.9)	24 (18.5)

The patients in the confirmed FMI F1CDx subset (n=375 patients) included most of the SAS dataset (n=386 patients). Overall the safety profile (AEs, SAEs, DAEs, Grade ≥3) was similar to the overall patient population. The confirmed Myriad gBRCAm subset (n=62 patients) included a smaller subset of the SAS dataset. Overall the safety profile (AEs, SAEs, DAEs, Grade ≥3) was similar to the overall patient population. In this subset analyses there were no DAEs and fatal AEs in the investigators choice of NHA arm, reflective of the small number of patients selected (n=19).

AE data for the Safety Switch Analysis Set (patients randomised to the investigators choice of NHA arm who switched to olaparib after confirmed BICR disease progression; n=72 patients) was similar to those for the SAS.

Safety profile in patients who switched to olaparib was quite similar with slightly less SAE and drug discontinuation as expected due to shorter time of olaparib exposure.

Comparison with olaparib 300mg bd pool

Table 51: Number (%) of patients who had at least 1 AE in any category

AE category	Number (%) of patients[a]	
	PROfound Cohort A+B SAS olaparib 300 mg bd[b] (N=256)	Olaparib 300 mg bd pool[c] (N=1585)
Any AE	244 (95.3)	1542 (97.3)
Any AE of CTCAE Grade 3 or higher	130 (50.8)	659 (41.6)
Any AE with outcome = death	10 (3.9)	19 (1.2)
Any SAE (including events with outcome = death)	91 (35.5)	365 (23.0)
Any AE leading to discontinuation of study treatment	46 (18.0)	148 (9.3)
Any AE leading to dose reduction of study treatment	57 (22.3)	339 (21.4)
Any AE leading to interruption of study treatment	115 (44.9)	630 (39.7)

Common Adverse events

In PROfound, the most commonly reported AEs occurring in ≥5% of patients in either treatment arm are presented in Table 52.

Table 52: Most common AE (occurring in >5% patients in either arm and adjusted by patient year exposure)

MedDRA preferred term	Olaparib 300 mg bd (N=256)		Investigators choice of NHA (N=130)	
	Number (%) of patients[a]	Event rate[b] (per 1000 patient years)	Number (%) of patients[a]	Event rate[b] (per 1000 patient years)
Any AE	**244 (95.3)**	**9029.48**	**114 (87.7)**	**7192.69**
Anaemia	118 (46.1)	1006.90	20 (15.4)	377.30
Nausea	106 (41.4)	869.70	25 (19.2)	515.45
Decreased appetite	77 (30.1)	549.08	23 (17.7)	455.25
Fatigue	67 (26.2)	461.84	27 (20.8)	552.39
Diarrhoea	54 (21.1)	348.02	9 (6.9)	169.75
Vomiting	47 (18.4)	298.55	16 (12.3)	306.76
Constipation	45 (17.6)	276.01	19 (14.6)	377.53
Asthenia	40 (15.6)	250.09	18 (13.8)	356.32
Back pain	35 (13.7)	208.96	15 (11.5)	286.32
Oedema peripheral	32 (12.5)	191.76	10 (7.7)	183.70
Cough	28 (10.9)	165.92	3 (2.3)	54.10
Dyspnoea	26 (10.2)	153.04	4 (3.1)	71.84
Arthralgia	24 (9.4)	138.93	14 (10.8)	274.92
Thrombocytopenia	22 (8.6)	124.95	2 (1.5)	35.78
Weight decreased	21 (8.2)	121.02	7 (5.4)	127.07
Urinary tract infection	18 (7.0)	101.69	15 (11.5)	280.50
Dyspepsia	18 (7.0)	105.54	3 (2.3)	54.10
Musculoskeletal pain	17 (6.6)	96.79	6 (4.6)	108.69
Dizziness	17 (6.6)	95.77	5 (3.8)	90.70
Dysgeusia	17 (6.6)	97.59	2 (1.5)	35.80
Pyrexia	16 (6.3)	89.03	6 (4.6)	109.25
Neutropenia	16 (6.3)	90.65	0	0
Headache	15 (5.9)	85.31	2 (1.5)	35.88
Musculoskeletal chest pain	14 (5.5)	78.29	6 (4.6)	111.09
Insomnia	14 (5.5)	77.95	4 (3.1)	72.18
Lymphopenia	13 (5.1)	74.04	1 (0.8)	17.96
Haematuria	7 (2.7)	38.68	9 (6.9)[c]	165.40[c]

The most commonly reported (≥30% of patients in the olaparib arm) AEs by system organ class (SOC) were: Gastrointestinal disorders (170 [66.4%] patients in the olaparib arm and 51 [39.2%] patients in the investigators choice of NHA arm); General disorders and administration site conditions (141 [55.1%] patients and 58 [44.6%] patients, respectively); Blood and lymphatic system disorders (132 [51.6%] patients and 23 [17.7%] patients, respectively); Metabolism and nutrition disorders (100 [39.1%] patients and 37 [28.5%] patients, respectively); Musculoskeletal and connective tissue disorders (96 [37.5%] patients and 51 [39.2%] patients, respectively); and Infections and infestations (78 [30.5%] patients and 32 [24.6%] patients, respectively). The proportion of patients with AEs in each of the SOCs was generally higher for the olaparib arm, compared with the investigators choice of NHA arm.

The largest differences in incidence between the 2 arms were for the AEs of anaemia and nausea: anaemia occurred at an incidence of 46.1% in the olaparib arm vs an incidence of 15.4% in the investigators choice of NHA arm (a difference of 30.7%); nausea occurred at an incidence of 41.4% in the olaparib arm vs an incidence of 19.2% in the investigators choice of NHA arm (a difference of 22.2%). Almost all of the AEs of nausea were CTCAE Grade ≤2 (only 3 [1.2%] olaparib-treated patients had AEs of nausea that were CTCAE Grade 3); however, over half of the AEs of anaemia were also CTCAE Grade ≤2, 55 (21.5%) olaparib-treated patients had AEs of anaemia that were CTCAE Grade ≥3, compared with 7 (5.4%) patients in the investigators choice of NHA arm.

Pulmonary embolism was reported in 11 (4.3%) patients in the olaparib arm and 1 (0.8%) patient in the investigators choice NHA arm. This imbalance was smaller after adjustment for duration of exposure: 62.24 (events per 1000 patient-years) and 17.88 (events per 1000 patient-years), respectively. Six (2.3%) patients in the olaparib arm and 1 (0.8%) patient in the investigators choice of NHA arm reported pulmonary embolism Grade ≥3. Treatment was interrupted in 2 patients in the olaparib arm and 1 patient in the investigators choice of NHA arm and 1 AE led to discontinuation of olaparib. Pulmonary embolism was reported as causally related by the investigator in 2 patients (0.8%) in the olaparib arm. Eight out of 11 patients continued olaparib at an unchanged dose. The outcome was reported as recovered in 5 patients, recovering in 2 patients, and not recovered in 4 patients in the olaparib arm and recovered in the 1 patient in the investigators choice of NHA arm with no reports of recurrence in either arm. The majority of patients with pulmonary embolism (9 out of 1) were 65 years or older in the olaparib arm. No difference has been detected in medical history between the olaparib and investigators choice NHA arms. None of the patients who developed pulmonary embolism had a history of venous thromboembolic events and none of them were on anticoagulation prior to the pulmonary embolism event in the olaparib arm. The time to onset of the events ranged between 6 and 337 days and 4 events occurred after the first 120 days of treatment in either arm. In the olaparib arm, 5 patients experienced CTCAE Grade 1 or Grade 2 AEs of pulmonary embolism, suggesting that these patients were asymptomatic and did not require hospitalisation.

Comparison with olaparib 300mg bd pool

The most common (≥30% of patients in the 300 mg bd pool) AEs consistently reported in PROfound and in the 300 mg bd pool were nausea, anaemia, fatigue and vomiting. In general, the most common events with olaparib were mild or moderate in severity and resolved on continued treatment. Table 53 shows the most commonly-reported AEs for the olaparib treatment arm in PROfound and the 300 mg bd pool.

The common (≥10% in either arm) AEs that were reported at a higher incidence (≥5% difference) in the PROfound SAS compared with the 300 mg bd pool were: anaemia and decreased appetite. The common (≥10% in either arm) AEs that were reported at a lower incidence (≥5 difference) in the PROfound SAS compared with the 300 mg bd pool were: abdominal pain, fatigue, headache, nausea, neutropenia and vomiting.

Table 53: Most common AEs (reported in ≥5% in the olaparib treatment arm of PROfound or the 300 mg bd pool)

MedDRA preferred term	Number (%) of patients[a]	
	PROfound Cohort A+B SAS olaparib 300 mg bd[b] (N=256)	Olaparib 300 mg bd pool[c] (N=1585)
Patients with any AE	**244 (95.3)**	**1542 (97.3)**
Anaemia	118 (46.1)	632 (39.9)
Nausea	106 (41.4)	944 (59.6)
Decreased appetite	77 (30.1)	371 (23.4)
Fatigue	67 (26.2)	589 (37.2)
Diarrhoea	54 (21.1)	412 (26.0)
Vomiting	47 (18.4)	514 (32.4)
Constipation	45 (17.6)	288 (18.2)
Asthenia	40 (15.6)	262 (16.5)
Back pain	35 (13.7)	196 (12.4)
Oedema peripheral	32 (12.5)	134 (8.5)
Cough	28 (10.9)	207 (13.1)
Dyspnoea	26 (10.2)	197 (12.4)
Arthralgia	24 (9.4)	201 (12.7)
Thrombocytopenia	22 (8.6)	131 (8.3)
Weight decreased	21 (8.2)	57 (3.6)
Dyspepsia	18 (7.0)	155 (9.8)
Urinary tract infection	18 (7.0)	132 (8.3)
Dizziness	17 (6.6)	181 (11.4)
Dysgeusia	17 (6.6)	173 (10.9)
Musculoskeletal pain	17 (6.6)	83 (5.2)
Neutropenia	16 (6.3)	200 (12.6)
Pyrexia	16 (6.3)	175 (11.0)
Headache	15 (5.9)	243 (15.3)
Insomnia	14 (5.5)	113 (7.1)
Musculoskeletal chest pain	14 (5.5)	58 (3.7)
Lymphopenia	13 (5.1)	53 (3.3)
Pain in extremity	12 (4.7)	98 (6.2)
Stomatitis	12 (4.7)	96 (6.1)
WBC count decreased	11 (4.3)	112 (7.1)
Abdominal pain	10 (3.9)	246 (15.5)
Blood creatinine increased	10 (3.9)	87 (5.5)
Rash	10 (3.9)	86 (5.4)
Upper respiratory tract infection	8 (3.1)	131 (8.3)
Leukopenia	7 (2.7)	114 (7.2)
Neutrophil count decreased	7 (2.7)	99 (6.2)
Nasopharyngitis	6 (2.3)	113 (7.1)
Myalgia	6 (2.3)	86 (5.4)
ALT increased	5 (2.0)	84 (5.3)
Abdominal pain upper	4 (1.6)	148 (9.3)
Muscle spasms	4 (1.6)	80 (5.0)

In relation to thromboembolism events, the MAH provided a comparison between PROfound and the olaparib monotherapy pool.

Table 54: PROfound and the 300 mg bd pool: Patients with venous thromboembolism events

Preferred term	Number (%) of patients[a]								
	PROfound Cohort A+B SAS[b]						Olaparib 300 mg bd pool[c] (N=1585)		
	Olaparib 300 mg bd (N=256)			Investigators choice of NHA (N=130)					
	Any AE	Grade ≥3	SAE	Any	Grade ≥3	SAE	Any	Grade ≥3	SAE
Pulmonary embolism	11 (4.3)	6 (2.3)	5 (2.0)	1 (0.8)	1 (0.8)	1 (0.8)	27 (1.7)	18 (1.1)	10 (0.6)
Embolism	4 (1.6)	2 (0.8)	1 (0.4)	0	0	0	8 (0.5)	3 (0.2)	2 (0.1)
Deep vein thrombosis	4 (1.6)	0	0	2 (1.5)	1 (0.8)	1 (0.8)	16 (1.0)	4 (0.3)	5 (0.3)
Thrombosis	0	0	0	1 (0.8)	0	0	5 (0.3)	0	0
Vena cava thrombosis	1 (0.4)	0	0	0	0	0	1 (0.1)	0	0
Venous thrombosis	1 (0.4)	0	0	1 (0.8)	0	0	2 (0.1)	0	0
Mesenteric vein thrombosis	1 (0.4)	0	0	0	0	0	1 (0.1)	0	0

- **Adverse events by treatment period**

The majority of AEs first occurred within the first 3 months of treatment. The majority of patients in both treatment arms were on study treatment at this stage in the study, enabling a direct comparison. The onset data for 0 to 3 months and 3 to 6 months presented in Table 55.

Most of the common AEs occurred at a higher frequency in the olaparib arm, compared with the investigators choice of NHA arm at both 0 to 3 months and 3 to 6 months of treatment.

