17 September 2020
EMA/523504/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lynparza

International non-proprietary name: olaparib

Procedure No. EMEA/H/C/003726/II/0035

Note

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

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List of abbreviations

ACMG	American College of Medical Genetics and Genomics
ADR	Adverse drug reaction
AE(s)	Adverse event(s)
AESIs	Adverse events of special interest
ALT	Alanine aminotransferase
ARCAGY	Association de Recherche sur les Cancers dont GYnécologiques
AST	Aspartate aminotransferase
AUC	Area under plasma concentration-time curve
AUCss	Area under plasma concentration-time curve during any dosing interval at steady state
BCRP	Breast Cancer Resistance Protein
bd	Twice daily
BICR	Blinded independent central review
BRCA	Breast cancer susceptibility gene
BRCAm	*gBRCA* or *sBRCA* mutated/mutation
*BRCA*wt/VUS	gBRCA and sBRCA wild type/variant of uncertain significance
CA-125	Cancer antigen-125 (tumour biomarker)
CDS	Core Data Sheet
CDx	Companion diagnostic
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments
Cmax (Cmax,ss)	Maximum plasma concentration (at steady state)
Cmin (Cmin,ss)	Minimum plasma concentration (at steady state)
CR	Complete response
CrCL	Creatinine clearance
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Common technical document
CYP	Cytochrome P450
DCO	Data cut-off

DDI	Drug-drug interaction
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EMA	European Medicines Agency
ENGOT	European Network for Gynaecological Oncological Trial groups
EORTC	European Organisation for Research and Treatment of Cancer
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIGO	Fédération Internationale de Gynécologie Obstétrique (International Federation of Gynaecology and Obstetrics)
gBRCA	Germline BRCA
gBRCAm	Germline BRCA mutated
gBRCAwt/VUS	Germline BRCA wild type/variant of uncertain significance
GCIG	Gynecologic Cancer InterGroup
GCP	Good Clinical Practice
Gmean	Geometric mean
GOG	Gynecologic Oncology Group
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/mutations
IC50	Half maximal inhibitory concentration
IC90	90% inhibitory concentration
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IDS	Interval debulking surgery
ILD	Interstitial lung disease
INCa	Institut National du Cancer
IND	Investigational new drug
ITT	Intention-to-treat
iv	Intravenous

IVD	In vitro diagnostic
IVIVc	in vitro-in vivo correlation
IVRS	Interactive voice response system
Ka	Absorption rate constant
LOH	Loss of heterozygosity
MATE	Human Multi-Drug and Toxin Extrusion Transporter
MCV	Mean corpuscular volume
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MTP	Multiple testing procedure
NCCN	National Comprehensive Cancer Network
NDA	New Drug Application
NE	Not estimable
NED	No evidence of disease
NR	Not reported
OAT	Organic anion transporter
OATP	Organic anion-transporting polypeptide
OCT	Organic cation-transporter
ORR	Objective response rate
OS	Overall survival
PARP	Polyadenosine 5'diphosphoribose polymerase
PBPK	Physiologically-based pharmacokinetic
PBRER	Periodic benefit-risk evaluation report
PD	Pharmacodynamic
PFS	Progression-free survival
PFS2	Time from randomisation to second progression or death
P-gp	P-glycoprotein
PK	Pharmacokinetic
PR	Partial response
PRO	Patient reported outcomes
PSR	Platinum-sensitive relapsed
PT	Preferred term
QC	Quality control

QLQ-OV28	Quality of Life Questionnaire for Ovarian Cancer
QLQ-C30	Quality of Life Questionnaire Core 30 item module
QSR	Quality Systems Regulation
QT wave	ECG interval measured from the beginning of the QRS complex to the end of the T
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
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety Analysis Set
sBRCA	Somatic BRCA (BRCA variant found in the tumour but not in the germline)
sBRCAm	Somatic BRCA mutated/mutation
sBRCA VUS	Somatic BRCA variant of uncertain significance
sd	Standard deviation
SmPC	Summary of Product Characteristics
t1/2	Half life
tBRCA	Tumour BRCA (mutations detected in the tumour)
tBRCAm	Tumour BRCA mutated/mutation
tBRCAwt/VUS	Tumour BRCA wild type/variant of uncertain significance
TDT	Time to discontinuation of treatment or death (defined as time from randomisation to discontinuation of study treatment or death)
TEAE	Treatment emergent adverse event
TFST	Time from randomisation to start of first subsequent therapy or death
TIM-1	TNO Intestinal Model
tmax	Time to reach maximum concentration
TOI	Trial outcome index
TSST	Time from randomisation to start of second subsequent therapy or death
UGT	UDP-glucuronosyltransferase
ULN	Upper limit of normal
US/USA	United States/United States of America
USPI	United States Prescribing Information
VEGF	Vascular endothelial growth factor

vs	Versus
VUS	Variant of uncertain significance
wt	Wild type

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AstraZeneca AB submitted to the European Medicines Agency on 21 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, II, IIIA and IIIB

Extension of indication to include the use of Lynparza tablets in combination with bevacizumab for the maintenance treatment of adult patients with 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 with bevacizumab. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 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. Furthermore, the PI is brought in line with the latest QRD template version 10.1. The RMP version 19 has also been submitted.

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

Information on paediatric requirements

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

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

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Alexandre Moreau Co-Rapporteur: Koenraad Norga

Timetable	Actual dates
Submission date	21 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	16 March 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	20 March 2020
Request for supplementary information (RSI)	26 March 2020
CHMP Rapporteur Assessment Report	5 June 2020
PRAC Rapporteur Assessment Report	29 May 2020
PRAC Outcome	11 June 2020
CHMP members comments	15 June 2020
Updated CHMP Rapporteur Assessment Report	19 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	7 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 initially applied indication is for Lynparza in combination with bevacizumab for the maintenance treatment of adult patients with 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 in combination with bevacizumab.

Epidemiology

Ovarian cancer is the leading cause of death from gynaecological cancers in the US and Europe, ranking as the fifth most common cause of cancer death in women (American Cancer Society 2019, Ferlay et al 2013). In 2019, it is estimated that there will be 22,530 newly diagnosed ovarian cancer cases in the US and approximately 13,980 women will die from ovarian cancer (American Cancer Society 2019). Across Europe, the estimated age standardised rate of newly diagnosed ovarian cancer cases in 2020 is 15.5/100,000 and the mortality is 10.3/100,000 (ECIS 2020).

The disease is predominantly diagnosed in post-menopausal women over 50 years of age (>80%) and the aetiology is unknown although family history and a woman's reproductive history are important risk factors (Ledermann et al 2013). Family history (patients having 2 or more first degree relatives with ovarian cancer) including linkage BRCA1 and BRCA2 genotypes is associated with early-onset disease.

Ovarian cancer remains one of the most difficult cancers to diagnose at an early curable stage; 75% of patients present with advanced disease at initial diagnosis (Stage III or IV) (Hennessy et al 2009). Most patients die from their disease, with 5-year survival rates of only 29% for advanced stages (American Cancer Society 2019, Siegel et al 2019).

Biologic features

More than 90% of malignant ovarian tumours are of epithelial origin, designated epithelial ovarian cancer (EOC). The most common and most lethal EOC is high-grade serous carcinoma (HGSC).

High grade epithelial ovarian cancers have two principal phenotypic characteristics that suggests PARP inhibitor sensitivity. Firstly, epithelial ovarian cancers are highly responsive to platinum-based chemotherapy. Underpinned by a similar dependence on HRR for the repair of platinum-induced DNA damage, in the relapsed setting, platinum sensitivity has been demonstrated as a useful biomarker of PARP inhibitor sensitivity (Gelmon et al 2011, Ledermann et al 2012). Secondly, using known measures of HRR-deficiency, approximately 50% of high grade serous ovarian cancers are expected to be HRR-deficient at diagnosis (Konstantinopoulos et al 2015). HRR-deficiency in ovarian tumours can arise through a number of different mechanisms including loss of function mutations in genes that encode proteins with essential roles in HRR (including BRCA1 and BRCA2) as well as epigenetic silencing of HRR genes (Kondrashova et al 2018).

Clinical presentation, diagnosis and stage/prognosis

Ovarian cancer is often asymptomatic in the early stages and is, therefore, first detected in advanced stages, when prognosis is poor. For women who do experience symptoms in the early stages, ovarian cancer is sometimes misdiagnosed because the majority of symptoms are nonspecific. These symptoms may overlap those of gastrointestinal and other diseases, and as a result, many patients may be treated incorrectly for months or years.

The 5-year overall survival (OS) rate in advanced ovarian cancer patients decreases from 42% for Stage IIIA, 32% for Stage IIIC, and 19% for Stage IV.

Management

Cytoreductive surgery and platinum-based chemotherapy are considered treatments of choice for patients with newly diagnosed advanced ovarian cancer (NCCN Ovarian 2019, Karam et al 2017, Ledermann et al 2013). Even though most newly diagnosed advanced ovarian cancer patients achieve complete response

at the end of first line treatment, approximately 70% relapse within the first three years of diagnosis (Ledermann et al 2013). Once ovarian cancer relapses, the disease becomes largely incurable.

The vascular endothelial growth factor (VEGF) inhibitor bevacizumab, given in combination with carboplatin and paclitaxel followed by bevacizumab as maintenance, is the first biological treatment to be approved in the first line ovarian cancer treatment setting. The approval of bevacizumab in EU was based on the primary analysis of the GOG-0218 (Bevacizumab SmPC 2018, Burger et al 2011) and ICON7 (BO17707) (Perren et al 2011, Oza et al 2015) studies.

Most recently, results of the SOLO1 trial led to the approval of olaparib as first targeted maintenance treatment for newly diagnosed advanced BRCAm ovarian cancer patients in the EU in June 2019. The results from SOLO1 demonstrated a substantial 70% reduction in risk of disease progression or death (HR 0.30; 95% CI 0.23 to 0.41).

2.1.2. About the product

Olaparib, is a potent oral human PARP inhibitor that exploits deficiencies in DNA repair pathways to preferentially target cancer cells carrying such deficiencies. Dysfunctional HRR in tumour cells results in reliance on error-prone repair pathways, leading to an accumulation of DNA damage and cell death in tumour cells.

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

Lynparza presented as tablet formulation is currently indicated in the following indications for the treatment of ovarian cancer:

-As monotherapy for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2- mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.

-As monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

The 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.

The initially claimed indication was for olaparib (300 mg twice daily [bd], tablet formulation) for the following indication:

"Lynparza in combination with bevacizumab for the maintenance treatment of adult patients with 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 with bevacizumab".

Pre-clinical data have suggested a potential clinical synergistic benefit may be achieved when combining VEGF and PARP inhibitors, as there have been multiple observations around the impact of hypoxia on cell stress, including the DNA damage response and specifically inhibition of HRR.

The clinical rationale for investigating the role of the combination of olaparib/bevacizumab in the PAOLA-1 trial was based on available non-clinical and clinical data to combine two effective targeted treatments in ovarian cancer after completion of platinum based chemotherapy, in the first line maintenance setting

where improvement in clinical outcomes can be most impactful to patients with significant delay in progression and relapse and potentially improvement in cure rates.

The recommended indication by CHMP is as follows:

Lynparza in combination with bevacizumab is indicated for the:

- maintenance treatment of adult patients with 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 in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a *BRCA1/2* mutation and/or genomic instability (see section 5.1).

Before Lynparza with bevacizumab treatment is initiated for the first-line maintenance treatment of EOC, FTC or PPC, patients must have confirmation of either deleterious or suspected deleterious BRCA1/2 mutation and/or genomic instability determined using a validated test.

The recommended dose of Lynparza in combination with bevacizumab 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.

When Lynparza is used in combination with bevacizumab for the first-line maintenance treatment of high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer following completion of first-line platinum-based therapy with bevacizumab, the dose of bevacizumab is 15 mg/kg once every 3 weeks. Please refer to the full product information for bevacizumab (see section 5.1).

Patients can continue treatment with Lynparza until radiological disease progression, unacceptable toxicity or for up to 2 years if there is no radiological evidence of disease after 2 years of treatment. Patients with evidence of disease at 2 years, who in the opinion of the treating physician can derive further benefit from continuous Lynparza treatment, can be treated beyond 2 years. Please refer to the product information for bevacizumab for the recommended overall duration of treatment of a maximum of 15 months including the periods in combination with chemotherapy and as maintenance (see section 5.1).

Detection of BRCA1/2 mutations

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. Homologous recombination deficiency (HRD) positive status can be defined by detection of a BRCA1/2 mutation classified as deleterious/suspected deleterious or pathogenic/likely pathogenic. Detection of these mutations could be combined with positive HRD score (below) to determine HRD positive status.

Detection of genomic instability

HR deficiency-associated genomic alterations that have been investigated in Paola-1 include genome-wide loss of heterozygosity, telomeric allelic imbalance and large scale transition, which are continuous measures with pre-defined criteria and score. Composite genomic instability score (GIS, also called HRD score) is determined when the combined measures and respective scores are used to assess the extent of specific genomic aberrations accumulated in tumour cells. Lower score defines lower likelihood of HR deficiency of tumour cells and higher score determines higher likelihood of HR deficiency of tumour cells

at the time of the sample collection relative to exposure to DNA damaging agents. Validated cut-offs should be used to determine GIS positive status.

HRD positive status can be defined by a composite GIS score for HR deficiency-associated genomic alterations tested by an experienced laboratory using a validated test.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP (see discussion on non-clinical aspects).

2.2.1. Ecotoxicity/environmental risk assessment

The risk of an adverse environmental impact from the use of the drug substance olaparib has already been evaluated and approved by the EMA (EMEA/H/C/003726). The present submission seeks approval for a change to the ovarian cancer indication, to register Lynparza, in combination with bevacizumab, for the maintenance treatment of adult patients with advanced, high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to first line platinum-based chemotherapy with bevacizumab.

Although the indication has been amended, potentially increasing the patient population contributing to environmental exposure, the dose has not changed, and the indication and patient population used in the original environmental risk assessment (ovarian cancer) is considered sufficiently broad to cover the proposed indication change for this variation. The approval of this variation will have no significant effect on the predicted environmental exposure concentration presented in the original indication. Therefore, in accordance with the European Medicines Agency guidance (CHMP 2006 and CHMP 2016), an environmental risk assessment for olaparib has not been provided with this variation.

2.2.2. Discussion and conclusion on non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP. Both olaparib and bevacizumab have an indication in the first line maintenance treatment of ovarian cancer patients. The contribution of olaparib in the combination is assessed as add-on therapy to bevacizumab used in both arms concurrently with chemotherapy and in maintenance setting as indicated in the SmPC.

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

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

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

The MAH has provided a statement to the effect that clinical trials conducted outside the community were

carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Type of study	Study identifier	Location of Study Report in Module 5	Objective(s) of the study	Study Design and Type of Control	Test Products, Dosage Regimen, Route of Administration	Number of Subjects randomised/ treated	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication									
Efficacy, Safety	D0817C00003 (PAOLA-1)	5.3.5.1	To determine the efficacy of olaparib vs placebo added to bevacizumab by PFS, time to earliest progression by RECIST or CA-125 or death, TFST, PFS2, TSST, and OS. To compare the effects of olaparib maintenance compared with placebo on HRQoL and PROs, with consideration of patient preference. To assess the safety and tolerability of olaparib maintenance compared with placebo.	Phase III double-blind, randomised, placebo-controlled, multicentre	Olaparib 300 mg bd tablet (oral) Bevacizumab 15 mg/kg of body weight every 3 weeks for 15 months (iv).	806/802	Patients with newly diagnosed, advanced (FIGO Stage IIIB-IV) high grade serous or high grade endometrioid[a] ovarian cancer, primary peritoneal cancer and/or fallopian tube cancer who are in CR or PR following completion of first line platinum-taxane based chemotherapy and bevacizumab. [a] Patients with other epithelial non-mucinous histology were also eligible provided they had a *gBRCA* mutation.	Patients were to start treatment with olaparib or matching placebo tablets at least 3 weeks and no more than 9 weeks after their last dose of chemotherapy. Patients could continue olaparib or placebo for 2 years or until disease progression as per modified RECIST 1.1 as assessed by the investigator. Patients who in the opinion of the investigator, in discussion with the Sponsor, could derive further benefit from continued treatment, could be treated beyond 2 years. Bevacizumab was to be dosed for a duration of 15 months in total/22 cycles in total (including combination with platinum-based chemotherapy)	Ongoing; full CSR (Final PFS analysis and interim PFS2 and OS analysis)

Patient PK and Initial Tolerability Study Reports									
PK, safety	D0810C00022	5.3.3.2	To determine the safety and tolerability of twice daily oral doses of olaparib when administered in combination with bevacizumab to patients with advanced solid tumours. To compare exposure to olaparib when given alone and in combination with bevacizumab.	Phase I study to assess the safety and tolerability of olaparib when used in combination with bevacizumab (Avastin®) in patients with advanced solid tumours. Open label, dual-centre study.	Cohort 1: olaparib 100 mg capsule bd (2 x 50 mg) starting on Day 1 (oral); bevacizumab 10 mg/kg iv every 14 days (cycle) starting on Day 8 Cohort 2: olaparib 200 mg capsule bd (4 x 50 mg) starting on Day 1 (oral); bevacizumab 10 mg/kg iv every 14	12/12	Patients with advanced solid tumours	Olaparib capsule bd starting on Day 1; bevacizumab 10 mg/kg iv every 14 days (cycle) starting on Day 8 and continued for a minimum of 2 cycles	Complete; full CSR
					days (cycle) starting on Day 8 Cohort 3: olaparib 400 mg capsule bd (8 x 50 mg) starting on Day 1 (oral); bevacizumab 10 mg/kg iv every 14 days (cycle) starting on Day 8				

2.3.2. Pharmacokinetics

Introduction

The proposed application is mainly based on data from the pivotal study, PAOLA-1. In addition to the original package, one additional phase I clinical study (study D0810C00022) has been submitted to support the proposed indication with the aim to assess the safety and tolerability of olaparib in combination with bevacizumab and to compare exposure to olaparib when given alone and in combination with bevacizumab.

Main PK properties of olaparib (ADME)

Olaparib is a biopharmaceutics classification system class IV compound possessing low solubility and moderate permeability. The commercial tablet dose and strengths are 2 x 150 mg tablets for 300 mg bd with the 100 mg strength tablet available to support dose reductions. It is also recommended that olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided.

PK parameters associated with rich PK sampling data, fasting conditions, olaparib as monotherapy and in normal renal and hepatic function groups are summarized below.

- Olaparib was rapidly absorbed following oral dosing in fasting conditions, with peak plasma concentrations observed typically after 1.5 hours post-dose and declined in a biphasic manner. After 300 mg single dose, the arithmetic mean values of elimination half-life (t1/2) and apparent clearance (CL/F) were respectively 14.9 hours (SD of 8.2 hours) and 7.40 L/h (SD of 3.9 L/h). The pooled tablet population PK analyses characterised the absorption phase of olaparib as a sequential zero- and first-order absorption and showed a significant impact of olaparib tablet strength on the absorption rate constant.

- Co-administration of olaparib tablet formulation with a high fat meal showed minimal impact on AUC (8% increase), the observed effect was a result of decrease in absorption rate: olaparib median time to reach maximum concentration (tmax) was 4 hours and mean Cmax was reduced by 21% compared to fasted data. These changes are not considered to be clinically relevant, therefore the olaparib tablet formulation can be given with or without food.

- Olaparib exhibited a high apparent volume of distribution (Vz/F) of 158 L (SD of 136). The plasma protein binding in vitro was moderate (81.9% at clinically relevant concentrations of 10 µg/mL).

- Following single dosing, exposure, measured by the area under the plasma concentration-time curve (AUC), increased approximately proportionally with dose for the tablet single dose range 25 to 450 mg; maximum observed plasma concentration of olaparib (Cmax) increased slightly less than proportionally for the same dose range.

- Following a single 100 mg dose of radiolabelled olaparib capsule, unchanged olaparib and oxidised metabolites were detected in plasma, urine and faeces. Metabolite profiles of plasma indicated that olaparib was the major component (70% of the circulating radioactivity). There were three major drug derived components in plasma M12 (AZ14102299, ring-open piperazin-3-ol), M15 (AZ14102296, 4-fluorophenol (hydroxy)methyl) and M18 (AZ14102567, piperazin-3-ol); each of them accounted for 9-14% of the plasma radioactivity. Drug-related material was eliminated in the urine (44% mean recovery) and in the faeces (42% mean recovery), predominantly as metabolites.

Dose proportionality and time dependencies

Exposure, measured by area under plasma concentration-time curve from zero to infinity (AUC), increased approximately proportionally with dose for the single dose tablet range 25 to 450 mg; maximum plasma concentration (Cmax) increased slightly less than proportionally for the same dose range.

Following bd dosing, an AUC mean accumulation ratio of 1.8 was observed at steady state. At the 300 mg bd dose, olaparib PK appeared to be time dependent, with mean temporal change parameter (TCP calculated as AUC during the dosing interval at steady state [AUCss]/AUC single dose) of 1.53 (SD 0.59).

Special populations

The key observations related to the intrinsic factors impacting olaparib PK are summarised below.

- The latest population PK analysis pooling PK data from studies with the tablet formulation did not identify gender, race, tumour location, age or body weight as significant covariates (Olaparib-MS-08). BRCA1/2 status was not identified as a significant covariate either, but there were 36% of missing values for this covariate. In addition, no race difference in the PK of olaparib was shown from the phase I Japanese PK studies with the tablet or capsule formulations (respectively D081BC00001 and D0810C00001 [Study 01]) or from the phase I Chinese PK study using the tablet formulation (D081BC00002). Therefore, dose adjustment based on race, gender, age or body weight is not required. The PK of olaparib in prostate cancer patients was similar to other cancer patients supporting the dose regimen of 300 mg bd in these patients.

- In patients with mild hepatic impairment (Child-Pugh Classification A), AUC increased by 15% and Cmax increased by 13%. In patients with moderate hepatic impairment (Child-Pugh Classification B), AUC increased by 8% and Cmax decreased by 13%. The changes in AUC and Cmax of olaparib in patients with mild or moderate hepatic impairment were not considered to be clinically relevant. No olaparib dose adjustment is warranted in patients with mild or moderate hepatic impairment. In the absence of safety and PK data, olaparib is not recommended for use in patients with severe hepatic impairment (Child-Pugh classification C).

- The effect of renal impairment on exposure to olaparib has been studied. In patients with mild renal impairment (creatinine clearance [CrCL] 51 mL/min to 80 mL/min), there was a small increase in mean olaparib exposure compared to patients with normal renal function; 15% for Cmax and 24% for AUC. This was not considered to be clinically relevant. No olaparib dose adjustment is warranted in patients with mild renal impairment. In patients with moderate renal impairment (CrCL 31 mL/min to 50 mL/min), Cmax and AUC values increased by 26% and by 44% compared to patients with normal renal function. Patients with moderate renal impairment are recommended to take an olaparib tablet dose of 200 mg bd (equivalent to

a total daily dose of 400 mg). Olaparib is not recommended for patients with severe renal impairment or end-stage renal disease (CrCL ≤30 mL/min) since there are no data in such patients.

- No studies have been conducted to investigate the pharmacokinetics of olaparib in paediatric patients.

Pharmacokinetic interaction studies

Study D0810C00022

The potential for drug-drug interaction of the co-administered drugs, olaparib and bevacizumab, has been investigated in the formal PK study D0810C00022 performed in the early development of olaparib. This investigation was conducted with the hard gelatin capsule formulation. This study is described below.

Study dates:

First patient enrolled: 13 June 2008

Last patient last visit: 25 March 2009

Objectives

The primary objective of this study was to determine the safety and tolerability of twice daily (bd) oral doses of olaparib (also known as AZD2281, KU-0059436) when administered in combination with bevacizumab to patients with advanced solid tumours by assessment of adverse events (AEs), vital signs, electrocardiograms (ECG), clinical chemistry, haematology, urinalysis and physical examination.

The secondary objective was to compare exposure to olaparib when given alone and in combination with bevacizumab, by assessment of appropriate derived pharmacokinetic (PK) parameters.

Study design

Successive cohorts of 4 to 6 patients received increasing doses of olaparib (100, 200 and 400 mg bd) continuously in combination with intravenous (iv) bevacizumab at a fixed dose of 10 mg/kg given every 14 days (1 cycle). A safety review of the data was performed at the end of each cycle of bevacizumab to determine if any dose-limiting toxicity (DLT) would prevent escalation to the next dose of olaparib. Dosing with bevacizumab started on Day 8 and continued for a minimum of 2 cycles. To be evaluable for PK assessment and potential dose escalation, patients had to complete at least 1 cycle of bevacizumab, and have a full PK profile for olaparib taken both in the monotherapy setting (on Day 4) and on the day of first administration of bevacizumab.

Target patient population and sample size

Up to 18 patients with histologically confirmed metastatic cancer, not amenable to surgery or radiation therapy with curative intent, with a life expectancy of at least 12 weeks and Eastern Co-operative Oncology Group (ECOG) Performance status 0 to 2.

Investigational product and comparator: dosage, mode of administration and batch numbers

Olaparib 50 mg capsules given orally bd at doses of 100, 200 and 400 mg.

Duration of treatment

A minimum of two 14-day cycles of bevacizumab. Patients could continue combinational study treatment indefinitely until they met a withdrawal criterion if, in the investigator's opinion, they were receiving some benefit.

Criteria for evaluation - pharmacokinetics (main variables)

Maximum and minimum plasma concentrations at steady state ($C_{max,ss}$, and $C_{min,ss}$), time to C_{max} (t_{max}) and area under the plasma concentration-time curve during the dosing interval at steady state (AUC_{ss}).

Criteria for evaluation - safety (main variables)

AEs, vital signs, ECG, haematology, clinical chemistry, urinalysis, physical examination.

Statistical methods

There was no formal statistical analysis of PK variables or of safety and tolerability data. Data have been listed and summarised.