Table 55: PROfound: Onset of AEs in the first 3 months and 3-6 months of treatment for the most common AEs (occurring in ≥5% of patients in either arm overall; Cohort A+B SAS)

Preferred term[a]	Number (%) of patients			
	Onset in 0-3 months		Onset in 3-6 months	
	Olaparib 300 mg bd (N=256)	Investigators choice of NHA (N=130)	Olaparib 300 mg bd (N=227)	Investigators choice of NHA (N=97)
Anaemia	84 (32.8)	10 (7.7)	31 (13.7)	8 (8.2)
Nausea	88 (34.4)	21 (16.2)	15 (6.6)	3 (3.1)
Decreased appetite	56 (21.9)	18 (13.8)	15 (6.6)	4 (4.1)
Fatigue	56 (21.9)	20 (15.4)	6 (2.6)	3 (3.1)
Diarrhoea	36 (14.1)	8 (6.2)	13 (5.7)	0
Vomiting	33 (12.9)	13 (10.0)	13 (5.7)	4 (4.1)
Constipation	28 (10.9)	13 (10.0)	9 (4.0)	5 (5.2)
Asthenia	29 (11.3)	14 (10.8)	12 (5.3)	2 (2.1)
Back pain	18 (7.0)	8 (6.2)	8 (3.5)	7 (7.2)
Oedema peripheral	19 (7.4)	10 (7.7)	12 (5.3)	0
Cough	10 (3.9)	1 (0.8)	12 (5.3)	1 (1.0)
Dyspnoea	15 (5.9)	4 (3.1)	10 (4.4)	0
Arthralgia	13 (5.1)	9 (6.9)	4 (1.8)	5 (5.2)
Thrombocytopenia	10 (3.9)	1 (0.8)	8 (3.5)	0
Weight decreased	11 (4.3)	4 (3.1)	6 (2.6)	2 (2.1)
Urinary tract infection	9 (3.5)	8 (6.2)	5 (2.2)	6 (6.2)
Dyspepsia	14 (5.5)	1 (0.8)	5 (2.2)	2 (2.1)
Musculoskeletal pain	7 (2.7)	3 (2.3)	4 (1.8)	2 (2.1)
Dizziness	8 (3.1)	3 (2.3)	4 (1.8)	1 (1.0)
Dysgeusia	12 (4.7)	1 (0.8)	2 (0.9)	1 (1.0)
Pyrexia	7 (2.7)	4 (3.1)	7 (3.1)	1 (1.0)
Neutropenia	8 (3.1)	0	6 (2.6)	0
Headache	6 (2.3)	1 (0.8)	6 (2.6)	1 (1.0)
Musculoskeletal chest pain	7 (2.7)	5 (3.8)	4 (1.8)	2 (2.1)
Insomnia	10 (3.9)	3 (2.3)	1 (0.4)	0
Lymphopenia	8 (3.1)	0	5 (2.2)	1 (1.0)
Haematuria	4 (1.6)	7 (5.4)	1 (0.4)	1 (1.0)

Data for first onset of AEs beyond the 6 month period (reported as first onset of AEs >112 days, showed that only 14 patients (6.4%) still receiving treatment in the olaparib arm, and 5 patients (6.3%) still receiving treatment in the investigators choice of NHA arm had a first onset of any AEs in the PROfound study after 112 days on treatment.

- **CTCAE Grade ≥3 AEs**

AEs of CTCAE Grade ≥3 were most commonly reported in the SOC of Blood and lymphatic system disorders in the olaparib arm and the SOC of General disorders and administration site conditions in the investigators choice of NHA. The incidence of CTCAE Grade ≥3 AEs in the olaparib arm was largely driven by the incidence of AEs of anaemia (55 of olaparib-treated patients [21.5%] had CTCAE Grade ≥3 AEs of anaemia).

Table 56: PROfound: CTCAE Grade ≥3 AEs occurring in >2 patients in either treatment arm (Cohort A+B SAS)

MedDRA SOC preferred term[b]	Number (%) of patients[a]	
	Olaparib 300 mg bd (N=256)	Investigators choice of NHA (N=130)
Patients with any CTCAE Grade ≥3 AE	**130 (50.8)**	**49 (37.7)**
Blood and lymphatic system disorders	**68 (26.6)**	**8 (6.2)**
Anaemia	55 (21.5)	7 (5.4)
Neutropenia	10 (3.9)	0
Thrombocytopenia	9 (3.5)	0
Lymphopenia	3 (1.2)	0
Infections and infestations	**18 (7.0)**	**10 (7.7)**
Pneumonia	6 (2.3)	1 (0.8)
Urinary tract infection	4 (1.6)	5 (3.8)
Sepsis	3 (1.2)	3 (2.3)
Lung infection	3 (1.2)	1 (0.8)
Respiratory, thoracic and mediastinal disorders	**18 (7.0)**	**2 (1.5)**
Pulmonary embolism	6 (2.3)	1 (0.8)
Dyspnoea	6 (2.3)	0
Pneumonia aspiration	3 (1.2)	0
Gastrointestinal disorders	**15 (5.9)**	**4 (3.1)**
Vomiting	6 (2.3)	1 (0.8)
Nausea	3 (1.2)	0
Investigations	**14 (5.5)**	**3 (2.3)**
Neutrophil count decreased	4 (1.6)	0
WBC count decreased	4 (1.6)	0
Musculoskeletal and connective tissue disorders	**12 (4.7)**	**6 (4.6)**
Muscular weakness	3 (1.2)	1 (0.8)
General disorders and administration site conditions	**10 (3.9)**	**11 (8.5)**
Asthenia	4 (1.6)	4 (3.1)
Fatigue	3 (1.2)	3 (2.3)
Injury, poisoning and procedural complications	**10 (3.9)**	**3 (2.3)**
Femur fracture	3 (1.2)	0
Metabolism and nutrition disorders	**9 (3.5)**	**7 (5.4)**
Decreased appetite	3 (1.2)	1 (0.8)
Nervous system disorders	**8 (3.1)**	**5 (3.8)**
Cerebrovascular accident	3 (1.2)	0
Vascular disorders	**6 (2.3)**	**5 (3.8)**
Hypertension	3 (1.2)	3 (2.3)

Few patients had CTCAE Grade 4 AEs: 7 patients (2.7%) in the olaparib arm had a total of 9 CTCAE Grade 4 AEs (lung infection and septic shock [both in 1 patient], pulmonary embolism [1 patient], respiratory failure and sepsis [both in 1 patient] and thrombocytopenia [4 patients]) compared with 4 patients (3.1%) in the investigators choice of NHA arm (AEs of sepsis [2 patients]; ALT increased and hypocalcaemia [1 patient each];

Comparison with olaparib 300mg bd pool

Table 57 shows the most commonly-reported Grade ≥3 AEs for the olaparib treatment arm in PROfound and the 300 mg bd pool. The most common CTCAE Grade ≥3 AEs were similar between PROfound and the 300 mg bd pool, however, a higher proportion of patients had CTCAE Grade ≥3 AEs in PROfound.

Table 57: Most common CTCAE Grade ≥3 AEs (occurring in ≥1% of patients in the olaparib treatment arm of PROfound and the 300 mg bd pool)

MedDRA SOC preferred term[b]	Number (%) of patients[a]	
	PROfound Cohort A+B SAS olaparib 300 mg bd[c] (N=256)	Olaparib 300 mg bd pool[d] (N=1585)
Patients with any CTCAE Grade ≥3 AE	**130 (50.8)**	**659 (41.6)**
Blood and lymphatic system disorders	**68 (26.6)**	**347 (21.9)**
Anaemia	55 (21.5)	284 (17.9)
Neutropenia	10 (3.9)	72 (4.5)
Thrombocytopenia	9 (3.5)	29 (1.8)
Lymphopenia	3 (1.2)	12 (0.8)
Leukopenia	0	23 (1.5)
Infections and infestations	**18 (7.0)**	**74 (4.7)**
Pneumonia	6 (2.3)	14 (0.9)
Urinary tract infection	4 (1.6)	15 (0.9)
Sepsis	3 (1.2)	9 (0.6)
Lung infection	3 (1.2)	4 (0.3)
Respiratory, thoracic and mediastinal disorders	**18 (7.0)**	**52 (3.3)**
Dyspnoea	6 (2.3)	18 (1.1)
Pulmonary embolism	6 (2.3)	18 (1.1)
Pneumonia aspiration	3 (1.2)	3 (0.2)
Gastrointestinal disorders	**15 (5.9)**	**102 (6.4)**
Vomiting	6 (2.3)	22 (1.4)
Nausea	3 (1.2)	16 (1.0)
Abdominal pain	2 (0.8)	20 (1.3)
Diarrhoea	2 (0.8)	17 (1.1)
Investigations	**14 (5.5)**	**103 (6.5)**
Neutrophil count decreased	4 (1.6)	42 (2.6)
WBC count decreased	4 (1.6)	27 (1.7)
Platelet count decreased	2 (0.8)	18 (1.1)
Musculoskeletal and connective tissue disorders	**12 (4.7)**	**35 (2.2)**
Muscular weakness	3 (1.2)	5 (0.3)
General disorders and administration site conditions	**10 (3.9)**	**83 (5.2)**
Asthenia	4 (1.6)	28 (1.8)
Fatigue	3 (1.2)	41 (2.6)
Injury, poisoning and procedural complications	**10 (3.9)**	**20 (1.3)**
Femur fracture	3 (1.2)	3 (0.2)
Metabolism and nutrition disorders	**9 (3.5)**	**44 (2.8)**
Decreased appetite	3 (1.2)	12 (0.8)
Nervous system disorders	**8 (3.1)**	**34 (2.1)**
Cerebrovascular accident	3 (1.2)	3 (0.2)
Vascular disorders	**6 (2.3)**	**24 (1.5)**
Hypertension	3 (1.2)	8 (0.5)

Serious adverse event/deaths/other significant events

- **Deaths**

A summary of patients who died in the PROfound study is presented in Table 58. The majority of deaths occurred over 30 days after the last treatment dose in both treatment arms and were related to the disease

under investigation only. A similar proportion of patients had AEs with an outcome of death in the olaparib arm compared with the investigators choice of NHA arm.

Table 58: PROfound: All deaths (Cohort A+B FAS)

Category	Number (%) of patients	
	Olaparib 300 mg bd (N=256)	Investigators choice of NHA (N=131)
Total number of deaths	**97 (37.9)**	**63 (48.1)**
Death related to disease under investigation only[a]	14 (5.5)	12 (9.2)
AE with outcome of death only[a]	6 (2.3)	5 (3.8)
Both related to disease under investigation and with AE outcome death[a]	2 (0.8)	2 (1.5)[b]
Deaths >30 days after last treatment dose, related to disease under investigation	70 (27.3)	40 (30.5)
AE with outcome of death only (AE start date falling >30 days after last treatment dose)	1 (0.4)	1 (0.8)[c]
Deaths >30 days after last treatment dose, related to disease under investigation and with AE outcome of death	1 (0.4)	0
Deaths >30 days after last treatment dose, unrelated to AE or disease under investigation	2 (0.8)	3 (2.3)
Patients with unknown reason for death[b]	1 (0.4)	0

Patients in PROfound whose deaths were not considered due to disease progression only are listed in Table 59, with relevant data on their treatment history in the study, and the investigator's opinion on the likelihood of a causal relationship between death and study treatment.

Table 59: PROfound: Key information for deaths not due to disease progression (Cohort A+B SAS)

Time from first dose to death (days)	Time from last dose to death (days)	Treatment period	Primary cause of death (MedDRA preferred term)	Secondary cause of death (MedDRA preferred term)	Comments, including causal relationship to olaparib[a]
Olaparib 300 mg bd					
125	41	Post-follow up	Prostate cancer	Pneumonia	The AE of pneumonia started on Day 114 and was considered unrelated to study treatment
282	1	On treatment	Cardiopulmonary failure	Pneumonia aspiration	The AE of cardiopulmonary failure started on Day 282 and was considered unrelated to study treatment.
332	23	Follow-up	Hormone-refractory prostate cancer	Cardiopulmonary failure	Patient had ongoing AEs of spinal stenosis and urinary retention (both started on Day 285). The AE of cardiopulmonary failure started on Day 330. The AEs of spinal stenosis and urinary retention were also reported to have led to death. None of the AEs were considered related to study treatment.
281	75	Post follow-up	Diverticulum intestinal	Multiple organ dysfunction syndrome	The AE of diverticulum intestinal started on Day 221 and was considered unrelated to study treatment.
271	24	Follow-up	Septic shock	Prostate cancer	The AE of septic shock started on Day 270 and was considered unrelated to study treatment.
15	1	On treatment	Sudden death	None stated	The AE of sudden death was considered unrelated to study treatment.
126	8	Follow-up	Budd-Chiari syndrome	None stated	The AE of Budd-Chiari syndrome started on Day 120 and was considered unrelated to study treatment.
80	1	On treatment	Cardiac failure acute	None stated	The AE of cardiac failure acute started on Day 80 and was considered unrelated to study treatment.

9	7	Follow-up	Lung infection	Neutropenia	The AEs of lung infection and neutropenia started on Day 3 and were considered related to study treatment.
20	12	Follow-up	Lung infection	None stated	The AE of lung infection started on Day 13 and was considered unrelated to study treatment.

Comparison with olaparib 300mg bd pool

Table 60 summarises the number of deaths in the olaparib treatment arm in PROfound and the 300 mg bd pool.

Table 60: Patients who died in the olaparib treatment arm of PROfound and the 300 mg bd pool

Category	Number (%) of patients	
	PROfound Cohort A+B FAS olaparib 300 mg bd (N=256)	Olaparib 300 mg bd pool (N=1585)
Total number of deaths	**97 (37.9)**	**462 (29.1)**
Death related to disease under investigation only	84 (32.8)	419 (26.4)
AE with outcome of death only	6 (2.3)	11 (0.7)
AE with outcome of death only (AE start date falling >30 days after last treatment dose)	1 (0.4)	2 (0.1)
Both related to disease under investigation and AE with outcome death	3 (1.2)	8 (0.5)
Patients with unknown/other reason for death[a]	3 (1.2)	22 (1.4)

- **Serious adverse events**

During PROfound, a higher proportion of patients reported SAEs in the olaparib arm compared with the investigators choice of NHA arm (Table 61). The most common SOC for reported SAEs in the olaparib arm was Blood and lymphatic system disorders and in the investigators choice of NHA arm was Infections and infestations. Most SAE preferred terms (PTs) were reported in fewer than 2 patients in each arm.

The most commonly reported SAE (≥5%) was anaemia (22 events in 22 patients [8.6%]) in olaparib arm and urinary tract infection (4 events in 4 patients [3.1%]) in the investigators choice of NHA arm.

In both the olaparib arm and the investigators choice of NHA arm, a low proportion of patients (13.7% and 3.8%, respectively) reported SAEs that were considered by the investigator to be causally related to study treatment.

The majority of the SAEs reported occurred whilst on treatment. A total of 27 patients (10.5%) in the olaparib arm and 14 patients (10.8%) in the investigators choice of NHA arm had SAEs with a date of onset during the safety follow-up period.