Patient population

Twelve patients (4 in each treatment group) with a mean age 49.7 years (range 22 to 71 years) were enrolled and received study treatment (olaparib and bevacizumab). Most patients (11/12) were White and 10/12 were female. Three patients were still receiving their initial treatment (olaparib and bevacizumab) at data cut-off (Last patient last visit: 25 March 2009). No patients experienced dose-limiting toxicity and so each dose of olaparib was received by 4 patients. Three patients were excluded from the PK analyses due to protocol deviations.

Summary of pharmacokinetic results

A summary of the PK parameters of olaparib for 200 and 400 mg bd, alone and in combination with bevacizumab, is presented in Table 1.

For both the 200 mg and 400 mg bd groups, the geometric mean (Gmean) AUC_{ss}, in combination with bevacizumab, were similar to that when given alone (26.57 ng.h/mL compared to 25.79 ng.h/mL for the 200 mg bd group, and 50.33 ng.h/mL compared to 58.08 ng.h/mL for the 400 mg bd group), with similar inter-patient variability (%CVs).

Similar results were observed for the Gmean $C_{max,ss}$. The mean ratios of olaparib AUC_{ss} and $C_{ss,max}$ (olaparib in combination with bevacizumab to olaparib alone) for both the 200 mg bd and 400 mg bd groups were both near to 1.0, at 1.030 and 0.867 for AUC_{ss} and 1.105 and 0.889 for $C_{max,ss}$, respectively. Of the 7 assessable patients, 4 patients had AUC_{ss} values in combination with bevacizumab that were within 10% of those values for olaparib alone, and 3 patients had values that were within 20%. These results were reflected in the data for the individual ratios of $C_{max,ss}$. For the 2 patients administered 100 mg olaparib bd that had $C_{max,ss}$ data, 1 patient had a $C_{max,ss}$ value in combination with bevacizumab that was within 15% of that for olaparib alone. The other patient showed approximately an apparent 40% decrease.

Table 1: Pharmacokinetic parameters of olaparib: PK analysis set, Study D0810C00022

PK parameter, units	Summary statistics	Olaparib dose (mg bd)			
		200 alone	200 + bevacizumab	400 alone	400 + bevacizumab
n		3	3	4	4
$C_{ss,min}$, μg/mL	Gmean (CV%)	0.544 (191.2)	0.612 (158.6)	1.602 (46.05)	1.254 (43.94)
$C_{ss,max}$, μg/mL	Gmean (CV%)	4.739 (35.56)	5.237 (49.04)	9.078 (27.18)	8.067 (17.15)

t_{max}, h	median (range)	NC	NC	NC	NC
AUC_{ss}, µ.h/mL	Gmean (CV%)	25.79 (70.02)	26.57 (78.12)	58.08 (29.37)	50.33 (23.05)
AUC_{ss} ratio[a]	Mean (range)	N/A	1.030 (11.96)	N/A	0.867 (6.082)
$C_{ss,max}$ ratio[b]	Mean (range)	N/A	1.105 (22.06)	N/A	0.889 (12.21)

a
Ratio of AUC_{ss} = AUC_{ss} for olaparib in combination with bevacizumab to AUC_{ss} for olaparib alone.

b
Ratio of $C_{ss,\,max}$ = $C_{ss,\,max}$ for olaparib in combination with bevacizumab to $C_{ss,\,max}$ for olaparib alone. AUC_{ss} Area under the plasma concentration-time curve during any dosing interval at steady state; bd Twice daily; $C_{max,ss}$ Maximum plasma (peak) concentration in plasma during dosing interval; $C_{min,ss}$ Minimum plasma (trough) concentration in plasma during dosing interval; CV Coefficient of variation; Gmean Geometric mean; N/A Not assessable; PK Pharmacokinetics; t_{max} Time to reach peak or maximum concentration or maximum response following drug administration.

2.3.3. Pharmacodynamics

Mechanism of action

No new study was submitted.

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

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

In BRCA1/2 deficient in vivo models, olaparib given after platinum treatment resulted in a delay in tumour progression and an increase in overall survival compared to platinum treatment alone that correlated with the period of olaparib maintenance treatment.

Primary and secondary pharmacology

No new study was submitted.

Evaluation of biomarkers associated with homologous recombination deficiency in PAOLA-1

Prospective tBRCA testing was conducted in all screened patients at recommended institutions in France. Patients were stratified based on their screening laboratory tBRCAm result. Note patients classified as "absence of deleterious mutation (tBRCAwt/VUS/unk)" also included patients who failed testing. gBRCA testing was not mandatory in the study; however, information regarding gBRCA status was requested for all randomised patients.

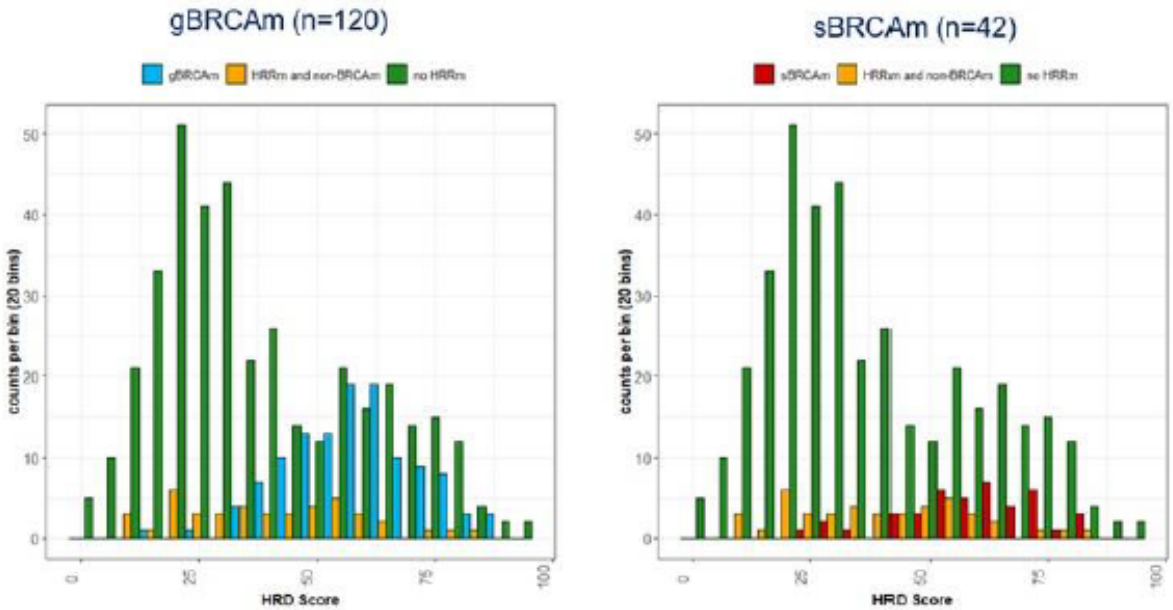
A blood sample collection for central germline BRCA testing of all patients was not included in the PAOLA-1 study. All sites were requested, but not required, to enter local gBRCA test results in the CRF (negative, positive or inconclusive, and where available, the mutation name). The laboratories that carried out screening tBRCA testing, also carried out gBRCA testing for patients enrolled at study sites in France. Of the 806 patients randomised into PAOLA-1, 404 (50.1%) patients reported a gBRCA result and 402 (49.9%) did not have a gBRCA result reported in the CRF. Out of the 404 patients with gBRCAm results in the CRF, 120 patients were reported to carry gBRCA mutation (29.7%).

Available tumour samples from PAOLA-1 patients were retrospectively tested post-randomisation (but prior to database lock) using the Myriad myChoice HRD Plus test in order to investigate efficacy in pre-defined biomarker subgroups. HRD positive status was determined as either tBRCAm and/or a genomic instability score (GIS) ≥ 42.

The Myriad myChoice CDx test has been developed using BRCA mutant breast and ovarian tumours. The GIS score is a continuous variable composed of an assessment of three different tumour measures of genomic instability (loss of heterozygosity, telomeric allelic imbalance and large-scale transition) and the 42-threshold is based on the 5th percentile of genome instability scores (GIS) observed in BRCA mutant tumours (i.e. 95% of ovarian BRCAm tumours have a GIS ≥42; Telli et al 2016). The ability of the myChoice test to discriminate patients that benefit from maintenance PARP inhibitors has been explored across a number of ovarian cancer studies, as well as the data from PAOLA-1. The 42-theshold has been evaluated prospectively in the NOVA (Mirza et al 2016) and PRIMA (Gonzalez-Martin et al 2019) studies and retrospectively in Study 19 (Hodgson et al 2018).

Considering the patients that had a local gBRCA result available in the CRF and had a germline/somatic status available from Myriad (n=91); this excludes patients with co-occurring BRCA mutations (one patient had 2 gBRCA1 mutations), the concordance between the CRF result and the Myriad prediction was considered high (91.0% PPA; 95.8% NPA).

Based on the local gBRCA status available in the CRF and the Myriad germline/somatic prediction, patients were allocated an overall tBRCAm classification of germline, somatic or not determined: 160 patients in PAOLA-1 were determined to be gBRCAm and 51 sBRCAm. For 38 Myriad tBRCAm patients, somatic/germline status could not be determined, which included 7 cases where somatic/germline status was discordant based on local germline results and Myriad predictions. For the subset of patients that have a GIS/HRD score available, somatic and germline BRCAm patients have a similar distribution of GIS/HRD scores.



Note: only patients with an HRD score available can be displayed on the plots.
HRD = homologous recombination deficient; *gBRCAm* = germline *BRCA* mutated; *sBRCAm* = somatic *BRCA* mutated.

Figure 1: Histograms showing HRD score distribution for patients classified as sBRCAm or gBRCAm in PAOLA-1

Table 2: PAOLA-1 PFS subgroup analyses by germline and somatic BRCAm status as determined by CRF and Myriad predictions

	Olaparib/bevacizumab (n=537)	Placebo/bevacizumab (n=269)
Myriad *tBRCAm*		
No. events/total no. pts (%)	44/158 (27.8)	52/77 (67.5)
Median PFS (95% CI) months	37.2	18.8
HR (95% CI)	0.28 (0.19-0.42)	
gBRCAm		
No. events/total no. pts (%)	29/103 (28.2)	34/57 (59.6)
Median PFS (months)	37.2	22.2
HR (95% CI)	0.38 (0.23-0.63)	
sBRCAm		
No. events/total no. pts (%)	6/33 (18.2)	15/18 (83.3)
Median PFS (95% CI) months	Not reached	14.4
HR (95% CI)	0.10 (0.04-0.25)	

BRCA = Breast cancer susceptibility gene; *BRCAm* = *BRCA* mutated; CI = confidence interval; *gBRCAm* = germline *BRCA* mutated; HR = hazard ratio; PFS = progression free survival; *sBRCAm* = somatic *BRCA* mutated; *tBRCAm* = tumour *BRCA* mutated.
Source: Table 2253.

BRCA1 vs BRCA2 mutations and large genomic rearrangements

The proportion of BRCA1 and BRCA2 mutated patients, expressed as a fraction of total BRCAm patients, in PAOLA-1 (67.7% BRCA1m, 31.9% BRCA2m and 0.4% BRCA1m and BRCA2m) was consistent with the SOLO1 study (72.8% BRCA1m, 26.4% BRCA2m and 0.8% BRCA1m and BRCA2m) and across recent first line ovarian cancer maintenance studies (GOG-218, Norquist et al 2018, and VELIA, Coleman et al 2019) with 65.5-69.2% of BRCAm patients carrying a BRCA1 mutation and 30.8%-34.5% carrying a BRCA2 mutation.

In PAOLA-1 (tBRCA) and SOLO1 (gBRCA), the proportion of large rearrangement in BRCA1 and BRCA2 were 4.2% and 5.7% respectively.

BRCA-locus specific loss of heterozygosity (LOH) data

BRCA-gene specific LOH was reported by Myriad using RUO methodology as part of the myChoice HRD plus assay. Of 235 Myriad tBRCAm patients, 193/235 (82.1%) were evaluable for determination of BRCA-locus specific LOH status. Bi-allelic loss of BRCA was determined in 183/193 (94.8%) of evaluable tumours. In 10/193 (5.2%) samples, BRCA loss was heterozygous, of which 9 were BRCA2m (5 gBRCA2m, 2 sBRCA2m and 2 somatic/germline status unknown) and 1 was BRCA1m (gBRCA1m).

TP53 mutations

Sequencing data for TP53 was available for the PAOLA-1 tumour samples analysed using the Myriad myChoice HRD Plus assay. It has been previously shown that TP53 mutations are present in almost all cases of high-grade serous ovarian cancer (Ahmed et al 2010) and 697/755 (92.3%) of PAOLA-1 tumour samples sequenced at Myriad harboured a mutation in TP53 predicted to affect protein function. Using the same classification schemes as described for Study 19 (Molina-Vila et al 2014; Poeta et al 2007), 350/697 (50.2%) of TP53 mutations in PAOLA-1 were predicted to be disruptive and 340/697 (48.9%) non-disruptive in nature. For 7/697 (1.0%) patients the disruptive vs non-disruptive status of the mutation could not be determined.

2.3.4. Discussion on clinical pharmacology

Olaparib tablets as monotherapy, is already approved in adult patients with 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 PKs (ADME) as well as the influencing intrinsic factors have been fully characterized and already evaluated with the hard gelatine capsules and the tablets.

The variation under review consists of the use of olaparib tablets in combination with bevacizumab in the same indication. The claimed dose of olaparib for the combination is identical to that approved in the monotherapy indication. The combination indication is not claimed for the hard gelatine capsule.

No new clinical PK investigations pertaining the claimed variation was submitted. No PK investigation (sparse sampling or formal PK) have been included in the pivotal PAOLA-1 study.

The results of Study D0810C00022, an open label, dual-centre, Phase I study to assess the safety and tolerability of olaparib when used in combination with bevacizumab in patients with advanced solid tumours were presented. The design of the study is far less than optimal to pertain to the claimed variation. The tested formulation is hard gelatin capsule and the tested doses were 200 and 400 mg. While the variation under review concerns the tablets and the daily dose is 600 mg. Bearing in mind that the absolute bioavailability of the capsule is much lower than that of tablets, the olaparib dose tested in this DDI interaction study is too low. Also, the very limited number of patients enrolled in each arm of the study (n=3-4) is an additional pitfall in the study., Although. no firm conclusion can be drawn due to

study limitations, the study did not indicate significant difference in the systemic exposure to olaparib when co-administered with bevacizumab.

Furthermore, as bevacizumab is not a cytokine modulator, it is not expected to have any effect on CYP450 enzymes (Kenny et al 2013) and on the PK/exposure of olaparib.

The impact of co-administration of olaparib on the PKs of bevacizumab was neither investigated nor discussed. The MAH argued that at the therapeutic dose of 15 mg/kg Q3W in PAOLA-1, the clearance of bevacizumab is predominantly mediated by catabolism and not by TMDD. Therapeutic mAbs which are cleared primarily by TMDD, typically exhibit dose-dependent PK (Betts et al 2018). Therefore, olaparib is unlikely to affect the clearance of bevacizumab via the TMDD pathway or via any other putative or plausible mechanisms. It is agreed that TMDD elimination pathway is plausibly saturated. Thus, the absence of interaction investigation is acceptable.

No investigation of Exposure-Safety Relationships for olaparib and bevacizumab has been carried out. This is mainly justified by the difficulty in deriving an unbiased and predictive multivariate ER model based on available data from PAOLA study. Therefore, no supportive data are available and the safety should be appreciated solely on the observational safety data collected in the PAOLA study. No investigation of Exposure-efficacy Relationship has been carried out as well.

Several biomarkers have been used to date to assess the extent of homologous recombination deficiency (HRD) in tumours. Based on mechanistical rationale, mutations in *BRCA1* and *BRCA2* genes (of germline and somatic origin) have been associated with HRD and have been largely used in clinical studies to inform on HRD status, although mutations in these genes might neither be necessary nor sufficient for response to PARPi. Homologous recombination deficiency (HRD) positive status can be defined by detection of a BRCA1/2 mutation classified as deleterious/suspected deleterious or pathogenic/likely pathogenic. Other biomarkers can be used to inform on the extent of HRD in tumour cells. Detection of BRCA1/2 mutations could be combined with positive HRD score to determine HRD positive status.

HR deficiency-associated genomic alterations that have been investigated in Paola-1 include genome-wide loss of heterozygosity, telomeric allelic imbalance and large scale transition, which are continuous measures with pre-defined criteria and score. Composite genomic instability score (GIS, also called HRD score) is determined when the combined measures and respective scores are used to assess the extent of specific genomic aberrations accumulated in tumour cells. Lower score defines lower likelihood of HR deficiency of tumour cells and higher score determines higher likelihood of HR deficiency of tumour cells at the time of the sample collection relative to exposure to DNA damaging agents. HRD positive status can be defined by a composite GIS score for HR deficiency-associated genomic alterations tested by an experienced laboratory using a validated test.

With regards to the evaluation of gBRCAm status, the concordance between the CRF result and the Myriad prediction was considered high (91.0% PPA; 95.8% NPA). The bi-allelic LOH was reported in the majority of tumours (95%). The OS data are currently too immature in PAOLA-1 to conduct a subgroup analysis for OS based on TP53 status. Submission of subgroup analyses is expected when final OS data become available (REC). The MAH is also recommended to submit additional exploratory analyses of tumour samples at progression upon finalisation in 2023. (REC)

Overall, there are no PK/PD data provided in support for the claimed dose of the combination in the applied indication. The currently approved doses of each drug in ovarian tumours was selected for the development of the combination (Study PAOLA-1). As discussed above, it is not expected that bevacizumab could have any effect on the PK/exposure of olaparib and vice-versa.

2.3.5. Conclusions on clinical pharmacology

The currently available PK data have been correctly summarised. The currently approved doses of each drug in solid tumours was selected for the development of the combination (Study PAOLA-1).

2.4. Clinical efficacy

2.4.1. Dose response study

No new dose response study was provided as part of this application (see discussion on clinical efficacy).

2.4.2. Main study

Study D0817C00003 (PAOLA-1)

A Randomized, Double-Blind, Phase III Trial of Olaparib vs. Placebo in Patients with Advanced FIGO Stage IIIB – IV High Grade Serous or Endometrioid Ovarian, Fallopian Tube, or Peritoneal Cancer treated with standard First Line Treatment, Combining Platinum-Taxane Chemotherapy and Bevacizumab Concurrent with Chemotherapy and in Maintenance (PAOLA-1).

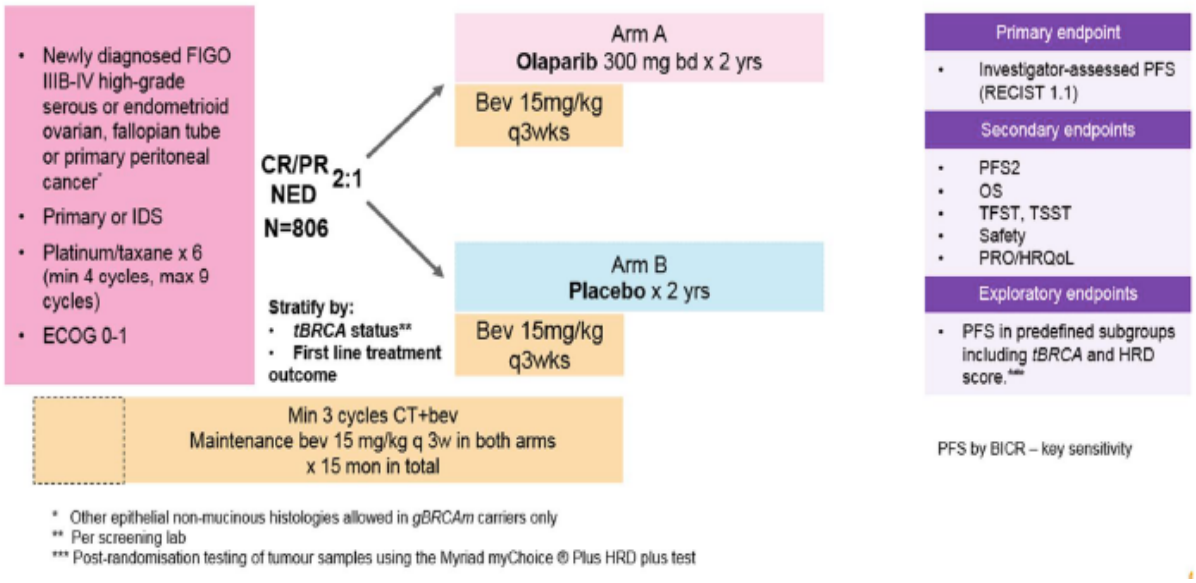


Figure 2: Overall study design – Study PAOLA-1

Methods

Study participants

Key inclusion criteria:

1) Patients must have been ≥18 years of age.
2) Patient with newly diagnosed:

- Ovarian cancer, primary peritoneal cancer and/or fallopian-tube cancer,

- Histologically confirmed (based on local histopathological findings): high grade serous or high grade endometrioid or other epithelial non mucinous ovarian cancer in a patient with germline BRCA 1 or 2 deleterious mutation.

- At an advanced stage: FIGO stage IIIB, IIIC, or IV of the 1988 FIGO classification.

3) Patients who had completed first line platinum-taxane chemotherapy prior to randomisation:

-The platinum-taxane based regimen must have consisted of a minimum of 6 and a maximum of 9 treatment cycles; however, if platinum-based therapy was discontinued early as a result of non-haematological toxicity specifically related to the platinum regimen, (i.e., neurotoxicity, hypersensitivity etc), patients must have received a minimum of 4 cycles of the platinum regimen.

-Intravenous, intraperitoneal, or neoadjuvant platinum-based chemotherapy was allowed; for weekly therapy, 3 weeks was considered to be 1 cycle. Interval debulking surgery was allowed.

4) Patients must have received prior to randomisation a minimum of 3 cycles of bevacizumab in combination with the last 3 cycles of platinum-based chemotherapy. Only in case of interval debulking surgery, it was allowed to realize only 2 cycles of bevacizumab in combination with the last 3 cycles of platinium-based chemotherapy. Bevacizumab treatment was to be administered at a dose of 15 mg/kg Q3W for up to a total of 15 months.

5) Patient must be prior to randomization without evidence of disease (NED) due to complete surgical resection or in complete response (CR) or partial response (PR) from first line platinum-containing chemotherapy and bevacizumab. There should be no clinical evidence of disease progression (physical exam, imagery, CA 125) throughout the first line treatment and prior to study randomization.

6) Patients must have been randomised at least 3 weeks and no more than 9 weeks after their last dose of chemotherapy (last dose is the day of the last infusion) and all major toxicities from the previous chemotherapy must have resolved to CTCAE Grade 1 or better (except for alopecia and peripheral neuropathy).

7) Patients must have normal organ and bone marrow function, serum creatinine ≤ 1.25 x institutional ULN and creatinine clearance > 50 mL/min, normal blood pressure or adequately treated and controlled hypertension.

8) ECOG performance status 0 to 1.

9) A formalin fixed, paraffin embedded tumour sample from the primary cancer must have been available for central BRCA testing and the test result must have been available for stratification.

Key exclusion criteria:

1) Patients whose tumours were of non-epithelial origin of the ovary, the fallopian tube or the peritoneum (i.e., germ cell tumours).

2) Patients with ovarian tumours of low malignant potential (e.g., borderline tumours) or mucinous carcinoma.

3) Patients with synchronous primary endometrial cancer, unless both of the following criteria were met:
-Stage <II
-Less than 60 years old at the time of diagnosis of endometrial cancer with Stage IA or IB Grade I or II, or Stage IA Grade III endometrial carcinoma OR ≥60 years old at the time of diagnosis of

endometrial cancer with Stage IA Grade I or II endometrioid adenocarcinoma. Patients with serous or clear cell adenocarcinoma or carcinosarcoma of the endometrium were not eligible.

4) Patients with another malignancy within the last 5 years except: adequately treated non melanoma skin cancer, curatively treated in situ cancer of the cervix, and ductal carcinoma in situ. Patients with a history of localised malignancy diagnosed over 5 years ago may be eligible provided they completed their adjuvant systemic therapy prior to randomisation and they remain free of recurrent or metastatic disease. Patients with a history of primary triple negative breast cancer may be eligible providing they completed their definitive anticancer treatment more than 3 years ago and they remain breast cancer disease free prior to the start of study treatment.
5) Patients with a history of myelodysplastic syndrome/acute myeloid leukaemia.
6) Patients who experienced for at least 1 cycle a delay >2 weeks during first line chemotherapy due to prolonged haematological recovery.
7) Patients who received radiotherapy within 6 weeks prior to study treatment.
8) Major surgery within 4 weeks of starting study treatment and patients must have recovered from any effects of any major surgery.
9) Any previous treatment with a PARP inhibitor, including olaparib.
10) Administration of other simultaneous chemotherapy drugs, any other anticancer therapy or anti-neoplastic hormonal therapy, or simultaneous radiotherapy during the study treatment period (hormonal replacement therapy is permitted as are steroidal anti emetics).
11) Prior history of hypertensive crisis (CTCAE Grade 4) or hypertensive encephalopathy.
12) Clinically significant (e.g., active) cardiovascular disease, including:

    -Myocardial infarction or unstable angina within ≤6 months of randomisation.

    -New York Heart Association ≥Grade 2 congestive heart failure.

    -Poorly controlled cardiac arrhythmia despite medication (patients with rate controlled atrial fibrillation are eligible), or any clinically significant abnormal finding on resting electrocardiogram.