The majority of SAEs had resolved with either no action taken, following a temporary dose interruption or dose reduction, or were resolving. In total, 28 patients (10.9%) in the olaparib arm and 6 patients (4.6%) in the investigators choice of NHA arm had SAEs that were 'not recovered/not resolved' at the DCO date for this analysis.

Table 61: PROfound: SAEs occurring in >2 patients in either treatment group (Cohort A+B SAS)

MedDRA SOC preferred term[b]	Number (%) of patients[a]	
	Olaparib 300 mg bd (N=256)	Investigators choice of NHA (N=130)
Patients with any SAE	**91 (35.5)**	**36 (27.7)**
Blood and lymphatic system disorders	**28 (10.9)**	**1 (0.8)**
Anaemia	22 (8.6)	0
Thrombocytopenia	4 (1.6)	0
Neutropenia	3 (1.2)	0
Infections and infestations	**22 (8.6)**	**11 (8.5)**
Pneumonia	8 (3.1)	1 (0.8)
Urinary tract infection	5 (2.0)	4 (3.1)
Sepsis	3 (1.2)	3 (2.3)
Lung infection	3 (1.2)	1 (0.8)
Respiratory, thoracic and mediastinal disorders	**17 (6.6)**	**2 (1.5)**
Pulmonary embolism	5 (2.0)	1 (0.8)
Dyspnoea	4 (1.6)	0
Pneumonia aspiration	3 (1.2)	0
Gastrointestinal disorders	**13 (5.1)**	**3 (2.3)**
Vomiting	4 (1.6)	1 (0.8)
General disorders and administration site conditions	**11 (4.3)**	**5 (3.8)**
Asthenia	4 (1.6)	1 (0.8)
Pyrexia	3 (1.2)	2 (1.5)
Injury, poisoning and procedural complications	**11 (4.3)**	**3 (2.3)**
Femur fracture	3 (1.2)	0
Renal and urinary disorders	**10 (3.9)**	**6 (4.6)**
Haematuria	3 (1.2)	0[c]
Metabolism and nutrition disorders	**6 (2.3)**	**3 (2.3)**
Dehydration	0	3 (2.3)
Nervous system disorders	**6 (2.3)**	**2 (1.5)**
Cerebrovascular accident	3 (1.2)	0

Comparison with olaparib 300mg bd pool

SAEs were reported at a higher frequency in PROfound compared with the 300 mg bd pooled dataset and may be explained by the differences in baseline characteristics (higher mean age, male population) in the PROfound study population compared with the 300 mg bd pool (see Table 62). The SOC where SAEs were most commonly reported was Blood and lymphatic system disorders and this was consistent for 300 mg bd pool data.

Table 62: Most common SAEs (reported by >1% of patients in the olaparib treatment arm of PROfound or in the 300 mg bd pool)

MedDRA System organ class Preferred term[b]	Number (%) of patients[a]	
	PROfound Cohort A+B SAS olaparib 300 mg bd[c] (N=256)	Olaparib 300 mg bd pool[d] (N=1585)
Patients with any SAE	**91 (35.5)**	**365 (23.0)**
Blood and lymphatic system disorders	**28 (10.9)**	**110 (6.9)**
Anaemia	22 (8.6)	89 (5.6)
Thrombocytopenia	4 (1.6)	9 (0.6)
Neutropenia	3 (1.2)	10 (0.6)
Infections and infestations	**22 (8.6)**	**77 (4.9)**
Pneumonia	8 (3.1)	18 (1.1)
Urinary tract infection	5 (2.0)	15 (0.9)
Sepsis	3 (1.2)	9 (0.6)
Lung infection	3 (1.2)	4 (0.3)
Respiratory, thoracic and mediastinal disorders	**17 (6.6)**	**37 (2.3)**
Pulmonary embolism	5 (2.0)	10 (0.6)
Dyspnoea	4 (1.6)	8 (0.5)
Pneumonia aspiration	3 (1.2)	3 (0.2)
Gastrointestinal disorders	**13 (5.1)**	**66 (4.2)**
Vomiting	4 (1.6)	12 (0.8)
General disorders and administration site conditions	**11 (4.3)**	**34 (2.1)**
Asthenia	4 (1.6)	7 (0.4)
Pyrexia	3 (1.2)	11 (0.7)
Injury, poisoning and procedural complications	**11 (4.3)**	**22 (1.4)**
Femur fracture	3 (1.2)	3 (0.2)
Renal and urinary disorders	**10 (3.9)**	**16 (1.0)**
Haematuria	3 (1.2)	4 (0.3)
Nervous system disorders	**6 (2.3)**	**25 (1.6)**
Cerebrovascular accident	3 (1.2)	4 (0.3)

Main adverse drug reactions for olaparib

Anaemia

Table 63 shows AEs of anaemia in the PROfound study and 300 mg bd pool (grouped term consisting of the PTs anaemia, anaemia macrocytic, erythropenia, haematocrit decreased, haemoglobin decreased, normochromic anaemia, normochromic normocytic anaemia, normocytic anaemia and red blood cell count decreased); AEs of anaemia were reported for a higher percentage of patients in the olaparib arm compared with the investigators choice of NHA arm. A higher percentage of patients in the olaparib arm compared with the investigators choice of NHA arm had AEs that were CTCAE Grade ≥3. These events rarely led to permanent discontinuation of treatment. In the olaparib arm, 18 of the 55 patients with CTCAE Grade ≥3 AEs of anaemia (single PT) were SAEs and no patient had a CTCAE Grade 4 AE.

Olaparib treatment was interrupted in 7 of the 18 patients with CTCAE Grade ≥3 SAEs of anaemia (single PT), the dose was reduced in 6 of the 18 patients and the SAE led to treatment discontinuation in 4 of these 18 patients. Nine of the 18 patients with CTCAE Grade ≥3 SAEs of anaemia had events that were reported as recovered.

Onset of anaemia was early, generally in the first 3 months of starting olaparib (median time to first onset was 1.87 months), although the risk of developing anaemia remained fairly constant throughout exposure with no evidence of cumulative effect.

Overall, 44 of 119 (37.0%) olaparib-treated patients had first events of anaemia that resolved (median time to resolution 3.88 months for first event.

Table 63: PROfound and the 300 mg pool: Patients who had at least 1 AE of anaemia (grouped term) reported in any category

AE category	Number (%) of patients[a]		
	PROfound Cohort A+B SAS[b]		
	Olaparib 300 mg bd (N=256)	Investigators choice of NHA (N=130)	Olaparib 300 mg bd pool[c] (N=1585)
Any AE	119 (46.5)	20 (15.4)	646 (40.8)
Any AE of CTCAE Grade 3 or higher	55 (21.5)	7 (5.4)	287 (18.1)
Any AE with outcome = death	0	0	0
Any SAE	22 (8.6)	0	93 (5.9)
AEs leading to dose reduction	40 (15.6)	0	194 (12.2)
AEs leading to treatment interruption	64 (25.0)	2 (1.5)	285 (18.0)
Any AE leading to discontinuation	18 (7.0)	1 (0.8)	40 (2.5)

Treatment of anaemia

In the olaparib arm, 72 (60.5%) of 119 patients with AEs of anaemia (grouped term) were treated for the AE compared with 14 (70.0%) of 20 patients in the investigators choice of NHA arm.

In PROfound, 62 (24.2%) patients in the olaparib arm received at least 1 blood transfusion as a concomitant medication. Thirteen (5.1%) olaparib-treated patients had treatment with an erythropoiesis stimulating agent.

In PROfound, 13 (10.0%) patients in the investigators choice of NHA arm received at least 1 blood transfusion as a concomitant medication. No investigators choice of NHA-treated patients had treatment with an erythropoiesis stimulating agent.

Neutropenia

Table 64 shows AEs of neutropenia (grouped term consisting of the PTs agranulocytosis, febrile neutropenia, granulocyte count decreased, granulocytopenia, idiopathic neutropenia, neutropenia, neutropenic infection, neutropenic sepsis and neutrophil count decreased); AEs of neutropenia were reported for a higher percentage of patients in the olaparib arm compared with the investigators choice of NHA arm. These events were predominantly Grade ≥3 in severity and rarely led to permanent discontinuation of treatment. Three patients had AEs of febrile neutropenia and 1 patient had an SAE of neutropenic sepsis. There were no patients with AEs of neutropenic infection in PROfound.

In the olaparib arm, 4 of the 15 patients with CTCAE Grade ≥3 AEs of neutropenia (grouped term) were SAEs.

One patient in the olaparib arm died due to SAEs of neutropenia and lung infection. On Day 3, SAEs of lung infection, neutropenia and thrombocytopenia were reported. The patient discontinued treatment the same day as onset and subsequently died on Day 9 due to the SAEs of lung infection and neutropenia.

There was no association between the development of neutropenia and the length of time on olaparib treatment; AEs of neutropenia (grouped term) were reported throughout the study period in the olaparib-

treated arm (median time to onset of first event was 3.27 months); the majority (19 of 24 [79.2%]) of first events with olaparib resolved (median time to resolution of 0.66 months for first event).

Table 64: PROfound and the 300 mg pool: Patients who had at least 1 AE of neutropenia (grouped term) reported in any category

AE category	Number (%) of patients[a]		
	PROfound Cohort A+B SAS[b]		
	Olaparib 300 mg bd (N=256)	Investigators choice of NHA (N=130)	Olaparib 300 mg bd pool[c] (N=1585)
Any AE	24 (9.4)	3 (2.3)	293 (18.5)
Any AE of CTCAE Grade 3 or higher	15 (5.9)	1 (0.8)	114 (7.2)
Any AE with outcome = death	1 (0.4)	0	1 (0.1)
Any SAE	4 (1.6)	1 (0.8)	18 (1.1)
AEs leading to dose reduction	4 (1.6)	0	44 (2.8)
AEs leading to treatment interruption	13 (5.1)	1 (0.8)	117 (7.4)
Any AE leading to discontinuation	4 (1.6)	0	10 (0.6)

Treatment of neutropenia

Of the patients in the olaparib arm with AEs of neutropenia (grouped term), 7 of 24 patients (29.2%) were treated for the AE compared with 1 of 3 patients (33.3%) in the investigators choice of NHA arm. Colony stimulating factor use in the olaparib arm was rare: 5 (2.0%) olaparib-treated patients received a colony stimulating factor.

Thrombocytopenia

Table 65 shows AEs of thrombocytopenia (grouped term consisting of the PTs platelet count decreased, platelet production decreased, plateletcrit decreased and thrombocytopenia). AEs of thrombocytopenia were reported for a higher percentage of patients in the olaparib arm compared with the investigators choice of NHA arm. Eleven patients (4.3%) in the olaparib arm had AEs of thrombocytopenia that were Grade ≥3 in severity. Reported events of thrombocytopenia rarely led to permanent discontinuation of treatment.

There were 3 patients (1.2%) with CTCAE Grade 4 SAEs and 1 patient (0.4%) with a Grade 3 SAE of thrombocytopenia in the olaparib arm; no patients had SAEs of thrombocytopenia (grouped term) in the investigators choice of NHA arm.

There was no association between the development of thrombocytopenia and the length of time on olaparib treatment. First onset of AEs of thrombocytopenia (grouped term) were reported throughout the first 12 months of study period in the olaparib-treated arm (median time to first onset was 2.63 months); 15 of 31 (48.4%) olaparib-treated patients had first events of thrombocytopenia that resolved (median time to resolution of first event of 1.02 months.

Table 65: PROfound and the 300 mg pool: Patients who had at least 1 AE of thrombocytopenia (grouped term) reported in any category

AE category	Number (%) of patients[a]		
	PROfound Cohort A+B SAS[b]		
	Olaparib 300 mg bd (N=256)	Investigators choice of NHA (N=130)	Olaparib 300 mg bd pool[c] (N=1585)
Any AE	31 (12.1)	4 (3.1)	197 (12.4)
Any AE of CTCAE Grade 3 or higher	11 (4.3)	0	47 (3.0)
Any AE with outcome = death	0	0	0
Any SAE	4 (1.6)	0	14 (0.9)
AEs leading to dose reduction	4 (1.6)	0	22 (1.4)
AEs leading to treatment interruption	17 (6.6)	1 (0.8)	61 (3.8)
Any AE leading to discontinuation	5 (2.0)	0	14 (0.9)

A total of 19 patients reported bleeding or haemorrhage events in PROfound. These were 14 patients (5.5%) in the olaparib arm (with AEs including anal haemorrhage, conjunctival haemorrhage, contusion, epistaxis, GI haemorrhage, gingival bleeding, haematotympanum, lower GI haemorrhage, petechiae and rectal haemorrhage) and 5 patients (3.8%) in the investigators choice of NHA arm (with AEs of contusion, epistaxis, gastric ulcer haemorrhage, haematochezia and intracranial haemorrhage). Two patients reported bleeding or haemorrhage events after switching to olaparib (epistaxis and petechiae; the patient with the event of epistaxis had previously had an AE of epistaxis while receiving investigators choice of NHA). Two events in the investigators choice of NHA arm were CTCAE Grade 3, the majority were CTCAE Grade 1 events). Only 1 of these patients in the olaparib arm had a CTCAE Grade ≥3 AE of thrombocytopenia. One patient had a CTCAE Grade 3 AE of thrombocytopenia which started on Day 57 which led to discontinuation of olaparib. The event was ongoing at the time of his death. On Day 150 the patient also had AEs of haematotympanum (CTCAE Grade 2) and rectal haemorrhage (CTCAE Grade 1).

Treatment of thrombocytopenia

Six of 31 olaparib-treated patients (19.4%) compared with no investigators choice of NHA-treated patients were treated for AEs of thrombocytopenia (grouped term).

Lymphopenia

Table 66 shows AEs of lymphopenia (grouped term consisting of the PTs B-lymphocyte count decreased, lymphocyte count decreased, lymphopenia and T-lymphocyte count decreased). AEs of lymphopenia were reported for a higher percentage of patients in the olaparib arm compared with the investigators choice of NHA arm. These events were predominantly Grade 1 or 2 in severity and none led to permanent discontinuation of treatment.

There was no association between the development of lymphopenia and the length of time on olaparib treatment. First onset of AEs of lymphopenia (grouped term) were reported throughout the first 12 months of study period in the olaparib-treated arm (median time to first onset was 2.83 months); 8 of 19 (42.1%) olaparib-treated patients had first events of lymphopenia that resolved (median time to resolution of first event of 3.42 months).

Table 66: PROfound and the 300 mg pool: Patients who had at least 1 AE of lymphopenia (grouped term) reported in any category

AE category	Number (%) of patients[a]		
	PROfound Cohort A+B SAS[b]		
	Olaparib 300 mg bd (N=256)	Investigators choice of NHA (N=130)	Olaparib 300 mg bd pool[c] (N=1585)
Any AE	19 (7.4)	1 (0.8)	82 (5.2)
Any AE of CTCAE Grade 3 or higher	4 (1.6)	0	21 (1.3)
Any AE with outcome = death	0	0	0
Any SAE	0	0	0
AEs leading to dose reduction	1 (0.4)	0	3 (0.2)
AEs leading to treatment interruption	2 (0.8)	0	11 (0.7)
Any AE leading to discontinuation	0	0	1 (0.1)

Treatment of lymphopenia

Only 1 of the 19 olaparib-treated patients (5.3%) with lymphopenia were treated for the AE; no investigators choice of NHA-treated patients received treatment for lymphopenia (grouped term).

Nausea and vomiting

As shown in Table 67, AEs of nausea and vomiting were reported for a higher percentage of patients in the olaparib arm compared with the investigators choice of NHA arm in PROfound. These events were predominantly Grade 1 or 2 in severity and rarely led to permanent discontinuation of treatment in the olaparib arm. Events of nausea and vomiting were generally reported early in the treatment period (median time to onset was 0.49 months and 0.95 months, respectively in the olaparib-treated arm.

The majority (74 of 106 patients [69.8%] with AEs of nausea and 44 of 47 patients [93.6%] with AEs of vomiting) of first events with olaparib resolved (median time to resolution of first event of 1.97 months and 0.16 months, respectively). Cumulative incidence plots for first incidence of nausea and vomiting illustrate first reports of nausea tended to occur early in treatment.

Prevalence plots for nausea and vomiting showed that the prevalence of nausea events remained fairly constant (between 15% and 30% of patients affected) on olaparib treatment. The prevalence of vomiting was approximately 0.05% for the duration of the study.

A total of 38 (35.8%) olaparib-treated patients reported both nausea and vomiting. Approximately half of the olaparib-treated patients with nausea or vomiting were treated for the AE (60 of 106 patients [56.6%] and 22 of 47 patients [46.8%], respectively); similar proportions of patients received treatment for nausea or vomiting in the investigators choice of NHA arm (15 of 25 patients [60.0%] and 7 of 16 patients [43.8%], respectively).

Table 67: PROfound and the 300 mg pool: Patients who had at least 1 AE of nausea and vomiting reported in any category

AE category	Number (%) of patients[a]					
	Nausea			Vomiting		
	PROfound Cohort A+B SAS[b]		Olaparib 300 mg bd pool[c] (N=1585)	PROfound Cohort A+B SAS[b]		Olaparib 300 mg bd pool[c] (N=1585)
	Olaparib 300 mg bd (N=256)	Investigators choice of NHA (N=130)		Olaparib 300 mg bd (N=256)	Investigators choice of NHA (N=130)	
Any AE	106 (41.4)	25 (19.2)	944 (59.6)	47 (18.4)	16 (12.3)	514 (32.4)
Any AE of CTCAE Grade 3 or higher	3 (1.2)	0	16 (1.0)	6 (2.3)	1 (0.8)	22 (1.4)
Any AE with outcome = death	0	0	0	0	0	0
Any SAE	2 (0.8)	1 (0.8)	6 (0.4)	4 (1.6)	1 (0.8)	12 (0.8)
AEs leading to dose reduction	6 (2.3)	1 (0.8)	31 (2.0)	5 (2.0)	0	15 (0.9)
AEs leading to treatment interruption	5 (2.0)	3 (2.3)	74 (4.7)	7 (2.7)	4 (3.1)	86 (5.4)
Any AE leading to discontinuation	2 (0.8)	0	12 (0.8)	2 (0.8)	0	10 (0.6)

Diarrhoea

Table 68 shows that AEs of diarrhoea (single PT) were reported for a higher percentage of patients in the olaparib arm compared with the investigators choice of NHA arm in the PROfound study. These events were predominantly Grade 1 or 2 in severity and only led to permanent discontinuation of treatment in 1 patient in the olaparib arm. Events of diarrhea were generally reported early in the treatment period (median time to onset was 1.35 months) and the majority (44 of 54 patients [81.5%]) of first events with olaparib resolved (median time to resolution of first event of 0.82 months). A higher proportion of patients in the olaparib arm with diarrhoea were treated for the AE (15 of 54 patients [27.8%]) compared with the investigators choice of NHA arm (1 of 9 patients [11.1%]).

Table 68: PROfound and the 300 mg pool: Patients who had at least 1 AE of diarrhoea reported in any category

AE category	Number (%) of patients[a]		
	PROfound Cohort A+B SAS[b]		
	Olaparib 300 mg bd (N=256)	Investigators choice of NHA (N=130)	Olaparib 300 mg bd pool[c] (N=1585)
Any AE	54 (21.1)	9 (6.9)	412 (26.0)
Any AE of CTCAE Grade 3 or higher	2 (0.8)	0	17 (1.1)
Any AE with outcome = death	0	0	0
Any SAE	1 (0.4)	0	2 (0.1)
AEs leading to dose reduction	1 (0.4)	0	3 (0.2)
AEs leading to treatment interruption	5 (2.0)	0	39 (2.5)
Any AE leading to discontinuation	1 (0.4)	0	1 (0.1)

Increase in creatinine

AEs of increased creatinine were reported for a higher percentage of patients in the olaparib arm compared with the investigators choice of NHA arm in the PROfound study, although overall numbers were low. These events were Grade 1 or 2 in severity and none led to permanent discontinuation of treatment.

Table 69: PROfound and the 300 mg pool: Patients who had at least 1 AE of blood creatinine increased reported in any category

AE category	Number (%) of patients[a]		
	PROfound Cohort A+B SAS[b]		
	Olaparib 300 mg bd (N=256)	Investigators choice of NHA (N=130)	Olaparib 300 mg bd pool[c] (N=1585)
Any AE	10 (3.9)	1 (0.8)	87 (5.5)
Any AE of CTCAE Grade 3 or higher	0	0	1 (0.1)
Any AE with outcome = death	0	0	0
Any SAE	0	0	2 (0.1)
AEs leading to dose reduction	2 (0.8)	0	2 (0.1)
AEs leading to treatment interruption	3 (1.2)	0	5 (0.3)
Any AE leading to discontinuation	0	0	0

In PROfound, the median change in creatinine from baseline to Week 12 for olaparib-treated patients was an increase of 9.0 µmol/L compared with 0 µmol/L for investigators choice of NHA-treated patients. Median creatinine levels for olaparib-treated patients then remained consistent over time (maximum median change 14.0 µmol/L, median change at the majority of time points between 9.0 and 12.0 µmol/L.

In PROfound, 97.6% of olaparib-treated patients with data available had normal creatinine levels at baseline, 2.0% had CTCAE Grade 1 at baseline and 0.4% of patients had CTCAE Grade ≥2 at baseline. A total of 188/248 (75.8%) olaparib-treated patients had a single worsening change in CTCAE Grade (most changes were normal to Grade 1) and 39/248 (15.7%) olaparib-treated patients had worsening 2 grade shifts in CTCAE Grade for creatinine (all were normal to Grade 2); 4 olaparib-treated patients had a shift from normal at baseline to CTCAE Grade 3 on treatment, no patients had worsening 4 grade shift. In the investigators choice of NHA arm of PROfound, 96.9% of patients with data available had normal creatinine at baseline and 3.1% had CTCAE Grade 1 at baseline; of these patients, 78/127 (61.4%) patients had a single worsening change in CTCAE Grade (most changes were normal to Grade 1) and 7/127 (5.5%) patients had worsening 2 grade shifts in CTCAE Grade (most changes were normal to Grade 2); no patients had more than a 2 grade shift in CTCAE Grade for creatinine.

Data from all patients in the 300 mg bd pool showed that a similar proportion of patients in the 300 mg bd pool had CTCAE grade shifts in creatinine, compared with PROfound. In the 300 mg bd pool, 92.4% of olaparib-treated patients had normal creatinine at baseline, 6.9% had CTCAE Grade 1 at baseline and 0.5% had CTCAE Grade 2 at baseline. A total of 1205/1573 (76.6%) patients had a single change in CTCAE Grade (changes were normal to Grade 1 in 1165/1573 [74.1%] patients); 243/1573 (15.4%) had 2 CTCAE grade shifts (all were normal to Grade 2) and 7/1573 (0.4%) patients had a 3 grade shift in creatinine (all were Grade 0 to Grade 3.

Dyspnoea

Table 70 shows that AEs of dyspnoea (grouped term consisting of the PTs dyspnoea and dyspnoea exertional) were reported for a higher percentage of patients in the olaparib arm than the investigators choice of NHA arm in the PROfound study. There were few CTCAE Grade ≥3 AEs or SAEs and no DAEs for dyspnoea (grouped term) in the PROfound study.

AEs of dyspnoea (grouped term) were reported throughout the study period (median time to first onset was 1.91 months). In the majority of patients (20 of 29 [69.0%] patients) the first events of dyspnoea resolved (median time to resolution of first event of 2.04 months). Seven of 29 patients (24.1%) in the olaparib arm of PROfound were reported by the investigator to have received treatment for the event, compared with no patients in the investigators choice of NHA arm.

Table 70: PROfound and the 300 mg pool: Patients who had at least 1 AE of dyspnoea (grouped term) reported in any category

AE category	Number (%) of patients[a]		
	PROfound Cohort A+B SAS[b]		
	Olaparib 300 mg bd (N=256)	Investigators choice of NHA (N=130)	Olaparib 300 mg bd pool[c] (N=1585)
Any AE	29 (11.3)	5 (3.8)	218 (13.8)
Any AE of CTCAE Grade 3 or higher	6 (2.3)	0	18 (1.1)
Any AE with outcome = death	0	0	0
Any SAE	4 (1.6)	0	8 (0.5)
AEs leading to dose reduction	1 (0.4)	0	2 (0.1)
AEs leading to treatment interruption	2 (0.8)	0	15 (0.9)
Any AE leading to discontinuation	0	0	2 (0.1)

Important potential risks

MDS/AML, pneumonitis and new primary malignancies have been classified in the Risk Management Plan as important potential risks. Reports for events of MDS/AML and new primary malignancies continue to be collected beyond 30 days after the last dose of olaparib: investigators are asked during the regular follow up for OS if the patient had developed MDS/AML or a new primary malignancy and prompted to report any cases to the Sponsor. A targeted safety questionnaire was also used to collect specific follow-up information on these cases.

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. For pneumonitis, in addition to cases from PROfound and the 300 mg bd pool, cases from the 400 mg bd capsule pool were also presented (i.e., the olaparib monotherapy combined therapeutic dose pool). For MDS/AML and new primary malignancies, this pool was further extended to include all patients who have received at least 1 dose of olaparib (tablet or capsule formulation) as monotherapy treatment in a monotherapy clinical study, at any dose (the olaparib monotherapy all doses pool). For MDS/AML and new primary malignancies, these pools are supplemented by data from the entire clinical programme to provide a comprehensive assessment of these risks.

Olaparib monotherapy combined therapeutic dose pool (n=2351 patients) consisted of all patients who have received olaparib monotherapy at the intended therapeutic dose of 300 mg bd for the tablet formulation or at the therapeutic dose of 400 mg bd for the capsule formulation (as a continuous dose). All patients from the 300 mg bd pool were included in the olaparib monotherapy combined therapeutic dose pool.

Olaparib monotherapy all doses pool (n=2783 patients) consisted 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 were included (a Phase II, open-label, randomised, comparative, multicentre study to compare the efficacy and tolerability of olaparib [capsule formulation] in combination with paclitaxel and carboplatin versus paclitaxel and carboplatin alone in patients with platinum sensitive advanced serous ovarian cancers). All patients from the olaparib monotherapy combined therapeutic dose pool were included in the olaparib monotherapy all doses pool.

The entire clinical programme as of 15 June 2019 (n=11919 patients) included all the studies shown in Table 44, any studies where olaparib is given in combination with other anticancer treatments, investigator-sponsored studies (ISSs) and data from the MAP.

Myelodysplastic syndrome/acute myeloid leukaemia

In PROfound, there were no events of MDS or AML in the olaparib or investigators choice of NHA treatment arms, which occurred on treatment or within the 30-day follow-up.

Table 71 shows the AEs and incidence rates of MDS/AML in PROfound, in the olaparib all doses monotherapy pool and across the entire olaparib clinical programme.

Table 71: Summary of AEs of MDS/AML occurring across the olaparib program

Data source	TEAEs[a] + AEs after 30 day follow-up			
	Olaparib		Comparator	
	Number of AEs	Incidence	Number of AEs	Incidence
PROfound N=256 olaparib N=130 investigators choice of NHA	0	0%	0	0%
Olaparib monotherapy, all doses pool N=2783 olaparib	30	1.1%	NA	NA
Entire clinical programme pool[b] N=11919 olaparib	70	0.6%	NA	NA

The incidence of events of MDS/AML in the olaparib arm of PROfound (no events) was consistent with the incidence for olaparib in other studies in breast cancer and pancreatic cancer (no AEs of MDS/AML were reported in the OlympiAD study or the POLO study) and lower than that seen for olaparib in studies in ovarian cancer (SOLO1 [1.9%], SOLO2 [2.1%] and Study 19 [1.5%]) and the larger monotherapy pool population for the olaparib clinical programme (0.6%).

In the entire clinical programme pool, largely composed of ovarian and breast cancer patients, there have been 70 reports of MDS/AML out of a total of 11919 patients estimated to have received olaparib in the clinical study programme, giving an estimated cumulative incidence of 0.6% for MDS/AML. The 70 reports of MDS/AML comprise the 30 reports from the olaparib monotherapy all doses pool, plus reports from ongoing open label monotherapy studies, the ongoing MAP program, combination studies with olaparib (including ISSs) and events from placebo-controlled, blinded monotherapy studies. Events in patients which are still on blinded treatment have been considered as olaparib cases in the calculation of incidence rates.