    -Peripheral vascular disease Grade ≥3 (eg, symptomatic and interfering with activities of daily living requiring repair or revision).
13) Previous cerebro-vascular accident, transient ischemic attack or sub-arachnoid haemorrhage within 6 months prior to randomisation.
14) History or evidence of haemorrhagic disorders within 6 months prior to randomisation.
15) Evidence of bleeding diathesis or significant coagulopathy (in the absence of coagulation).
16) History or clinical suspicion of brain metastases or spinal cord compression. Computed tomography/magnetic resonance imaging (MRI) of the brain is mandatory (within 4 weeks prior to randomisation) in case of suspected brain metastases. Spinal MRI is mandatory (within 4 weeks prior to randomisation) in case of suspected spinal cord compression. History or evidence upon neurological examination of central nervous system (CNS) disease, unless adequately treated with standard medical therapy (e.g. uncontrolled seizures).
17) Non-healing wound, active ulcer or bone fracture. Patients with granulating incisions healing by secondary intention with no evidence of facial dehiscence or infection are eligible but require 3-weekly wound examinations.

18) History of VEGF-therapy related abdominal fistula or gastrointestinal perforation or active gastrointestinal bleeding within 6 months prior to the first study treatment.

19) Current, clinically relevant bowel obstruction, including sub-occlusive disease, related to the underlying disease.

20) Patients with evidence of abdominal free air not explained by paracentesis or a recent surgical procedure.

21) Pregnant or lactating women.

22) Patients who are unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication.

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

24) Immunocompromised patients, e.g., with known active hepatitis (i.e., Hepatitis B or C) due to risk of transmitting the infection through blood or other body fluids or patients who are known to be serologically positive for human immunodeficiency virus.

tBRCA testing and HRD testing is described under clinical pharmacology.

Treatments

• Olaparib tablets per os 300 mg twice daily,

• Placebo tablets per os twice daily.

It was recommended that patient begins study treatment as soon as possible after randomization, within 7 days and ideally concomitant with bevacizumab administration.

Bevacizumab, as standard of care therapy, was administered in both arms as followed:

• 15 mg/kg, d1, q3w, for a total duration of 15 months / 22 cycles (including combination with platinum-based chemotherapy).

Patients continued bevacizumab in the maintenance setting and started treatment with Lynparza after a minimum of 3 weeks and up to a maximum of 9 weeks following completion of their last dose of chemotherapy. Treatment with Lynparza was continued until progression of the underlying disease, unacceptable toxicity or for up to 2 years. Patients who in the opinion of the treating physician could derive further benefit from continuous treatment could be treated beyond 2 years.

Objectives

Primary objective:

To determine the efficacy by progression free survival (PFS1) investigator based according to modified Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) of olaparib maintenance compared to placebo in high grade epithelial ovarian, fallopian tube, or peritoneal cancer that are in clinical complete response or partial response following first line platinum-taxane based chemotherapy plus bevacizumab, and planned to pursue bevacizumab in the maintenance phase up to a total of 15 months.

Secondary objectives:

1. To determine:

-time to earliest progression by RECIST or Cancer Antigen-125 (CA-125) or death,

-time from randomization to first subsequent therapy or death (TFST),

- time from randomization to second progression (PFS2),

- time from randomization to second subsequent therapy or death (TSST),

- overall survival (OS).

2. To assess the safety and tolerability of olaparib and bevacizumab maintenance compared to bevacizumab alone.

3. To compare the effects of olaparib maintenance compared to placebo on Health-Related Quality of Life (HRQoL) and patient reported outcomes (PROs), with consideration of patient preference.

4. To evaluate the impact of treatment and disease on resource use.

Exploratory objectives:

1. To explore pre planned subgroup analyses of efficacy (including PFS1 and OS) based on relevant potential prognostic factors, including, but not limited to stratification factors, clinical characteristics and tumour HR deficiency status (BRCAm, mutations in other HR genes and Myriad HRD scar status)

2. Explore the time to next severe toxicity (grade 4 neutropenia lasting > 7 days, grade ≥3 febrile neutropenia, grade 4 thrombocytopenia with bleeding or platelet transfusion, grade ≥ 3 non-hematological toxicity) in both arms.

3. To explore the correlation between geriatric assessment and efficacy and tolerance of olaparib versus placebo for patients > 70 years old.

4. To explore the efficacy of olaparib by assessment of overall survival (OS) adjusting for the impact of spontaneous switching (outside of study design) to Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerization (PARP) inhibitors or other potentially active investigational agents.

5. Biological biomarkers analysis: to determine the frequency of somatic BRCA mutation (sBRCAm) in tumour samples and to compare this with germline BRCA mutation (gBRCAm) status. To determine a HR deficiency signature correlated with olaparib efficacy combined with bevacizumab.

6. To explore whether resistance mechanisms to olaparib can be identified through analysis of tumour and blood samples – archival tumour and blood sample at baseline (mandatory), tumour biopsy and blood sample on progression (optional).

7. Future exploratory research into factors that may influence response to study treatment (where response is defined broadly to include efficacy, tolerability or safety) and may be performed on the collected and stored archival tumour samples that were mandatory for entry onto the study or on optional tumour biopsy samples collected during the course of the study.

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

Outcomes/endpoints

Primary endpoint:

PFS was defined as the time from randomization until the date of the first objective radiological disease progression according to investigator assessment of RECIST version 1.1 or death (by any cause in the

absence of progression) regardless of whether the patient withdraws from randomized study treatment or receives another anti-cancer therapy prior to progression.

Secondary endpoints:

1. OS was defined as the time from the date of randomization until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

2. Time to earliest progression by RECIST v. 1.1 or CA-125 or death was defined as the time from randomization to the earliest date of RECIST or CA-125 progression or death by any cause. Progression according to CA-125 was assessed according to GCIG

3. PFS2. Time from randomization to second progression is defined as the time from the date of randomization to the earliest of the progression event subsequent to that used for the primary variable PFS1, or date of death. The date of second progression will be recorded by the investigator and defined according to local standard clinical practice and may involve any of; objective radiological, CA-125 or symptomatic progression or death. Second progression status will be reviewed regularly following the progression event used for the primary variable PFS (PFS1) and recorded. Patient alive and for whom a second disease progression has not been observed should be censored at the last time known to be alive and without a second disease progression, i.e. censored at the latest of the tumor assessment date if the patient has not had a second progression or death).

4. TFST is defined as the time from the date of randomization to the earliest of the date of anti-cancer therapy start date following study treatment discontinuation, or death.

5. TSST is defined as the time from the date of randomization to the earliest of the date of second subsequent anti-cancer therapy start date following study treatment discontinuation, or death.

6. Patient reported outcomes (PROs) variables (EORTC QLQ-C30 and OV-28), with consideration of patient preference.

7. Geriatric assessment will be performed using the Geriatric Vulnerability Score (GVS).

Sample size

The study was calibrated to detect a treatment effect hazard ratio (HR) of 0.75, translating in an improvement in median PFS1 from 15.8 months (control arm) to 21.1 months (olaparib arm), (Herzog et al., 2014) with a 2:1 randomization, allowing patients to have only 1 chance out 3 to get placebo. A total of 458 events in the study would have approximately > 80% power to show statistically significant PFS1 at a 2-sided alpha. Considering a recruitment duration of 24 months and a 21-month follow-up for the last included patient (estimated total duration from first randomized patient to PFS1 assessment: 45months), assuming a common exponential dropout rate of 1%, 762 patients will be randomized in the study (508 patients in the olaparib arm and 254 patients in the placebo arm) so that maturity of the PFS1 data is approximately 60%.

Approximately 24 patients were planned to be randomized in Japan by the Gynecologic Oncology Trial and Investigation Consortium of North Kanto (GOTIC) in addition to the 762 randomized patients. The patients randomized in Japan were to be included in the Full Analysis Set provided there are no clinical data from the ongoing olaparib program suggesting different efficacy or safety with olaparib tablet in Japanese patients with high grade epithelial ovarian cancer.

Randomisation

Approximately 762 patients were planned to be randomized in a 2:1 ratio to the treatments with olaparib or placebo.

Stratification was to be done by:

• *First line treatment outcome at screening* as defined below:

1. No Evidence of Disease (*) with complete macroscopic resection at initial debulking surgery,

2. No Evidence of Disease/ Complete response (*) with complete macroscopic resection at interval debulking surgery,

3. No Evidence of Disease (*) / Complete Response at screening, in patients who had either incomplete resection (at initial or interval debulking surgery) or no debulking surgery (Debulking surgery considered as not feasible),

4. Partial Response.

(*) Patients without assessable disease after initial debulking surgery will be considered to have NED at the end of first-line chemotherapy and surgery strategy if the disease has not progressed. Those with measurable or assessable disease after initial surgery or at the start of neo-adjuvant chemotherapy and whose disease is no more detectable at the end of the chemotherapy and surgery strategy will be considered to have achieved a complete response (CR).

Table 3: Stratification categories by first line treatment outcome at screening

Surgery with maximal debulking effort (initial, interval, none): Presence or not of residual disease	Disease status before randomization (CTScan /MRI)	Strata
Initial surgery without interval surgery		
Complete macroscopic resection	NED* Presence of disease	1 Not eligible
Incomplete resection	NED or Complete Response** Partial Response Stable or Progressive disease	3 4 Not eligible
Interval surgery		
Complete macroscopic resection	Complete Response or NED Presence of disease***	2 Not eligible
Incomplete resection	Complete Response or NED Partial Response Stable or Progressive disease	3 4 Not eligible
No debulking surgery	Complete Response or NED Partial Response Stable or Progressive Disease	3 4 Not eligible

**NED: No evidence of disease on CTscan or MRI (No measurable/assessable disease according to RECIST1.1*
***Complete response: Disappearance of all measurable/assessable disease which was present at the start of chemotherapy and normalization of CA125 blood level*
****Presence of disease on CTScan/MRI or abnormal CA125 level*

• *tBRCA status* determined by prospective local testing (result of BRCA testing on tumor tissue):

- Deleterious mutation,

- Absence of deleterious mutation.

Blinding (masking)

This study is double-blind.

Statistical methods

The primary endpoint is progression-free survival (PFS1) defined as the time from the date of randomization to the first documented disease progression (according to RECIST v1.1) or death from any cause, whichever occurs first.

Patients had RECIST 1.1 tumour assessments at baseline and every 24 weeks (CT/MRI at 12 weeks if clinical or CA 125 progression) for up to 42 months or until objective radiological disease progression.

PFS was to be estimated using the Kaplan-Meier method and to be described in terms of median PFS1 per arm, and hazard ratio for progression between the 2 arms. Associated 2-sided 95% CI for the estimates were to be provided. The HR comparing randomised treatments (and associated CI) were estimated from a stratified Cox Proportional Hazards model (with ties=Efron and the stratification variables as strata) and the CI was calculated using a profile likelihood approach. The HR (olaparib/bevacizumab vs placebo/bevacizumab) together with its corresponding 95% CI and p-value were presented.

PFS distributions were to be compared between the 2 study arms using a 2-sided Log-Rank test (significance level of 5%) stratified by response to first line treatment and tBRCA status, supported by a stratified Cox regression.

This analysis was to be performed when approximately 458 PFS1 events have occurred.

Multiple testing procedure and hierarchical testing strategy

In order to strongly control the type I error at 5% 2-sided for key label claims, a multiple testing procedure (MTP) was to be employed across the primary endpoint (PFS1) and key secondary endpoints (PFS2 and OS).

A hierarchical testing strategy was to be employed where PFS1 is tested first using the full test mass (full test mass = alpha) and key secondary endpoints of PFS2 and OS will then be tested using a MTP with a recycling strategy (i.e., the MTP will recycle the test mass to the endpoint not yet rejected in the hierarchy). The hierarchical testing strategy is detailed below.

PFS2 was to be only be tested if statistical significance was shown for PFS1. OS was only to be tested if the null hypothesis (of no difference) was rejected for PFS2.

PFS2 analysis

An interim PFS2 analysis (IA) was to be performed at the time of the PFS1 analysis. Final PFS2 analysis was planned to be performed when the PFS2 data were approximately 53% mature (approximately 411 events) OR after a maximum duration of 1 year following the PFS1 analysis, whichever occurred first.

OS analysis

An interim OS analysis (IA) was to be performed when statistical significance was shown for PFS2 (interim or final PFS2 analysis). Final OS analysis was planned to be performed when the OS data were approximately 60% mature OR after a 3-year duration from the main PFS1 analysis, whichever occurred first.

The complete multiple testing procedure accounting for the inclusion of interim PFS2 and OS analyses is detailed below.