Most of the 30 patients with events of MDS/AML in the olaparib monotherapy all doses pool were receiving treatment for ovarian, peritoneal or fallopian tube cancer (n=28), with 2 other events occurring in patients with breast cancer. Twenty-six patients had a documented BRCA mutation, 2 patients were gBRCA wildtype and in 2 patients, the BRCA mutation status was unknown.

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

The time to death after olaparib was discontinued ranged from 17 to 667 days (median 191 days). In 4 of the 30 cases, patients died due to other causes (progressive disease [2 patients], bone marrow transplant complications [1 patient], and disseminated intravascular coagulation [1 patient]). In 6 cases, MDS/AML was ongoing at the time of reporting and in 2 cases the outcome was reported as recovered.

There have also been reports of MDS/AML from post marketing surveillance.

New primary malignancy events

In PROfound, a review of the SOC of "Neoplasms benign, malignant and unspecified (including cysts and polyps)" showed that during treatment, 4 patients (1.6%) in the olaparib arm and 4 patients (3.1%) in the investigators choice of NHA arm had events in this SOC.

The following events were excluded for the reasons described below:

- AEs of cancer pain (1 patient in the olaparib arm) and tumour pain (1 patient in the olaparib arm and 2 patients in the investigators choice of NHA arm) were excluded due to being pain events.

- An AE of skin papilloma (1 patient in the olaparib arm) was excluded as it was a benign tumour.

Therefore, there was 1 patient in the olaparib arm and 2 patients in the investigators choice of NHA arm with new primary malignancies.

Table 72 shows the AEs of new primary malignancies in PROfound compared with other studies in the clinical programme, and provides incidence rates. When larger populations of olaparib-treated patients are considered the incidence remains below 1.5%.

All patients in the 300 mg bd pool had other potential factors that offer alternative explanations for the development of the new primary tumour, such as: a history of smoking, alcohol consumption or exposure to strong sunlight; a documented breast cancer gene (BRCA1 or 2) mutation; a medical history of previous cancers; exposure to previous chemotherapy agents including multiple cycles of platinum containing chemotherapies that are known DNA-damaging agents and taxanes, anthracyclines and other alkylating and DNA-damaging agents; and prior radiotherapy.

Table 72: Summary of AEs of new primary malignancies occurring across the olaparib programme

Data source	TEAEs[a] + AEs after 30 day follow-up			
	Olaparib		Comparator	
	Number of AEs	Incidence	Number of AEs	Incidence
PROfound N=256 olaparib N=130 investigators choice of NHA	1	0.4%	2	1.5%
Olaparib monotherapy, all doses pool N=2783 olaparib	36	1.3%	NA	NA
Entire clinical programme pool[b] N=11919 olaparib	96	0.8%	NA	NA

Of the 36 AEs in the olaparib monotherapy all doses pool, 12 patients had skin cancers as follows: basal cell carcinoma (n=6), skin cancer (n=2), malignant melanoma (n=2), 1 patient reported both a basal cell carcinoma and squamous cell carcinoma and 1 patient reported squamous cell carcinoma unspecified. The non-skin cancer events were: breast cancers (n=9), GI cancers (n=5), thyroid cancer (n=2), plasma cell myeloma (n=2), lung cancer (n=2), bladder cancer, myeloma cancer, squamous cell carcinoma of the oral cavity, lip and/or oral cavity cancer (n=1 of each). Of the 36 patients in the olaparib monotherapy all doses pool with new primary malignancies, 31 patients had a documented BRCA mutation, 1 patient was gBRCA wildtype and in 4 patients, the BRCA mutation status was unknown.

Including all patients exposed to olaparib during clinical development (i.e., including data from ongoing studies, blinded studies, combination studies, ISS studies and the MAP) provides data for 11 919 patients (as of 15 June 2019). In this population, there have been 96 reports of new primary malignancies out of a total of 11919 patients estimated to have received olaparib in the clinical study programme, giving an estimated cumulative incidence of 0.8%. 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.

Pneumonitis

At the time of the DCO for PROfound (4 June 2019), it was reported that 5 (2.0%) patients in the olaparib arm and 2 (1.5%) patients in the investigators choice of NHA arm had an AE of pneumonitis on treatment and no patients had AEs of pneumonitis in the post-follow-up period.

The pneumonitis AEs reported with olaparib in PROfound were generally mild or moderate; 3 of the 5 AEs were CTCAE Grade 1 or 2 and 3 of the 5 cases were non-serious. In 1 olaparib-treated patient, the pneumonitis AE led to treatment discontinuation.

Table 73 shows the rates of pneumonitis in the clinical program, and provides incidence rates. In the larger pool (therapeutic dose pool), the incidence of pneumonitis events was 0.9%.

Table 73: Summary of AEs of pneumonitis occurring across the olaparib program

Data source	TEAEs[a] + AEs after 30 day follow-up			
	Olaparib		Comparator	
	Number of AEs	Incidence	Number of AEs	Incidence
PROfound N=256 olaparib N=130 investigators choice of NHA	5	2.0%	2	1.5%
Olaparib monotherapy combined therapeutic dose pool N=2351 olaparib	20	0.9%	NA	NA

Of the 20 pneumonitis AEs in the olaparib monotherapy combined therapeutic dose pool (N=2351, including PROfound data), 15 were CTCAE Grade 1 or 2 and the remaining 5 AEs were CTCAE Grade 3. Thirteen of the 20 pneumonitis AEs were non-serious and 7 were SAEs. Twelve of the 20 AEs were reported to have recovered/resolved or recovering/resolving and the remaining 8 AEs did not resolve. In 8 of the 20 patients with pneumonitis AEs, treatment was continued without interruption, in a further 6 patients the dose of olaparib was interrupted or reduced and in the remaining 6 patients, olaparib treatment was permanently discontinued.

Overall, the majority of pneumonitis AEs reported in the olaparib monotherapy therapeutic dose pool were mild or moderate, non-serious and resolved without treatment discontinuation.

None of the 20 pneumonitis AEs in the pool had a fatal outcome. The MAH's global Patient Safety database contains all AE reports, from spontaneous sources (e.g., healthcare professionals, Regulatory Authorities, literature, consumers, and others), whether or not they meet regulatory authorities' definition of SAE, and reports from clinical study use that are defined as SAEs. Non-SAE reports from clinical study use are usually only entered into the clinical study database, but in some (but not all) olaparib studies, non-serious pneumonitis events were also entered into the safety database. A search of the MAH safety database up to 15 June 2019, retrieved 161 case reports; 75 case reports from clinical studies, 49 case reports from the post-marketing setting and the remaining 37 case reports from other solicited sources (eg, post marketing non-interventional studies or patient assistance programmes). Of the 75 case reports from clinical studies (including PROfound), 66 reported a pneumonitis SAE and 9 reported a non-serious pneumonitis event.

Five of the events in these 161 case reports had a fatal outcome; all of these patients were receiving olaparib in combination with other therapies (including other chemotherapies and/or radiation) and 2 of these 5 were being treated for non-small cell lung cancer. In addition, 2 events in the 86 case reports from the post-marketing setting and other solicited sources had a fatal outcome. One patient had a history of interstitial lung changes before starting olaparib therapy and was receiving concomitant simvastatin and had a recent cycle of carboplatin, which are potential confounders. The patient discontinued olaparib 25 days before the onset of the event. The other patient who developed fatal pneumonitis had lung metastases, pleural effusion and bronchitis, requiring home oxygen use as potential confounders before starting olaparib treatment.

Discontinuation due to adverse events

In PROfound, a higher proportion of patients had AEs that led to discontinuation of treatment (DAEs) in the olaparib arm, compared with the investigators choice of NHA arm (Table 74).

The most common DAE in the olaparib arm (reported in ≥5% of patients) was anaemia, all other events occurred in ≤2.0% of patients. The majority of DAEs were Grade 3 and non-serious.

Table 74: PROfound: AEs leading to treatment discontinuation occurring in >1 patient in either treatment group (Cohort A+B SAS)

MedDRA preferred term[b]	Number (%) of patients[a]	
	Olaparib 300 mg bd (N=256)	Investigators choice of NHA (N=130)
Patients with any AE leading to discontinuation	**46 (18.0)**	**11 (8.5)**
Anaemia	18 (7.0)	1 (0.8)
Thrombocytopenia	5 (2.0)	0
Neutropenia	4 (1.6)	0
Fatigue	3 (1.2)	2 (1.5)
Pneumonia	3 (1.2)	1 (0.8)
Asthenia	2 (0.8)	1 (0.8)
Musculoskeletal pain	2 (0.8)	0
Nausea	2 (0.8)	0
Vomiting	2 (0.8)	0

Comparison with olaparib 300mg bd pool

AEs leading to discontinuation of olaparib in PROfound occurred at a higher frequency compared with the 300 mg bd pool. Table 75 summarises these data, which show that anaemia was the most common AEs leading to discontinuation in PROfound and the 300 mg bd pool.

Table 75: Most common AEs leading to discontinuation (reported by >1 patient in the olaparib treatment arm of PROfound or the 300 mg bd pool)

MedDRA System organ class Preferred term[b]	Number (%) of patients[a]	
	PROfound Cohort A+B SAS olaparib 300 mg bd[c] (N=256)	Olaparib 300 mg bd pool[d] (N=1585)
Patients with any AE leading to discontinuation	**46 (18.0)**	**148 (9.3)**
Blood and lymphatic system disorders	**25 (9.8)**	**57 (3.6)**
Anaemia	18 (7.0)	40 (2.5)
Thrombocytopenia	5 (2.0)	11 (0.7)
Neutropenia	4 (1.6)	8 (0.5)
Leukopenia	0	2 (0.1)
Infections and infestations	**6 (2.3)**	**12 (0.8)**
Pneumonia	3 (1.2)	5 (0.3)
Gastrointestinal disorders	**5 (2.0)**	**25 (1.6)**
Nausea	2 (0.8)	12 (0.8)
Vomiting	2 (0.8)	10 (0.6)
Gastric ulcer	1 (0.4)	2 (0.1)
General disorders and administration site conditions	**5 (2.0)**	**21 (1.3)**
Fatigue	3 (1.2)	11 (0.7)
Asthenia	2 (0.8)	4 (0.3)
Malaise	0	2 (0.1)
Pyrexia	0	2 (0.1)
Respiratory, thoracic and mediastinal disorders	**4 (1.6)**	**11 (0.7)**
Pneumonitis	1 (0.4)	4 (0.3)
Interstitial lung disease	1 (0.4)	2 (0.1)
Dyspnoea	0	2 (0.1)
Musculoskeletal and connective tissue disorders	**3 (1.2)**	**7 (0.4)**
Musculoskeletal pain	2 (0.8)	2 (0.1)
Arthralgia	0	2 (0.1)
Metabolism and nutrition disorders	**2 (0.8)**	**6 (0.4)**
Decreased appetite	1 (0.4)	4 (0.3)
Psychiatric disorders	**1 (0.4)**	**4 (0.3)**
Insomnia	1 (0.4)	2 (0.1)
Depression	0	2 (0.1)
Investigations	**0**	**9 (0.6)**
Platelet count decreased	0	3 (0.2)
Neutrophil count decreased	0	2 (0.1)
WBC count decreased	0	2 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**8 (0.5)**
Acute myeloid leukaemia	0	2 (0.1)
Myelodysplastic syndrome	0	2 (0.1)

- **Adverse events leading to treatment interruption**

The most commonly reported AEs (>2 patients in either treatment group) leading to interruption of treatment dosing (of any duration) are presented in Table 76. AEs leading to dose interruption occurred more frequently in olaparib-treated patients compared with investigators choice of NHA-treated patients. The most common (≥5%) AEs leading to treatment interruption in the olaparib arm were: anaemia and

thrombocytopenia. There were no AEs leading to treatment interruptions reported in ≥5% of patients in the investigators choice of NHA arm.

Table 76: PROfound: AEs leading to treatment interruption occurring in >2 patients in either treatment group (Cohort A+B SAS)

MedDRA preferred term[b]	Number (%) of patients[a]	
	Olaparib 300 mg bd (N=256)	Investigators choice of NHA (N=130)
Patients with any AE leading to dose interruption	**115 (44.9)**	**24 (18.5)**
Anaemia	64 (25.0)	2 (1.5)
Thrombocytopenia	14 (5.5)	0
Neutropenia	9 (3.5)	0
Vomiting	7 (2.7)	4 (3.1)
Nausea	5 (2.0)	3 (2.3)
Diarrhoea	5 (2.0)	0
Fatigue	4 (1.6)	2 (1.5)
Neutrophil count decreased	4 (1.6)	1 (0.8)
WBC count decreased	4 (1.6)	0
Decreased appetite	3 (1.2)	2 (1.5)
Asthenia	3 (1.2)	2 (1.5)
Platelet count decreased	3 (1.2)	1 (0.8)
Blood creatinine increased	3 (1.2)	0
Urinary tract infection	2 (0.8)	3 (2.3)

In the olaparib arm, the median total treatment duration was similar to the actual treatment duration, which shows that that the duration of any treatment interruptions was short. The median time to first treatment interruption of olaparib (for any reason) was 2.3 months (range 0 to 13 months) and median duration of first interruption of olaparib was short (12 days [range 2 to 49 days]).

Comparison with olaparib 300mg bd pool

The proportion of patients who had AEs leading to dose interruption was similar for PROfound (115 patients [44.9%]) compared with the 300 mg bd pool (630 patients [39.7%]). Anaemia, vomiting and neutropenia were the most common AEs leading to dose interruption in the 300 mg bd pool and anaemia and thrombocytopenia were the most common in PROfound.

- **Adverse events leading to dose reduction**

AEs leading to dose reduction occurred more frequently in olaparib-treated patients compared with investigators choice of NHA-treated patients (Table 77). The most common (≥5% of patients) AE leading to dose reduction in the olaparib arm was anaemia. There were no AEs leading to dose reduction reported in ≥5% of patients in the investigators choice of NHA arm.

Table 77: PROfound: AEs leading to dose reduction (Cohort A+B SAS)

MedDRA preferred term[b]	Number (%) of patients[a]	
	Olaparib 300 mg bd (N=256)	Investigators choice of NHA (N=130)
Patients with any AE leading to dose reduction	**57 (22.3)**	**5 (3.8)**
Anaemia	40 (15.6)	0
Nausea	6 (2.3)	1 (0.8)
Vomiting	5 (2.0)	0
Thrombocytopenia	4 (1.6)	0
Fatigue	3 (1.2)	2 (1.5)
Asthenia	3 (1.2)	1 (0.8)
Neutropenia	3 (1.2)	0
Blood creatinine increased	2 (0.8)	0
Creatinine renal clearance decreased	2 (0.8)	0
Leukopenia	2 (0.8)	0
Bone pain	1 (0.4)	0
Diarrhoea	1 (0.4)	0
Dizziness	1 (0.4)	0
Dyspnoea exertional	1 (0.4)	0
Lymphopenia	1 (0.4)	0
Neuropathy peripheral	1 (0.4)	0
Neutrophil count decreased	1 (0.4)	0
Renal impairment	1 (0.4)	0
Vertigo positional	1 (0.4)	0
WBC count decreased	1 (0.4)	0
Decreased appetite	0	1 (0.8)
Hypertension	0	1 (0.8)
Malaise	0	1 (0.8)

The median time to first dose reduction of olaparib (for any reason) was 3.0 months (range 0 to 10 months). It should be noted that once a patient was on a reduced dose, the dose could not be re-escalated.

Comparison with olaparib 300mg bd pool

The proportion of patients who had AEs leading to dose reduction was similar for PROfound (57 patients [22.3%]) and the 300 mg bd pool (339 patients [21.4%]). Anaemia was the most common AE leading to dose reduction in the 300 mg bd pool and PROfound.

In PROfound study, dose reduction was more reported in olaparib group compared to NHA group (22.3% vs 3.8%). Anaemia was the main reason for dose modification (15.6% of cases) and the median time to first dose reduction of olaparib for any reason was 3.0 months. However, most patients were able to receive their treatment with a dose between 500 and 600mg daily (from 82.8% up to 3 months to 55.8% up to 12 months of treatment).

Dose reduction data in PROfound study were consistent with data from olaparib 300mb bd pool (22.3% 21.4%).

Laboratory findings

- **Haematology**

Changes in the laboratory values for the haematology parameters of haemoglobin, neutrophils, platelets, lymphocytes and leukocytes are presented in Table 78.

In PROfound, a higher proportion of patients in the olaparib arm had ≥2 grade changes in haematological laboratory parameters, compared with patients in the investigators choice of NHA arm. The proportion of patients with a maximum CTCAE Grade of 3 or 4 lymphocytes during the study was 23.1% in the olaparib arm and 12.9% in the investigators choice of NHA arm and for haemoglobin was 13.4% in the olaparib arm and 4.0% in the investigators choice of NHA arm; the proportion of patients in either treatment arm with a maximum CTCAE Grade of 3 or 4 for other haematological parameters was ≤5%. The frequency of CTCAE Grade ≥3 AEs of lymphopenia (grouped term) was 1.6% in the olaparib-treated arm whilst anaemia was the most frequently reported CTCAE Grade ≥3 AE, SAE and DAE.

Table 78: PROfound: Number (%) of patients with maximum overall CTCAE grades during treatment for key haematological parameters (Cohort A+B SAS)

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Haemoglobin					
Olaparib 300 mg bd	5/247 (2.0%)	110/247 (44.5%)	99/247 (40.1%)	33/247 (13.4%)	0
Investigators choice of NHA	33/124 (26.6%)	62/124 (50.0%)	24/124 (19.4%)	5/124 (4.0%)	0
Platelets					
Olaparib 300 mg bd	189/247 (76.5%)	39/247 (15.8%)	15/247 (6.1%)	3/247 (1.2%)	1/247 (0.4%)
Investigators choice of NHA	109/124 (87.9%)	13/124 (10.5%)	2/124 (1.6%)	0	0
Leukocytes					
Olaparib 300 mg bd	117/247 (47.4%)	57/247 (23.1%)	64/247 (25.9%)	9/247 (3.6%)	0
Investigators choice of NHA	98/124 (79.0%)	21/124 (16.9%)	5/124 (4.0%)	0	0
Neutrophils					
Olaparib 300 mg bd	164/247 (66.4%)	53/247 (21.5%)	22/247 (8.9%)	8/247 (3.2%)	0
Investigators choice of NHA	113/124 (91.1%)	8/124 (6.5%)	3/124 (2.4%)	0	0
Lymphocytes					
Olaparib 300 mg bd	93/247 (37.7%)	2/247 (0.8%)	95/247 (38.5%)	52/247 (21.1%)	5/247 (2.0%)
Investigators choice of NHA	82/124 (66.1%)	0	26/124 (21.0%)	16/124 (12.9%)	0

Comparison with olaparib 300mg bd pool

In general, the laboratory evaluations for PROfound and the 300 mg bd pool were comparable. Changes in haemoglobin, neutrophils, leukocytes, lymphocytes and platelets were the only significant haematological parameters with clinically relevant changes; these parameters are recognised ADRs for olaparib. The majority of the changes in laboratory haematological parameters on olaparib had a worst grade of CTCAE Grade 1 or 2; there were few patients with Grade 3 or 4 changes in these haematological parameters.

- **Clinical chemistry**

There were no new clinical chemistry changes observed during PROfound (Table 79).

Table 79: PROfound: Number (%) of patients with maximum overall CTCAE grades during treatment for key chemistry parameters (Cohort A+B SAS)

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
ALT					
Olaparib 300 mg bd	207/248 (83.5%)	36/248 (14.5%)	4/248 (1.6%)	1/248 (0.4%)	0
Investigators choice of NHA	110/124 (88.7%)	12/124 (9.7%)	1/124 (0.8%)	0	1/124 (0.8%)
AST					
Olaparib 300 mg bd	199/248 (80.2%)	44/248 (17.7%)	3/248 (1.2%)	2/248 (0.8%)	0
Investigators choice of NHA	100/124 (80.6%)	21/124 (16.9%)	1/124 (0.8%)	1/124 (0.8%)	1/124 (0.8%)
ALP					
Olaparib 300 mg bd	126/248 (50.8%)	70/248 (28.2%)	33/248 (13.3%)	18/248 (7.3%)	1/248 (0.4%)
Investigators choice of NHA	56/125 (44.8%)	39/125 (31.2%)	15/125 (12.0%)	13/125 (10.4%)	2/125 (1.6%)
Bilirubin					
Olaparib 300 mg bd	237/248 (95.6%)	7/248 (2.8%)	2/248 (0.8%)	2/248 (0.8%)	0
Investigators choice of NHA	119/124 (96.0%)	4/124(3.2%)	1/124 (0.8%)	0	0
Creatinine					
Olaparib 300 mg bd	13/248 (5.2%)	189/248 (76.2%)	42/248 (16.9%)	4/248 (1.6%)	0
Investigators choice of NHA	41/127 (32.3%)	79/127 (62.2%)	6/127 (4.7%)	1/127 (0.8%)	0

Comparison with olaparib 300mg bd pool

The only significant change in clinical chemistry parameters occurred for creatinine: creatinine increases are a recognised ADR for olaparib and are discussed above. For PROfound, small increases were observed early in olaparib treatment, which then stabilised; this pattern of effect is consistent with OCT2 and MATE-1 inhibition.

Assessment of the potential for drug-induced liver injury

There were no confirmed or suspected Hy's Law cases. Although 1 patient randomised to receive olaparib and 1 patient who switched to olaparib after progression in PROfound had concurrent elevations of bilirubin and ALT/AST, there were alternative explanations for the elevated liver function test results in these patients.

- **Vital signs, physical findings, and other observations related to safety**

There were no clinically relevant changes noted in vital signs or physical examination safety parameters in the olaparib or in the investigators choice of NHA arm, and no individual abnormalities raised any safety concerns.

Safety in special populations

Intrinsic factors

- **Effect of gender**

As all patients in the PROfound study were male, an analysis of the effects of gender has been conducted in the 300 mg bd pool.

It should be noted that 256 of the 408 male patients in the 300 mg bd pool were recruited in the PROfound study and 52 of the 408 male patients in the 300 mg bd pool were recruited in the POLO study (pancreatic cancer). These 308 patients constitute nearly all of the male patients who have been recruited in Phase III studies with olaparib. The vast majority of the remaining 100 male patients were recruited to a variety of Phase I studies; therefore approximately one quarter of the male patients in the 300 mg bd pool were treated in studies that were generally of short duration and conducted early in the development of the olaparib tablet formulation. In contrast, a large proportion (approximately three-quarters) of the female

patients in the 300 mg bd pool have been recruited to Phase III studies with long durations of treatment (eg, SOLO1 [304 patients, including the China cohort], SOLO2 [217 patients including the China cohort], SOLO3 [178 patients] and OlympiAD [205 patients]).

Table 78 shows the distribution of AEs in the olaparib 300 mg bd pool by patient gender; this shows that the incidence of AEs in each category was generally similar for male and female patients on olaparib treatment.

Table 80: 300 mg bd pool: Number (%) of patients reporting at least 1 AE by gender (SAS)

AE category	Number (%) of patients[a]	
	Male (N=408)	Female (N=1177)
Any AE	392 (96.1)	1150 (97.7)
Any AE CTCAE Grade 3 or higher	184 (45.1)	475 (40.4)
Any AE with outcome = death	12 (2.9)	7 (0.6)
Any SAE (including events with outcome = death)	124 (30.4)	241 (20.5)
Any AE leading to dose interruption of treatment	158 (38.7)	472 (40.1)
Any AE leading to dose reduction of treatment	73 (17.9)	266 (22.6)
Any AE leading to discontinuation of treatment	55 (13.5)	93 (7.9)

Common (≥10% of either sex) AEs which occurred with a different frequency between male and female patients on olaparib treatment (a difference in incidence of ≥5% between males and females) were as follows:

- The only AE that occurred more frequently in male patients was: decreased appetite (27,7% vs 21,9%).

- AEs that occurred more frequently in female patients were: abdominal pain, abdominal pain upper, diarrhoea, dizziness, dysgeusia, fatigue, headache, nausea, neutropenia, upper respiratory tract infection and vomiting. These imbalances are likely to be related to differences in the diseases under treatment; the majority of female patients were treated for ovarian cancer.

An analysis of AEs of CTCAE Grade ≥3 by gender showed that no CTCAE Grade ≥3 AEs occurred more frequently (≥5% difference between genders) in female patients compared with male patients.

- **Effect of age**

Table 81 shows the distribution of AEs by patient age. A similar proportion of patients had AEs in all age categories; a higher proportion of patients had SAEs in the ≥85 years age category compared with the other age categories; however, as there were only 6 patients in the ≥85 years age category these results should be interpreted with caution. A higher proportion of patients had DAEs in the 75 to 84 years and ≥85 years age category, compared with <65 years and 65 to 74 years categories. The proportion of patients who were hospitalised or who had prolonged hospitalisation increased with increasing age. Seven fatal AEs were reported in the age <65 years age category, 9 fatal AEs were reported in the 65 to 74 years age category, 3 fatal AEs were reported in the 75 to 84 years age category and none were reported in the ≥85 years age category.

Table 81: 300 mg bd pool: Number (%) of patients reporting at least 1 AE by age group (SAS)

AE Category	Number (%) of patients[a]			
	Age <65 years (N=1142)	Age 65 to 74 years (N=334)	Age 75 to 84 years (N=103)	Age ≥85 years (N=6)
Any AE	1111 (97.3)	326 (97.6)	99 (96.1)	6 (100)
SAEs[b]	233 (20.4)	94 (28.1)	34 (33.0)	4 (66.7)
Fatal	6 (0.5)[c]	9 (2.7)	3 (2.9)	0
Hospitalisation/prolong existing hospitalisation	215 (18.8)	86 (25.7)	33 (32.0)	4 (66.7)
Life-threatening	28 (2.5)	17 (5.1)	3 (2.9)	1 (16.7)
Disability/incapacity	5 (0.4)	4 (1.2)	1 (1.0)	0
Other (medically significant)	63 (5.5)	24 (7.2)	9 (8.7)	2 (33.3)
DAEs	85 (7.4)	39 (11.7)	22 (21.4)	2 (33.3)

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, 75 to 84 years and ≥85 years. Nausea and vomiting were the only AEs that occurred at a higher incidence (≥5% difference) in the <65 years category compared with 65 to 74, 75 to 84 and ≥85 years age 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 was: oedema peripheral. AEs that occurred at a lower incidence (≥5% difference) when compared with <65 years age category were: nausea and vomiting.

For the 75 to 84 years age category, AEs that occurred at a higher incidence (≥5% difference) when compared with <65 years were: anaemia, decreased appetite, dyspnoea, hypotension, muscular weakness, oedema peripheral and pneumonia. AEs that occurred at a lower incidence (≥5% difference) when compared with <65 years age category were: abdominal pain, abdominal pain upper, dysgeusia, headache, leukopenia, nasopharyngitis, nausea and vomiting.

An analysis of AEs by the SOCs/SMQs most relevant to elderly patients, and age is provided in Table 82.