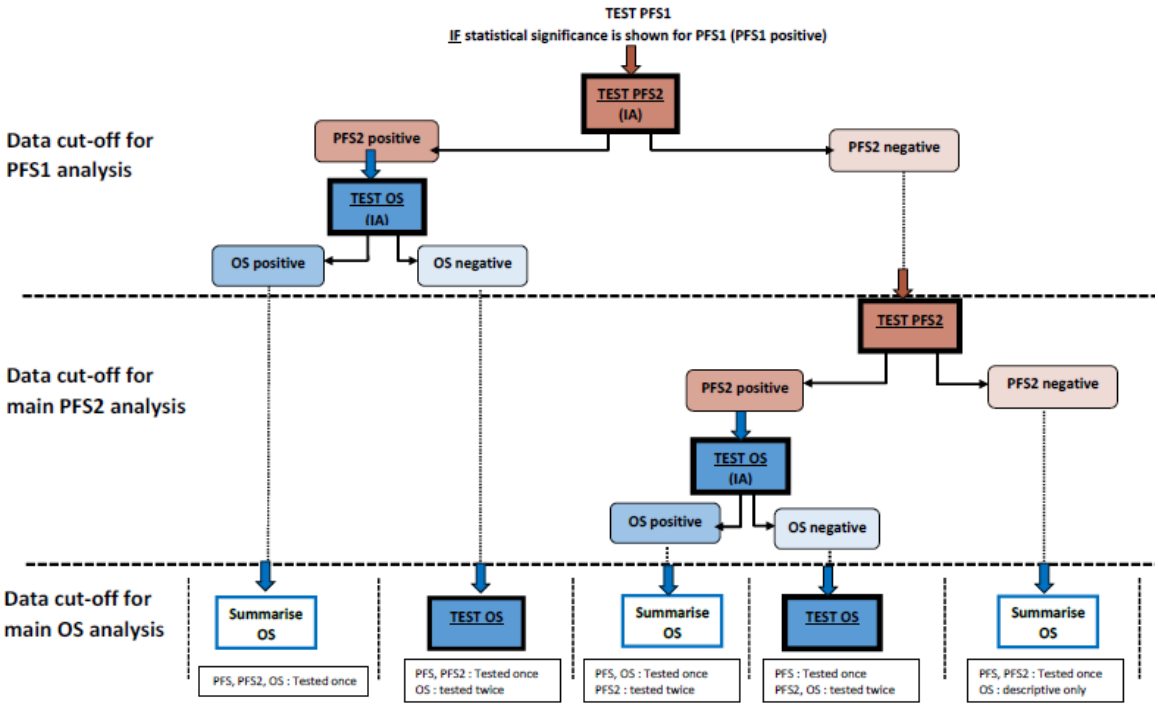


Figure 3: Complete MTP including PFS2 and OS interim analysis in the hierarchical testing strategy

Adjustment for interim PFS2 analysis

If statistical significance was shown for PFS1, the full test mass (alpha) was to be carried forward to PFS2. In order to adjust for the inclusion of an interim PFS2 analysis, the Lan and DeMets approach that approximates the O'Brien and Fleming spending function was to be used (Lan and DeMets 1983). The 1-sided significance level at the interim analysis was to be calculated based on the information fraction observed at this time; the information fraction was defined as the ratio between the number of events observed at the time of the interim analysis and the total number of events required for the final analysis. As an example, if 358 PFS2 events have occurred at the interim analysis, translating in an information fraction of 87%, then the significance level will be 1.6% at the interim analysis.

If the null hypothesis for PFS2 was not rejected at the first analysis time point, then accounting for the expected correlation between the proportion of events at the interim and at the final analysis, the 1-sided significance level at the final PFS2 analysis was to be approximately 2% (final significance level was to be determined once the exact correlation between the interim and final PFS2 analyses was known).

Adjustment for interim OS analysis

If PFS2 was significant at either the interim or final analyses, the full test mass (alpha) was to be carried forward to OS. Statistical significance was to be declared at the interim analysis for OS if the null hypothesis for PFS2 was rejected and the observed p-value for OS was $p<0.0001$. This allows the significance level at the final analysis for OS to be controlled at the 2.5% level (1-sided) (Haybittle J L 1971)).

Analysis

PFS2 and OS were to be analyzed using the same methodology as described for the PFS1 analysis, taking into account the MTP described above. Should PFS1 not be statistically significant, the study would still continue to final OS timepoint for descriptive/research purposes.

Patient reported outcome analysis

Quality of Life (QoL) were to be analysed descriptively. Descriptive statistics, graphs and listings were to be reported to evaluate the effect of olaparib maintenance on symptoms, HRQoL and PROs. The relationship between patient-reported outcomes, progression and AEs was to be assessed.

Exploratory endpoints analysis

Subgroup analyses of PFS1 and OS were to be conducted to assess consistency of treatment effect across predefined subsets, and to identify predictive factors of olaparib efficacy as maintenance therapy.

Subgroups considered were to include, but may not be limited to:

Stratifications factors:

• tBRCA status as per randomisation (tBRCAm vs tBRCAwt/VUS/unk)

• First line treatment outcome

Tumour characteristics as assessed by Myriad MyChoice HRD plus assay:

• Tumour BRCA mutation status (tBRCAm vs non-tBRCAm)

• Tumour HRR associated including BRCAm (HRRm* vs non-HRRm)

• Tumour Myriad HRD status cut off 42 (HRD positive vs HRD negative).

• Tumour Myriad HRD status cut off 33 (HRD positive vs HRD negative)

• Tumour HR deficiency status (tBRCAm or HRRm or HRD (42) + vs absence of HR deficiency biomarker)

• Tumour HR deficiency status (tBRCAm or HRRm or HRD (33) + vs absence of HR deficiency biomarker)

Main clinical characteristics:

• Age at randomisation (<65 vs. ≥ 65)

• FIGO stage at disease (FIGO III vs IV)

• Histological subgroups (HGSOC vs others)

• ECOG performance status at baseline (0 or 1)

• Baseline CA-125 value (≤ ULN vs > ULN)

• BRCA mutation type (BRCA1, BRCA2 or BRCA1/2 (both)

• Cytoreductive surgery outcome (no residual disease vs residual disease)

• Timing of cytoreductive surgery (upfront vs interval debulking)

• Duration of chemotherapy plus bevacizumab before randomization

• Region (Europe vs Japan)

• Other exploratory molecular subgroups

• QoL, safety

Response rate, best objective response rate and duration of response

For patients, in partial response at the randomization, the objective response rate (complete or partial response) was to be presented in each treatment arm by a proportion together with its 95% confidence interval and will be compared between the two arms using a Fisher exact test.

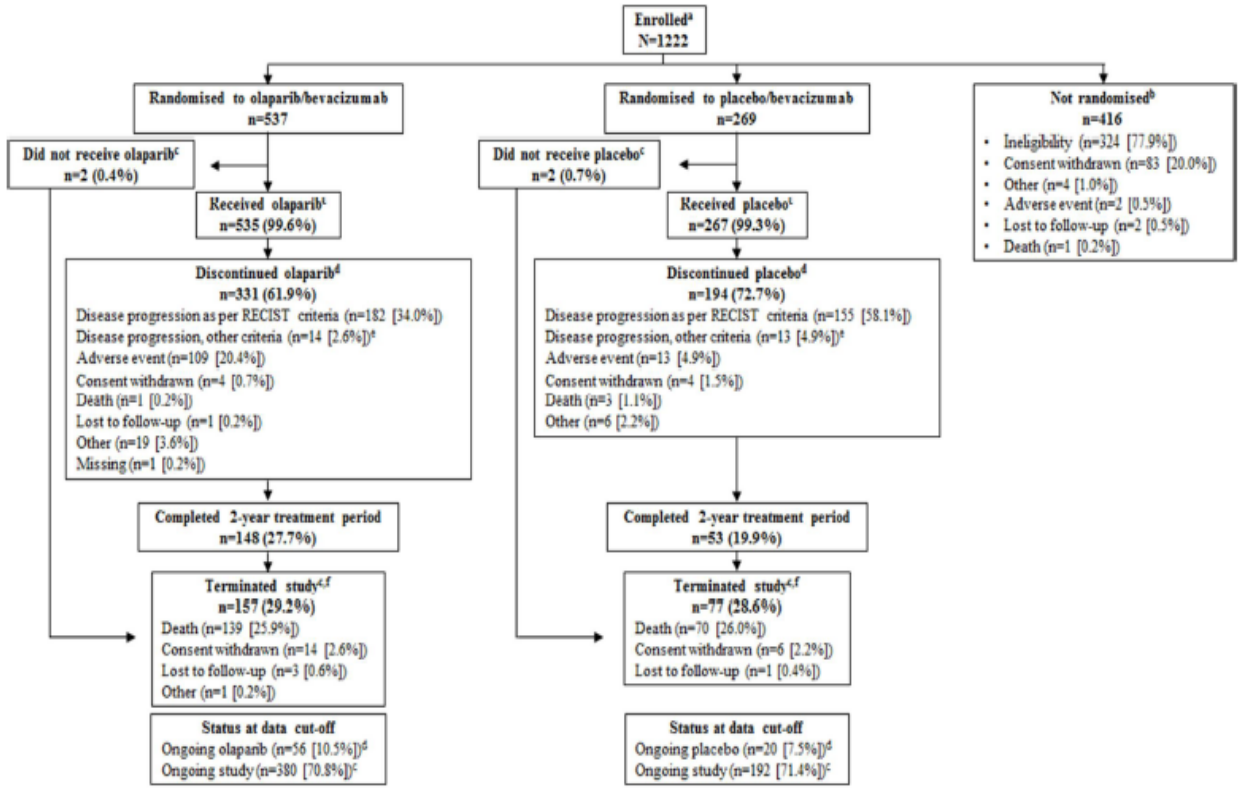
Primary endpoint Supportive (sensitivity) analysis

If the primary PFS1 analysis according to investigator assessment is positive, a sensitivity analysis for progression free survival as measured by central review assessment might be performed to support primary PFS1 results.

No adjustment to the significance level for testing was to be made since this analysis was only to be considered as supportive of the primary analysis of PFS1.

Results

Participant flow



[a] Informed consent received.
[b] Percentages are calculated from number of patients not randomised.
[c] Percentages are calculated from number of patients randomised.
[d] Percentages are calculated from number of patients who received treatment.
[e] Includes events reported as symptomatic deterioration.
[f] Includes patients who never received study treatment.
Data derived from Table 14.1.1.

Figure 4: PAOLA-1: Patient disposition (All patients)

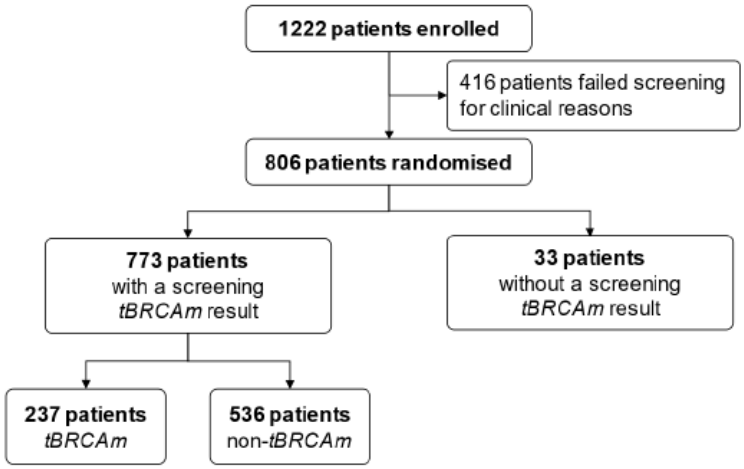


Figure 5: Routes to randomisation and stratification by tumour BRCA1/2 status

Recruitment

The first patient was enrolled into the study on 10 July 2015 and the last patient on 31 August 2017. Patients were randomised in 137 study centres in 11 countries worldwide (97% in Europe and 3% in Japan): Austria (6 centres), Belgium (3 centres), Denmark (1 centre), Finland (2 centres), France and Monaco (44 centres), Germany (51 centres), Italy (9 centres), Japan (7 centres), Spain (13 centres) and Sweden (1 centre). 24 patients were randomised in Japan centers and are included in the FAS. The majority of patients were randomised in France (327 patients), Germany (251 patients), Italy (85 patients) and spain (55 patients).

The DCO date for the primary analysis was 22 March 2019, 44 months after the first patient enrolment.

Conduct of the study

Protocol amendments

The original study protocol (Version 1.1) is dated 18 December 2014). The last protocol version 7.0 is dated 28 Feb 2019. Additional amendments to the protocol have been done and one SAP version issued by AstraZeneca and dated 14 May 2019, after the DCO in March 2019, has been provided.