Table 82: 300 mg bd pool: Number (%) of patients with, and reports of AEs within the SOCs/SMQs of most relevance to elderly patients, by age (SAS)

Category	Number (%) of patients[a]			
	Age <65 years (N=1142)	Age 65 to 74 years (N=334)	Age 75 to 84 years (N=103)	Age ≥85 years (N=6)
Patients with any AE	1111 (97.3)	326 (97.6)	99 (96.1)	6 (100)
Psychiatric disorders (SOC)	199 (17.4)	54 (16.2)	16 (15.5)	0
Accidents and injuries (SMQ)	77 (6.7)	25 (7.5)	12 (11.7)	1 (16.7)
Cardiac disorders (SOC)	64 (5.6)	24 (7.2)	6 (5.8)	0
Vascular disorders (SOC)	129 (11.3)	45 (13.5)	15 (14.6)	0
Central nervous system vascular disorders (SMQ)	8 (0.7)	5 (1.5)	1 (1.0)	1 (16.7)
Infections and infestations (SOC)	494 (43.3)	141 (42.2)	39 (37.9)	2 (33.3)
Quality of life decreased (PT)	0	0	0	0
Sum of orthostatic hypotension, fall, loss of consciousness, syncope, dizziness, ataxia and fractures AEs	164 (14.4)	55 (16.5)	18 (17.5)	1 (16.7)

Analysis of AE by age revealed that although proportion and distribution of AE by SOC were similarly reported in all age categories (<65 years old, 65-74 years old, 75-84 years old ,>85 years old), seriousness increases with age (SAE respectively of 20.4%, 28.1%, 33%, 66.7%) as well as discontinuation of treatment due to AE (7.4%, 11.7%, 21.4%, 33.3%).

- **Effect of race**

The safety profile in the 300 mg bd pool for olaparib in White, Asian and other non-White patients was generally similar. Safety data are presented for the 371 non-White patients who received the proposed dose of 300 mg bd as a monotherapy across the clinical program.

The majority of these patients 331 (85.8%) were of Asian origin, 19 (4.9%) patients were of Black or African-American origin, 9 (2.3%) were of American Indian or Alaska Native origin, 1 (0.3%) was of Native Hawaiian or Other Pacific Islander origin and 11 (2.8%) were of other racial origin. Numbers of Asian and other non-White patients represent 20.9% of patients and 2.5% of patients (331/1585 and 40/1585 patients) in the 300 mg bd pool, respectively.

The most common AE (≥20% patients) in the Asian patient population were: nausea, anaemia, vomiting, decreased appetite, fatigue and WBC count decreased. The most common (≥20% patients) in the other non-White patient population were: anaemia, nausea, diarrhoea, fatigue, decreased appetite, vomiting, headache and neutropenia.

AEs that occurred at a higher incidence in Asian patients (≥5% difference) compared with White patients were: ALT increased, anaemia, AST increased, decreased appetite, malaise, muscle spasms, neutrophil count decreased, platelet count decreased, upper respiratory tract infection and WBC count decreased. AEs that occurred at a lower incidence in Asian patients (≥5% difference) compared with White patients were: abdominal pain, abdominal pain upper, arthralgia, asthenia, back pain, constipation, diarrhoea, dyspnoea, fatigue, headache, nausea, oedema peripheral and urinary tract infection.

AEs that occurred at a higher incidence in other non-White patients (≥5% difference) compared with White patients were: anaemia, decreased appetite, hyperglycaemia, hypertension, hypokalaemia, leukopenia, neutropenia, upper respiratory tract infection, vertigo and WBC count decreased. AEs that occurred at a lower incidence in other non-White patients (≥5% difference) compared with White patients were: asthenia, dyspepsia, fatigue, nausea, pyrexia, rash and vomiting.

AEs of CTCAE Grade ≥3 that occurred at a higher incidence in Asian patients (≥5% difference) compared with White patients were: anaemia, neutrophil count decreased and WBC count decreased. The only CTCAE Grade ≥3 AE that occurred at a higher incidence (≥5% difference) in other non-White patients compared with White patients was anaemia.

Anaemia, neutrophil count decreased and WBC count decreased were the only AEs that resulted in a dose modification that occurred at a higher incidence in Asian patients (≥5% difference) compared with White patients. Anaemia was the only AE that resulted in a dose modification that occurred at a higher incidence (≥5% difference) in other non-White patients compared with White patients.

There were no AEs leading to treatment discontinuation that occurred at a higher incidence in Asian patients (≥5% difference) compared with White patients. Anaemia was the only AE leading to treatment discontinuation that occurred at a higher incidence (≥5% difference) in other non-White patients compared with White patient.

Post marketing experience

The capsule formulation of olaparib is currently approved in more than 55 countries worldwide for the treatment of patients with ovarian cancer. As of 2 October 2019, the tablet formulation of olaparib has received marketing approval in more than 50 countries (including the US, European Union [EU; via the centralised procedure], Japan, China and Canada) for the maintenance treatment of patients with PSR ovarian cancer. As of 2 October 2019, the olaparib tablet formulation has received marketing approval in

more than 40 countries (including the US, EU [via the centralised procedure], Japan, Canada, Australia and Brazil for the maintenance treatment of ovarian cancer patients with BRCAm advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Furthermore, as of 2 October 2019, the olaparib tablet formulation has been approved in more than 45 countries, (including the US, EU [via the centralised procedure], Japan, Canada and Australia) for gBRCAm HER2-negative metastatic breast cancer.

The PSUR reports received did not change the benefit-risk profile of olaparib.

Access programme and ongoing studies

As of 15 June 2019, a total of 847 patients have been dosed with olaparib capsules or tablets in the following Global Access Programmes: Named Patient Supply Scheme, French Authorisation of Temporary Use, Turkish Compassionate Use Programme, UK Early Access to Medicines Scheme, UK Compassionate Use Programme, German Compassionate Use Programme, Dutch Compassionate Use Programme, and USA Early Access programme. In addition, there are a number of ongoing clinical studies in which patients have been dosed with either olaparib tablets or a blinded comparator agent.

Safety data from these ongoing studies are available in the PSUR. In summary, no new or important safety information resulting in changes to the safety profile of olaparib has been identified from the ongoing studies or patient access programme. No new signal emerged from last PSUR.

2.5.1. Discussion on clinical safety

Safety assessment is mainly based on pivotal study PROfound in patients with metastatic prostate cancer with HRR mutation who have failed prior treatment with an NHA (abiraterone or enzalutamide depending on investigators choice). These data were thereafter compared with a large pool of 1585 patients which received the same dose of olaparib as monotherapy in other indications. This methodology is acceptable and available data are considered sufficient to ensure an effective analysis of the safety profile of olaparib in the scope of the requested indication.

Study PROfound collected data from 386 patients (256 in olaparib arm and 130 in NHA arm). Patients were divided into two cohorts based on HRR gene mutation status. The MAH provided additional analysis showing that underlying genetic mutations do not affect the safety profile of olaparib.

In Study PROfound, median duration of olaparib treatment was 1.9 times longer than in the NHA group (7.5 months vs 3.9 months) with a maximum of 692 days in olaparib group. Treatment interruptions and dose reductions were reported during the study, mainly due to AE occurrence. However, considering comparable total and actual treatment duration of olaparib (242.8 vs 229.6 days), interruption appears to be short and the majority of patients were able to receive a dose between 500 and 600 mg daily (82.8% of patients for a period up to 3 months and 55.8% of patients for a period > 12 months of treatment). Overall, 20.3% of patients in the olaparib arm remained on treatment for ≥ 1 year, compared to 3.8% of patients in the investigators choice of NHA arm. Due to a longer exposure, exposure adjusted rates have been provided for AEs which is considered appropriate.

Compared with the olaparib arm of PROfound, median treatment duration in the 300 mg bd pool was similar. A higher proportion (26.3%) of patients in the 300 mg bd pool had a treatment duration of ≥ 18 months compared with 3.9% in the olaparib arm of PROfound; only 10 of the 417 patients (2.4%) who have received ≥18 months olaparib treatment in the 300 mg bd pool were recruited in PROfound. This reflects the diverse nature of patients that comprise the 300 mg bd pool, including the use of olaparib as first-line maintenance treatment.

It is noted that olaparib 300mb bd pool provided supportive safety data from longer exposure to olaparib (> 48 months) but mainly in women with ovarian, fallopian tube or primary peritoneal cancer.

In PROfound study, patient's demographics were consistent across treatment groups and nearly reflect the population of the proposed indication despite lower median age compared to mCRPC population. All patients were men with mean age of 69 years old and more white patients were represented. Compared to the pool of olaparib 300 mg bd, the population included was older in PROfound study. There is also limited experience in men from other clinical trials included in the pool of olaparib 300 mg bd.

Overall, the safety profile reported in PROfound study was consistent with that observed in previous studies with olaparib monotherapy.

The proportions of patients with SAEs, AEs leading to treatment (olaparib) discontinuation, CTCAE Grade ⩾3 AEs and AEs leading to death were higher in PROfound compared with the 300 mg bd pool. This might be explained by differences in baseline characteristics such as higher mean age, male population of the PROfound population compared with the 300 mg bd pool, as suggested by higher rates of SAEs, including those with a fatal outcome also observed in the PROfound investigators choice of NHA arm, compared with the 300 mg bd pool.

The majority of AEs occurred within the first 3 months of treatment. Most commonly AE reported pertained to the SOC Hematologic disorders (anaemia (46,1%), thrombocytopenia (8,6%), neutropenia (6,3%) and lymphopenia (5,1%)), SOC Gastro-intestinal disorders (nausea (41,4%), decrease appetite (30,1%), diarrhoea (21,1%), vomiting (18,4%), constipation (17,6%), dyspepsia (7%), dysgueusia (6,6%), SOC General disorders (fatigue (26,2%), asthenia (15,6%)), SOC respiratory disorders (cough (10,9%), dyspnoea (10,2%)) and Nervous system disorders (dizziness (6,6%), headache (5,9%)).

All of the AEs reported with a higher incidence of ≥5% for patients in the olaparib arm compared with the investigators choice of NHA were known ADRs for olaparib. AE were mainly manageable by treatment interruption or dose reduction and supportive treatment. Treatment discontinuation was reported in 18% of cases with anaemia as the AE responsible for most discontinuation.

Most deaths reported in PROfound study were related to the disease under investigation. Only two fatal cases might be related to olaparib in patients who presented lung infection 3 and 13 days after treatment initiation respectively. In one of them, neutropenia was also associated. Appropriate warnings are mentioned in the SmPC to closely monitor haematotoxicity including neutropenia during olaparib treatment.

Compared to olaparib pool, similar proportion of AE were reported, with slight differences such as anaemia and decrease appetite which were reported with a higher incidence in PROfound study (46,1% vs 39,9% and 30,1% vs 23,4% respectively). Slightly more SAE (35,5% vs 23%) and AE of CTACE Grade≥3 were also reported (50.8% vs 41.6%). Differences observed could be related to baseline characteristics (higher median age of patients and male population).

Compared to investigator NHA group, proportion of AE reported was higher in olaparib group (95.3% vs 87.7%), as well as proportion of SAE (35.5% vs 27.7%) and proportion of AE of CTCAE Grade≥3 (50.8% vs 37.7%). The differences between both groups were mainly driven by anaemia (46.1% in olaparib group vs 15.4% in NHA group) including of CTCAE Grade≥3 anaemia (21.5% vs 5.4% in NHA arm) and nausea (41.4% vs 19.2%). Treatment discontinuation was also more frequently observed (18% vs 8.5%). Similar rate of deaths was reported (3.9% vs 3.8%).

Small imbalances were noted in the incidence of oedema peripheral (12.5% in the olaparib arm versus 7.7% in the investigators choice of NHA arm) and pulmonary embolism (4.3% in the olaparib arm versus 0.8% in the investigators choice of NHA arm) that are not recognized as part of the known safety profile of olaparib. All AEs of oedema peripheral were classed as low grade (CTCAE Grade 1 or 2) and none were

classed as serious. The exposure adjusted event rate was similar between the treatment arms and therefore these events are most likely due to underlying disease.

The difference between arm in the rate of pulmonary embolism persisted but decreased after adjustment by treatment duration. No differences of medical history were detected between both groups. Among the 11 patients who presented pulmonary embolism, risk factors were retrieved in 8 cases and 5 cases were detected on routine follow-up CT as incidental finding. Among other venous thromboembolic events reported, no difference was retrieved between both arms. The rate of pulmonary embolism was also higher compared to olaparib 300 mg bd pool (1.7%) but populations differ in terms of underlying diseases, types of cancer, median age, time of olaparib exposure and gender since olaparib pool mainly included women with ovarian and breast cancers. No imbalances in pulmonary embolism or deep vein thrombosis events were observed between the olaparib and the comparator arms in individual studies. Thus, it is considered plausible that the observed imbalance in incidence of pulmonary embolism between both treatment arms is rather a finding by chance.

Anaemia is a known and common ADR of olaparib which has been more reported in olaparib group than in NHA arm in PROfound study (46,5% vs 15,4%, 119 vs 20 patients). 21,5% were CTCAE Grade≥3 and 8.6% were serious. Anaemia occurred generally within the first 3 months of treatment but was reported throughout the course of treatment with no evidence of cumulative effect. Anaemia after olaparib treatment remained manageable and necessitated interruption (64 patients out of 119; 53,8%) or reduction of the olaparib dose (40 out of 119; 33,6%) or blood transfusions (62 out of 119; 52,1%) or erythropoiesis stimulating agent (13 out of 119; 10,9%). Treatment discontinuation was infrequently required (18 out of 119; 15,1%). Despite a slight increase in incidence, anaemia events in PROfound study are consistent with results from the olaparib 300 mg bd pool. Appropriate warnings are mentioned in the SmPC to prevent, monitor and minimize haematological toxicity including anaemia (baseline testing and monthly monitoring).

Overall, neutropenia, thrombocytopenia, lymphopenia events in PROfound study were also consistent with results from the 300 mg bd pool and already adequately addressed in the SmPC.

Regarding potential risks, no new information emerged from PROfound study. No case of MDS/AML and only one case (0.4%) of new primary malignancy was reported in olaparib group. However, despite similar and consistent rates reported compared to olaparib entire program (0.8%) and NHA arm (1.5%), low rates reported make the interpretation of differences observed difficult between groups.

The types of new primary cancers reported in the olaparib clinical trial programme were generally in line with secondary cancers observed in ovarian and breast cancer populations reported in the literature (Bergfeldt et al 1995, Fowble et al 2001, Wesolowski et al 2007) or were cancers, such as skin cancer, known to be the most common cancer in the general population and associated with high cure rates.

Due to mechanism of action of olaparib which leads to accumulation of DNA damage, a contributory role of olaparib in MDS/AML and new primary malignancy by creating genomic instability in the absence of apoptosis cannot be excluded and these safety concerns are included in the RMP as potential risks. Appropriate warnings are mentioned in the product information and a targeted questionnaire has been implemented to better document cases reported. No new information emerged from PROfound study and this risk will continue to be closely monitored in post-marketing setting.

Five cases of pneumonitis (2%) were reported in olaparib group in patients with confounding factors (previous treatment with docetaxel, presence of baseline respiratory metastases or concomitant use of leuprorelin). Similar incidence of pneumonitis were reported in pivotal studies SOLO1 (1.9%) and SOLO2 (1.5%). The statement in the SmPC that "Pneumonitis, including events with a fatal outcome, has been reported in <1.0% of patients treated with Lynparza in clinical studies" is based on calculation of pooled data from across the entire programme, remains valid after inclusion of the PROfound population.

Pneumonitis is a potential risk which is adequately addressed in the product information and in the RMP. These events will continue to be closely monitored in post-marketing setting.

Laboratory findings were also consistent with available data on olaparib pool.

Safety in special population do not seem to differ with gender despite low number of men included. In addition, similar proportion of AE was reported among the different age population with an increase of seriousness and discontinuation of treatment from younger to older groups which could be explained by a higher median age, cancer stage and ECOG PS and different cancer types in PROfound study. Considering the higher number of patients over 75 years old included in the entire clinical program with PROfound study (>100 patients), update of SmPC sections 4.2 and 4.8 has been made to remove the reference to limited clinical data in patients aged 75 years and over.

Although there appears to be some variability in the reporting of individual terms, particularly with respect to reporting of laboratory values as AEs, no clinically significant differences in the safety profile of olaparib in White versus Asian or other non-White patients have been observed and no effect of race on the PK of olaparib has been identified. Consistent data were reported by race but these data should be interpreted with caution due to over representation of White patients compared to non-White patients.

The SmPC has been revised with updated safety data (updating frequencies of ADRs) based on pooled data from 2351 patients with solid tumours treated with olaparib monotherapy in clinical trials at the recommended dose (see also variation II/35).

2.5.2. Conclusions on clinical safety

Overall, the safety profile of olaparib tablet formulation is well characterised, generally manageable and considered acceptable for the intended population.

The study PROfound provided significant evidence and results showed no high differences in risk when compared to pooled safety data from other studies. However, the safety profile was slightly less favourable compared to treatment with a new hormonal agent (enzalutamide or abiraterone acetate), with higher incidences of AEs of any grade, of AEs ≥ Grade 3, of SAEs, of AEs leading to treatment discontinuation, of AEs leading to dose reduction and of AEs leading to treatment interruption.

Patients experiencing ADRs need to be carefully followed by physicians as indicated in the SmPC and more data are needed to assess the causal relationship between olaparib exposure and development of important potential risks. These risks will continue to be closely monitored.

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 MAH submitted an updated RMP version with this application.

The CHMP endorsed the Risk Management Plan version 20.3 with the following content:

Safety concerns

Table 96 - Summary of the safety concerns

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

Pharmacovigilance plan

There are no on-going or planned additional pharmacovigilance activities for olaparib.

Risk minimisation measures

Table 97 - Description of routine risk minimisation measures by safety concern

Safety concern	**Routine risk minimisation activities**
MDS/AML	**Routine risk communication:** • SmPC Section 4.4 • PL Section 2 and 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** **SmPC Section 4.4:** Guidance is provided for monitoring and management. **PL Section 2:** Advice regarding low blood counts and the signs and symptoms to look out for. **PL Section 4:** Provides information on side effects and signs and symptoms, commonly shown in blood tests, to look out for.
New primary malignancy	There are no risk minimisation activities for new primary malignancy.

Table 97 - Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
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.
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:** Includes a 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 **Other routine risk minimisation measures beyond the Product Information:** Distinct differences in the appearance of medication and packaging for tablets and capsules (presentation [tablets as blister strips vs capsules in bottles], colour scheme, label design, and dosing statements on the packaging). **Additional risk minimisation measures:** Direct Healthcare Professional Communication (DHPC) - To provide clear information and guidance to the prescriber and pharmacist on the 2 available formulations of olaparib (capsule and tablet) and their appropriate administration showing clear differentiation between the 2 posologies.

Table 97 - Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Effects on embryofoetal survival and abnormal development	**Routine risk communication in:** • SmPC Sections 4.4, 4.6 • PL Section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** **SmPC Section 4.4, 4.6:** Advice on contraception and pregnancy. **PL Section 2:** Advice on contraception and pregnancy
Long term exposure to/potential toxicity to olaparib	None.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC are updated. The PL is updated accordingly. In addition, sections 4.2, 4.4 and 4.8 of the SmPC for Lynparza hard capsules are revised based on updated safety data analysis and the structure section 5.3 is revised. The RMP version 20.3 has also been accepted.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable because the changes to the package leaflet are limited in Section 1 and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The purpose of the current submission was to seek marketing approval for olaparib for the following indication: Lynparza tablets as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer and BRCA1/2-mutations (germline and/or somatic) who have progressed following a prior new hormonal agent.

3.1.2. Available therapies and unmet medical need

According to ESMO guideline on cancer of the prostate (October 2015), the recommended treatment of CRPC are abiraterone or enzalutamide for asymptomatic/mildly symptomatic men with chemotherapy-naïve metastatic CRPC, radium-223 for men with bone-predominant symptomatic metastatic CRPC

without visceral metastases, docetaxel for men with metastatic CRPC and Sipuleucel-T is an option in asymptomatic/mildly symptomatic patients with chemotherapy-naïve metastatic CRPC.

Bone protective agents are recommended to be used in men with mCRPC to prevent fractures.

The optimal sequence or combination of these agents (abiraterone, enzalutamide, radium-223, docetaxel and Sipuleucel-T) is unknown. In practice, sequencing decisions will be made in the light of the distribution, extent and pace of disease, co-morbidities, patient preferences and drug availability.

3.1.3. Main clinical studies

The main study is the PROfound study which was a Phase III, randomised, open-label, multicentre trial to assess the efficacy and safety of olaparib monotherapy in patients with mCRPC that have qualifying HRR gene mutations that were predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function) who have failed prior treatment with an NHA.

Patients with mutations in BRCA1, BRCA2 or ATM were randomised in Cohort A (irrespective of co-occurring mutations in one of the 12 other HRR genes), whereas patients with mutations among 12 other genes involved in the HRR pathway were randomised in Cohort B.

The primary objective was to determine the efficacy (as assessed by rPFS) of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with mCRPC with BRCA1, BRCA2 or ATM qualifying mutations (Cohort A). Key secondary endpoints included: Confirmed ORR by BICR assessment in patients with measurable disease using RECIST 1.1 (soft tissue) and PCWG-3 (bone) criteria in cohort A; rPFS by BICR using RECIST 1.1 (soft tissue) and PCWG-3 (bone) criteria in cohort A+B; Pain progression based on BPI-SF Item 3 "worst pain in 24 hours" and opiate analgesic use (AQA score) in cohort A and Overall survival in cohort A.

3.2. Favourable effects

The primary endpoint of the pivotal study was met with a statistically significative improvement of rPFS in Cohort A for olaparib (HR=0.34, p<0.0001) with a prolongation of the median rPFS of 3.8 months (median rPFs of 7.39 months in olaparib arm vs 3.55 months in NHA).

This was supported by statistically significative improvements of confirmed ORR in Cohort A (Odds ratio = 20.86, p<0.0001), rPFS in Cohort A+B (median rPFS prolongation of 2.3 months with HR=0.49, p<0.0001) and TTPP in Cohort A (HR=0.44; p=0.0192).

A statistically significant OS benefit in olaparib-treated patients compared with investigators choice of NHA-treated patients [60.4% maturity] was shown in Cohort A (HR=0.69, 95% CI 0.50, 0.97; p=0.0175) with a median OS in olaparib arm of 19.1 months vs 14.7 months in NHA arm (median OS difference of 4.4 months).

However, the benefit of olaparib was more pronounced in patients with a BRCA1 and/or BRCA2 mutation, with a median improvement of rPFS of 6.83 months (HR=0.22, 95% CI 0.15, 0.32), a median OS improvement of 5.67 months (HR=0.63, 95% CI 0.42, 0.95) and a rate of responders of 43.9% for olaparib vs 0 in the comparator arm.

3.3. Uncertainties and limitations about favourable effects

There are no remaining uncertainties regarding the favourable effects in the patients with metastatic castration-resistant prostate cancer and BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent.

3.4. Unfavourable effects

Overall, the safety profile of olaparib is well characterised and is consistent with previous data from olaparib monotherapy. Most commonly AE reported pertained to the SOC Hematologic disorders (anaemia, thrombocytopenia, neutropenia and lymphopenia), SOC Gastro-intestinal disorders (nausea, decrease appetite, diarrhoea, vomiting), SOC General disorders (fatigue and asthenia), SOC respiratory disorders (cough and dyspnoea and SOC Nervous system disorders (dizziness and headache).

Adverse events were mainly manageable by treatment interruption (44.9%) or dose modification (22.3%) and supportive treatment.

Compared to olaparib 300 mg bd pool, higher incidences of CTCAE Grade ≥3 AEs (50.8% vs. 41.6%, respectively), of SAEs (35.5% vs. 27.7%, respectively), of AEs leading to treatment discontinuation (18.0% vs. 9.3%, respectively), of AEs leading to dose interruption (44.9% vs. 39.7%, respectively) were noted which might be explained by baseline characteristics.

Compared to the controlled group of abiraterone or enzalutamide treatment, median duration of olaparib treatment was 1.9 times longer. Proportion of AE reported was slightly higher in olaparib group (95.3% vs 87.7%), as well as proportion of SAE (35.5% vs 27.7%) and proportion of AE of CTCAE Grade≥3 (50.8% vs 37.7%). The differences between both groups were mainly driven by anaemia (46.1% vs 15.4%) including CTCAE Grade≥3 anaemia (21.5% vs 5.4% in NHA arm) and nausea (41.4% vs 19.2%). Treatment discontinuation due to AE was also more frequently observed (18% vs 8.5%) as well as dose interruption (44.9% vs 18.5%) and dose reduction due to AE (22.3% vs 3.8%). Similar rate of deaths was reported (3.9% vs 3.8%).

3.5. Uncertainties and limitations about unfavourable effects

Uncertainties remain on potential risks of AML/MDS, new primary malignancies and pneumonitis. These safety concerns will continue to be closely monitored in post-marketing setting.

In addition, the safety data available are considered limited in terms of number of patients and long-term follow-up. The MAH is recommended to submit complete long-term safety data of the clinical study PROfound.

3.6. Effects Table

Table 83. Effects Table for Lynparza – Prostate cancer (DCO 04 June 2019 and updated OS DCO 20 March 2020)

Effect	Short description	Unit	Treatment (olaparib)	Control (investigator choice of NHA)	Uncertainties / Strength of evidence	References
Favourable Effects						

Effect	Short description	Unit	Treatment (olaparib)	Control (investigator choice of NHA)	Uncertainties / Strength of evidence	References
rPFS in BRCA1 and/or BRCA2	Time from randomisation to radiological progression or death (DCO 04 June 2019)	Median (months)	9.8	3.0	95% CI 0.15, 0.32	PROfound study
		HR	0.22	1		
OS in BRCA1 and/or BRCA2	Time from randomisation until death (DCO 20 March 2020)	Median (month)	20.1	14.4		
		HR	0.63	1	95%CI 0.42, 0.95	
ORR in BRCA1 and/or BRCA2	Number of patients with a CR and PR / total number of patients (DCO 04 June 2019)	%	43.9	0	Odds ratio not calculable	
Unfavourable Effects						
AE of CTCAE Grade ≥3		%	50.8	37.7		PROfound study
AE with death outcome		%	3.9	3.8		
Serious AEs		%	35.5	27.7		
AEs leading to discontinuation of study treatment		%	18.0	8.5		
AEs leading to dose reduction of study treatment		%	22.3	3.8		
AEs leading to interruption of study treatment		%	44.9	18.5		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The pivotal study PROfound met its primary endpoint with a statistically significative improvement of rPFS in Cohort A, supported by the key secondary endpoints in Cohort A and Cohort A+B. However, it is questionable how much the results in Cohort A+B are driven by the Cohort A, and especially by BRCAm patients. The benefit of olaparib has not been established in Cohort B, and the efficacy results in the gene subgroup analysis showed no difference in rPFS between olaparib and the comparator groups and very limited numerical OS improvement in ATM subgroup whereas BRCA1/2 subgroup represented the best

responders to olaparib among the HRRm subjects. Moreover, the efficacy results overall in non-BRCAm patients showed no difference on rPFS and OS between olaparib arm and the comparator and the numbers of patients with alterations in particular genes are limited. Further, the available non-clinical data on sensitivity of tumour cells harbouring particular non-BRCA HRR gene alterations to olaparib are reported mainly for a gene/protein loss and do not appear to translate into clinical setting for a range of alterations in functionally divers proteins with potentially differential functional impact on homologous recombination repair pathways. Taking into account the overall available evidence on biomarkers conferring sensitivity to PARP inhibitors, the biology of prostate cancer and the results of the PROfound trial, a clinically relevant benefit can only be concluded for patients with BRCA1/2 mutations.

Overall, olaparib was well tolerated with a manageable safety profile which is sufficiently characterised although data for long-term safety remain limited. While ADRs of hematologic and lymphatic system occurred at a high frequency, they are generally of low grade and easily manageable.

3.7.2. Balance of benefits and risks

A clinically meaningful improvement in terms of relevant endpoints has been demonstrated for patients with BRCA1/2 mutations.

Safety results of PROfound seem to be in line with the safety profile of olaparib from other studies and post-marketing information. Measures to minimize the risk are well addressed in the RMP submitted by the MAH. The safety profile is considered acceptable for this patient population.

The benefit-risk balance is considered positive in patients with BRAC1/2m mCRPC.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Lynparza as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer and BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent, is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus 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 metastatic castration-resistant prostate cancer and BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC are updated. The PL is updated accordingly. In addition, sections 4.2, 4.4 and 4.8 of the SmPC for Lynparza hard capsules are revised based on updated safety data analysis and minor changes are made to section 5.3. The RMP version 20.3 has also been accepted.

Amendments to the marketing authorisation

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