Table 4: Protocol amendments and other significant changes to study conduct

Protocol 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 before the start of patient recruitment			
Version 1.2 (12 March 2015)	Clarification of inclusion criteria to allow for inclusion of patients with other (non-high-grade serous or non-high-grade endometrioid histology) epithelial non-mucinous ovarian cancer only for patients carrying *gBRCAm* (Section 9.3.1).	Inclusion criteria updated following publication showing that patients with *gBRCAm* ovarian cancer have higher rates of platinum sensitivity and improved OS (Pennington et al 2014).	ARCAGY-GINECO Research
	Clarification that collection of QoL questionnaires and pharmaco-economic information was restricted to the first 2 years of treatment (calculated from 1st study drug administration) (Sections 9.8.4.8, 11.1.3 and 11.1.4).	To have the same period of data collection for pharmaco-economic information as for dose administration.	
Amendments made after the start of patient recruitment			
Version 2.0 (14 January 2016)	Pneumonitis added to the list of AESIs (Sections 9.1 and 12.2.3).	Pneumonitis had been missed off the list of AESIs in error.	ARCAGY-GINECO Research
	Clarification that blood samples for exploratory biomarker analysis would only be taken from patients recruited at study centres in France (change also covered in local amendment version 3.0 in France; Section 11.6).	Due to sample importation regulations, only samples collected from sites in France could be analysed for exploratory biomarkers.	
Version 3.0 (15 February 2016)	Modification of selection criteria to allow patients having IDS to have only 2 cycles of bevacizumab in combination with the last 3 cycles of platinum-based chemotherapy (instead of the protocol requirement for a minimum of 3 cycles of bevacizumab in combination with the 3 last cycles of platinum-based chemotherapy) and to clarify that patients on a stable dose of oral anticoagulants could be recruited to the study (Section 9.3.1).	To bring the CSP in line with standard clinical practices for patients having IDS.	ARCAGY-GINECO Research

	Modification of the CT/MRI schedule to require collection of data for a minimum of 42 months or until the date when total number of PFS events was reached (Sections 9.1, 9.8.3 and 11.1).	The imaging (CT or MRI scans) were scheduled for each randomised patient until PFS. Thereafter, patients were followed according to the local procedures of the investigator site. It was expected that the total number of PFS events (n=372) would be reached when the first patient had been followed for 42 months. For patients whose disease would not be expected to progress during the treatment phase, imaging would be performed according to the CSP until 42 months or until the number of PFS events (n=372) was reached.	
Version 4.0 (06 January 2017)	An increase of the number of randomised patients from 612 to 762 patients and prolongation of recruitment period from 18 to 24 months (Sections 9.8 and 11.1).	Amendment made due to expanding knowledge of the benefit of PARP inhibitors in treating patients with ovarian cancer, with emerging evidence that different levels of benefit may be achieved depending on the genetic pre-disposition of an individual patient. The planned sample size was increased to be able to detect a significant difference in the ITT population.	ARCAGY Research
	Addition of an exploratory objective: "Explore the time to next severe toxicity (Grade 4 neutropenia lasting >7 days, Grade ≥3 febrile neutropenia, Grade 4 thrombocytopenia with bleeding or platelet transfusion, Grade ≥3 non-haematological toxicity) in both arms." (Section 8).	To explore whether olaparib when compared with placebo can delay the occurrence of a severe toxicity during study and subsequent treatment administration.	
	Modification of guidance for management of AEs of anaemia (only olaparib or placebo treatment was to be interrupted until haemoglobin levels returned to ≥10 g/dL) (Section 12.1).	Clarification that bevacizumab treatment could be maintained during AEs of anaemia unless CTCAE Grade 3 or worse, with onset of neutropenia and/or thrombocytopenia.	
	Modification of Sponsor's name from ARCAGY GINECO to ARCAGY Research (Section 6.1 and throughout CSR).	Administrative purposes.	

Version 5.0 (22 December 2017)	Removal of the planned interim efficacy analysis (after 229 PFS events) (Sections 9.8 and 11.1).	The interim efficacy analysis was due to occur shortly after study recruitment was completed and was considered of limited value at that point as all patients were already recruited and undisputable efficacy could not be declared with such a short follow-up.	ARCAGY Research
	Modification of the frequency of haematology testing during Month 6 to Month 12 on study (Sections 9.8.6 and 12.4.1).	To bring haematology testing requirements in line with olaparib labelling recommendations.	
Version 6.0 (03 October 2018)	Expansion of the exploratory objective exploring pre-planned subgroup analyses of efficacy to include clinical characteristics and tumour homologous recombination deficiency status (Sections 8, 9.8.3 and 11.1.5).	Emerging data from the NOVA trial on the importance of different HR deficiency subgroups on efficacy of PARP inhibitors with different levels of benefit observed according to the genetic profile of the tumour (*BRCAm*, HRD positive/negative; Mirza et al 2016).	ARCAGY Research
	Clarification that olaparib or placebo treatment should be stopped after 2 years of exposure unless the investigator considered that the patient could get a clinical benefit by prolonging the experimental treatment (Sections 9.5 and 12.1).	Amendment made to bring the CSP in line with olaparib labelling recommendations.	
	Clarification that an exploratory analysis of efficacy (PFS and OS) by region (Europe vs Japan) would be performed. Note the Japanese cohort were to be included in the FAS per protocol (Sections 9.8 and 11.1).	An analysis by region was not originally planned, but was subsequently considered to be useful.	

Version 7.0 (28 February 2019)	Modification of statistical methodology to add an IA of PFS2 and OS at the same time as PFS analysis (Section 9.8).	Interim analyses were not originally planned, but were subsequently considered to be required for regulatory purposes.	ARCAGY Research
	Addition of visits during the follow-up of patients (Section 9.1).	Additional visits added for follow-up of patients whose last visit occurred more than 12 weeks prior to any DCO date for data analysis, to update the disease status.	
	Addition of clarification for the definition of an SAE (excluding planned hospitalisations or hospitalisations without other related seriousness criteria) (Sections 9.8.6 and 12.3.1.1).	Accurate reporting of SAEs.	
	Addition of details regarding the data protection methodology (Section 5.2).	Compliance with EU data protection regulations.	

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

Protocol deviations

Table 5: Important protocol deviations (FAS)

	Number (%) of patients		
	Olaparib/ bevacizumab (N=537)	**Placebo/ bevacizumab (N=269)**	**Total (N=806)**
Number of patients with at least 1 important deviation[a]	35 (6.5)	13 (4.8)	48 (6.0)
Inclusion criterion not met (platinum-taxane based regimen must have consisted of a maximum of 9 treatment cycles)	0	1 (0.4)	1 (0.1)
Inclusion criterion not met (patients must have been randomised no more than 9 weeks after their last dose of chemotherapy)	2 (0.4)	1 (0.4)	3 (0.4)
Inclusion criterion not met (histologically confirmed high-grade serous, endometrioid, or other epithelial non mucinous ovarian cancer in a patient with *gBRCA1* or *2* deleterious mutation).[b]	1 (0.2)	0	1 (0.1)
Baseline RECIST scan >28 days (+14 days window) before randomisation	5 (0.9)	3 (1.1)	8 (1.0)
GCP violation: SAE reporting[c]	8 (1.5)	0	8 (1.0)
Lack of RECIST scans on >2 occasions before evidence of disease progression according to RECIST	1 (0.2)	1 (0.4)	2 (0.2)
Other malignancy within the last 5 years except history as described in protocol	1 (0.2)	0	1 (0.1)
Patients randomised but who did not receive olaparib/matching placebo due to site error	2 (0.4)	2 (0.7)	4 (0.5)
Patients randomised who received a treatment bottle other than that to which they were allocated[d]	15 (2.8)	5 (1.9)	20 (2.5)

a Important protocol deviations before the start of treatment and during treatment. b Patient with clear cell histology with no evidence of gBRCA mutation. c Late reporting of an AESI for olaparib or Suspected Unexpected Serious Adverse Reactions. d The majority of patients received 1 incorrect bottle. The maximum number of incorrect bottles

received was 6. Note: No patient had more than 1 important protocol deviation (see Appendix 16.2.2.1). Data derived from Table 14.1.2.

Patients who missed two or more consecutive RECIST assessments were 7 (1.3%) and 3 (1.1%) in the olaparib-bevacizumab and placebo-bevacizumab arms, respectively, whereas patients who missed one RECIST assessment were 112 (20.9%) and 44 (16.4%) in the olaparib-bevacizumab and placebo-bevacizumab arms, respectively. There were 229 (42.6%) and 66 (24.5%) patients censored less than or equal to one scheduled tumour assessment interval (+ 2 weeks) before DCO in the olaparib-bevacizumab and placebo-bevacizumab arm, respectively. There were 28 (5.2%) and 9 (3.2%) patients censored more than one scheduled tumour assessment interval (+ 2 weeks) before DCO in the olaparib-bevacizumab and placebo-bevacizumab arm, respectively.

Baseline data

Table 6: Selected demographics and baseline characteristics (FAS)

	Olaparib/bevacizumab (n=537)	**Placebo/bevacizumab (n=269)**
Demographics		
Age (years)		
Mean (SD)	60.8 (9.4)	59.2 (10.1)
Median (range)	61.0 (32-87)	60.0 (26-85)
Age group (years), n (%)		
<50	67 (12.5)	47 (17.5)
≥50 to <65	265 (49.3)	135 (50.2)
≥65	205 (38.2)	87 (32.3)
Disease characteristics		
ECOG Performance status, n (%)		
(0) Normal activity	378 (70.4)	189 (70.3)
(1) Restricted activity	153 (28.5)	76 (28.3)
Missing	6 (1.1)	4 (1.5)
Tumour characteristics		
Primary tumour location, n (%)		
Ovary	456 (84.9)	238 (88.5)
Fallopian tubes	39 (7.3)	11 (4.1)
Primary peritoneal	42 (7.8)	20 (7.4)
FIGO Staging, n (%)		
IIIB	43 (8.0)	17 (6.3)
IIIC	335 (62.4)	169 (62.8)
IV	159 (29.6)	83 (30.9)
CA-125 status at baseline, n (%)		
CA-125 levels ≤ULN	463 (86.2)	234 (87.0)
CA-125 levels >ULN	74 (13.8)	34 (12.6)
Missing	0	1 (0.4)
Histology type, n (n%)		
Serous	519 (96.6)	253 (94.1)
Endometrioid	12 (2.2)	8 (3.0)

	Olaparib/bevacizumab (n=537)	Placebo/bevacizumab (n=269)
Clear cell	2 (0.4)	0
Undifferentiated	1 (0.2)	6 (2.2)
Other	3 (0.6)	2 (0.7)
Type of surgery and outcome		
Any surgery, n (%)	499 (92.9)	248 (92.2)
Residual macroscopic disease	176 (35.3)	88 (35.5)
No residual macroscopic disease	323 (64.7)	160 (64.5)
Patients with initial debulking surgery, n (%)	271 (50.5)	138 (51.3)
Residual macroscopic disease	111 (41.0)	53 (38.4)
No residual macroscopic disease	160 (59.0)	85 (61.6)
Patients with interval debulking surgery, n (%)	228 (42.5)	110 (40.9)
Residual macroscopic disease	65 (28.5)	35 (31.8)
No residual macroscopic disease	163 (71.5)	75 (68.2)
Patients without surgery, n (%)	38 (7.1)	21 (7.8)
First line treatment outcome at screening (obtained from the randomisation schedule)		
NED with complete macroscopic resection at initial debulking surgery	170 (31.7)	86 (32.0)
NED/CR with complete macroscopic resection at interval debulking surgery	166 (30.9)	84 (31.2)
NED/CR at screening, in patient who had either incomplete resection (at initial or interval debulking surgery) or no debulking surgery	82 (15.3)	40 (14.9)
Partial response	119 (22.2)	59 (21.9)
First line treatment outcome at screening (obtained from the eCRF)		
NED with complete macroscopic resection at initial debulking surgery	158 (29.4)	83 (30.9)
NED/CR with complete macroscopic resection at interval debulking surgery	158 (29.4)	75 (27.9)
NED/CR at screening, in patient who had either incomplete resection (at initial or interval debulking surgery) or no debulking surgery	80 (14.9)	36 (13.4)
Partial response	134 (25)	73 (27.1)
Not applicable as per eCRF	7 (1.3)	2 (0.7)
Screening laboratory *tBRCA* status (obtained from the randomisation schedule)		
Deleterious mutation	161 (30.0)	80 (29.7)
Absence of deleterious mutation[b]	376 (70.0)	189 (70.3)
Screening laboratory *tBRCA* status on tumour tissue (obtained from the eCRF)		
tBRCAm	157 (29.2)	80 (29.7)
Non-tBRCAm	380 (70.8)	189 0.3)

[a] Stage III combined. b Includes test cancelled/failed patients (i.e., inconclusive and unknown groups). 26 patients on the olaparib/bevacizumab arm and 7 patients on the placebo/bevacizumab arm.

In the HRD-positive subgroup, 65% of patients had complete cytoreduction and 35% of patients had residual microscopic disease.

Table 7: Previous treatments for ovarian cancer (FAS)

Treatment category	Previous treatment modality	Number (%) of patients		
		Olaparib/ bevacizumab (N=537)	Placebo/ bevacizumab (N=269)	Total (N=806)
Platinum	Carboplatin	536 (99.8)	268 (99.6)	804 (99.8)
	Cisplatin	5 (0.9)	3 (1.1)	8 (1.0)
Taxane	Paclitaxel	533 (99.3)	265 (98.5)	798 (99.0)
	Docetaxel	14 (2.6)	8 (3.0)	22 (2.7)
	No taxane	0	1 (0.4)	1 (0.1)
Bevacizumab	Yes	537 (100)	269 (100)	806 (100)

Patients are counted once per treatment modality for the categories platinum and taxane.
FAS Full Analysis Set.
Data derived from Table 14.1.10.1.

The study randomised 806 patients (2:1 randomisation: 537 olaparib/bevacizumab: 269 placebo/bevacizumab) who had no evidence of disease (NED) due to complete surgical resection, or who were in complete response (CR), or partial response (PR) following completion of first-line platinum-containing chemotherapy and bevacizumab. Patients had completed a minimum of 4 and a maximum of 9 cycles, with the majority (63%) having received 6 cycles of first line platinum-taxane based chemotherapy, including a minimum of 2 cycles of bevacizumab in combination with the 3 last cycles of chemotherapy. The median number of bevacizumab cycles prior to randomisation was 5.

Table 8: Number of cycles of previous first line treatment prior to randomisation (FAS)

Number of cycles	Number (%) of patients		
	Olaparib/ bevacizumab (N=537)	Placebo/ bevacizumab (N=269)	Total (N=806)
Platinum/taxane			
<4	1 (0.2)	2 (0.7)	3 (0.4)
4	1 (0.2)	0	1 (0.1)
5	18 (3.4)	9 (3.3)	27 (3.3)
6	341 (63.5)	165 (61.3)	506 (62.8)
7	73 (13.6)	41 (15.2)	114 (14.1)
8	61 (11.4)	27 (10.0)	88 (10.9)
9	42 (7.8)	23 (8.6)	65 (8.1)
>9	0	1 (0.4)	1 (0.1)
No platinum/taxane	0	1 (0.4)	1 (0.1)
Platinum			
<4	0	0	0
4	0	0	0
5	4 (0.7)	2 (0.7)	6 (0.7)
6	341 (63.5)	164 (61.0)	505 (62.7)
7	78 (14.5)	48 (17.8)	126 (15.6)
8	63 (11.7)	28 (10.4)	91 (11.3)
9	51 (9.5)	26 (9.7)	77 (9.6)
>9	0	1 (0.4)	1 (0.1)
No platinum	0	0	0
Bevacizumab			
1	0	0	0
2	21 (3.9)	12 (4.5)	33 (4.1)
3	87 (16.2)	41 (15.2)	128 (15.9)
4	100 (18.6)	56 (20.8)	156 (19.4)
5	120 (22.3)	42 (15.6)	162 (20.1)
>5	209 (38.9)	118 (43.9)	327 (40.6)
No bevacizumab	0	0	0

Patients were counted as to have received a cycle of therapy as soon as the infusion had started. Platinum-taxane based regimen must have consisted of a minimum of 6 treatment cycles and a maximum of 9. However, if platinum-based therapy was discontinued early as a result of non-haematological toxicities specifically related to the platinum regimen, (i.e., neurotoxicity, hypersensitivity etc), patients must have received a minimum of 4 cycles of the platinum regimen. Patients must have received, prior to randomisation, a minimum of 3 cycles of bevacizumab in combination with the 3 last cycles of platinum-based chemotherapy. Only in cases of interval debulking surgery, was it permitted to receive only 2 cycles of bevacizumab in combination with the last 3 cycles of platinum-based chemotherapy.

Table 9: Allowed concomitant medications during study treatment (FAS)

Medication class	Number (%) of patients		
	Olaparib/ bevacizumab (N=537)	Placebo/ bevacizumab (N=269)	Total (N=806)
Number of patients with any allowed concomitant medication	433 (80.6)	193 (71.7)	626 (77.7)
Antibiotic	244 (45.4)	116 (43.1)	360 (44.7)
Antihypertensive drug	142 (26.4)	110 (40.9)	252 (31.3)
Continuous or intermittent antiemetic agent	192 (35.8)	45 (16.7)	237 (29.4)
Anticoagulant	85 (15.8)	33 (12.3)	118 (14.6)
Red blood cell transfusion	100 (18.6)	4 (1.5)	104 (12.9)
Erythropoietin	30 (5.6)	3 (1.1)	33 (4.1)
Granulocyte-colony stimulating factor	7 (1.3)	4 (1.5)	11 (1.4)
Platelet transfusion	5 (0.9)	1 (0.4)	6 (0.7)

Includes medication with an onset date on or after the date of first dose and up to and including 30 days following the date of last dose of olaparib or placebo. Also includes medication with an onset date prior to the date of first dose but continued after the date of first dose.
FAS Full Analysis Set.
Data derived from Table 14.1.14.1.

Table 10: Disallowed concomitant medications during study treatment (FAS)

Medication class	Number (%) of patients		
	Olaparib/ bevacizumab (N=537)	Placebo/ bevacizumab (N=269)	Total (N=806)
Number of patients with any disallowed concomitant medication	4 (0.7)	3 (1.1)	7 (0.9)
Antibiotic	4 (0.7)	2 (0.7)	6 (0.7)
Clarithromycin	4 (0.7)	2 (0.7)	6 (0.7)
Antihypertensive drug	0	1 (0.4)	1 (0.1)
Carmen	0	1 (0.4)	1 (0.1)

Includes medication with an onset date on or after the date of first dose and up to and including 30 days following the date of last dose of olaparib or placebo. Also includes medication with an onset date prior to the date of first dose but continued after the date of first dose.
FAS Full Analysis Set.
Data derived from Table 14.1.14.2.

BRCA mutation status

In the overall patient population enrolled, 30% of patients in both arms were tBRCAm (deleterious/pathogenic mutation) at screening by local testing and for 4% of patients the BRCAm status was unknown. Retrospective analysis of available clinical samples was conducted in 97% of patients to confirm tBRCAm status and investigate genomic instability score. Among non-tBRCAm patients, 29% (19% of the overall population) had positive GIS pre-defined in this study as composite score ≥42. When tBRCAm status and positive GIS were combined, patients with HRD-positive, HRD-negative and HRD unknown status in their tumours represented 48%, 34% and 18% of the overall patient population.

Table 11: Deleterious and suspected deleterious tumour/germline BRCA1/2 mutations, tumour HRR mutation types and Myriad HRD Status (FAS)

	Number of patients (%)		
	Olaparib/ bevacizumab (N=537)	Placebo/ bevacizumab (N=269)	Total (N=806)
Myriad *tBRCA* status			
tBRCAm	158 (29.4)	77 (28.6)	235 (29.2)
tBRCA1m	111 (20.7)	48 (17.8)	159 (19.7)
tBRCA2m	46 (8.6)	29 (10.8)	75 (9.3)
tBRCA1m and tBRCA2m	1 (0.2)	0	1 (0.1)
non-*tBRCAm*[a]	346 (64.4)	174 (64.7)	520 (64.5)
tBRCA test cancelled/failed	17 (3.2)	10 (3.7)	27 (3.3)
tBRCA missing	16 (3.0)	8 (3.0)	24 (3.0)
Myriad HRD status (*tBRCAm* or ≥42 cut-off)			
Myriad HRD status positive	255 (47.5)	132 (49.1)	387 (48.0)
Myriad HRD status positive excluding *tBRCAm*	97 (18.1)	55 (20.4)	152 (18.9)
Myriad HRD status negative	192 (35.8)	85 (31.6)	277 (34.4)
Myriad HRD status test cancelled/failed	74 (13.8)	44 (16.4)	118 (14.6)
Myriad HRD status missing	16 (3.0)	8 (3.0)	24 (3.0)
Myriad HRD status (*tBRCAm* or ≥33 cut-off)			
Myriad HRD status positive	292 (54.4)	145 (53.9)	437 (54.2)
Myriad HRD status positive excluding *tBRCAm*	134 (25.0)	68 (25.3)	202 (25.1)
Myriad HRD status negative	155 (28.9)	72 (26.8)	227 (28.2)
Myriad HRD status test cancelled/failed	74 (13.8)	44 (16.4)	118 (14.6)
Myriad HRD status missing	16 (3.0)	8 (3.0)	24 (3.0)
Myriad tumour HRRm status[b]			
HRRm status positive including *tBRCAm*	192 (35.8)	97 (36.1)	289 (35.9)
HRRm status positive excluding *tBRCAm*	34 (6.3)	20 (7.4)	54 (6.7)
non-HRRm	312 (58.1)	154 (57.2)	466 (57.8)
HRR test cancelled/failed	17 (3.2)	10 (3.7)	27 (3.3)
HRR missing	16 (3.0)	8 (3.0)	24 (3.0)

[a] Non-*tBRCAm* = *tBRCAwt*/VUS

[b] HRR genes of interest included in the panel are: *BRCA1*, *BRCA2*, *ATM*, *BRIP1*, *PALB2*, *RAD51C*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PPP2R2A*, *RAD51B*, *RAD51D*, *RAD54L*.

BRCA breast cancer susceptibility gene; eCRF electronic case report form; FAS Full Analysis Set; *gBRCA* germline *BRCA*; *gBRCAm* germline *BRCA* mutated; HRR homologous recombination repair; HRRm homologous recombination repair gene mutated/mutations; *sBRCA* somatic *BRCA*; *sBRCAm* somatic *BRCA* mutated; *tBRCA* tumour *BRCA*; *tBRCAm* tumour *BRCA* mutated; *unk* unknown; VUS variant of uncertain significance; *wt* wild type.

Source: Table 14.1.8.2.

Table 12: Summary of BRCA mutation status by Screening laboratory tBRCA and Myriad tBRCA (Full analysis set)

		Screening laboratory tumour BRCA status			
	Myriad tumour BRCA status	BRCA mutated	No BRCA mutation	Cancelled/ Failed	Missing
Olaparib + bevacizumab (N=537)	Deleterious	140 (26.1)	5 (0.9)	3 (0.6)	0
	Suspected deleterious	5 (0.9)	5 (0.9)	0	0
	VUS	2 (0.4)	16 (3.0)	1 (0.2)	0
	No mutation detected	0	311 (57.9)	16 (3.0)	0
	Unknown [a]	4 (0.7)	8 (1.5)	5 (0.9)	0
	Missing	6 (1.1)	9 (1.7)	1 (0.2)	0
Placebo + bevacizumab (N=269)	Deleterious	65 (24.2)	7 (2.6)	1 (0.4)	0
	Suspected deleterious	1 (0.4)	3 (1.1)	0	0
	VUS	2 (0.7)	11 (4.1)	0	0
	No mutation detected	3 (1.1)	152 (56.5)	6 (2.2)	0
	Unknown [a]	6 (2.2)	4 (1.5)	0	0
	Missing	3 (1.1)	5 (1.9)	0	0
Total (N=806)	Deleterious	205 (25.4)	12 (1.5)	4 (0.5)	0
	Suspected deleterious	6 (0.7)	8 (1.0)	0	0
	VUS	4 (0.5)	27 (3.3)	1 (0.1)	0
	No mutation detected	3 (0.4)	463 (57.4)	22 (2.7)	0
	Unknown [a]	10 (1.2)	12 (1.5)	5 (0.6)	0
	Missing	9 (1.1)	14 (1.7)	1 (0.1)	0

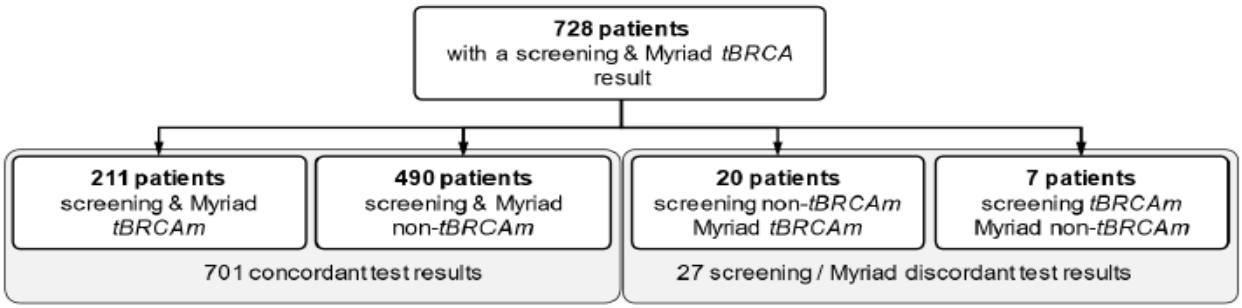


Figure 6: tBRCA concordance in PAOLA-1

Numbers analysed

Table 13: Analysis sets

	Number (%) of patients		
	Olaparib/ bevacizumab	**Placebo/ bevacizumab**	**Total**
Patients randomised	537	269	806
Patients included in FAS	537 (100)	269 (100)	806 (100)
Patients included in SAS	535 (99.6)	267 (99.3)	802 (99.5)
Combination Phase only	534 (99.4)	267 (99.3)	801 (99.4)
Patients excluded from SAS[a]	2 (0.4)	2 (0.7)	4 (0.5)
Did not receive olaparib or placebo	2 (0.4)	2 (0.7)	4 (0.5)

[a] An individual patient could have been excluded for more than 1 reason. FAS: all randomised patients analysed on an ITT basis. SAS: all patients who received at least 1 dose of study treatment and had at least 1 safety follow-up. Combination phase was from the first dose of combination treatment (bevacizumab/olaparib or placebo) until the last dose of bevacizumab +21 days whilst on combination treatment. FAS Full Analysis Set; ITT intention-to-treat; SAS Safety Analysis Set.

Outcomes and estimation

Primary endpoint: PFS by investigator assessment

PFS (based on investigator assessment) was the primary variable for the study and was analysed based on the primary DCO (22 March 2019) using the FAS population.

At the time of PFS analysis, the median duration of treatment with Lynparza was 17.3 months and 15.6 months for placebo. The median duration of bevacizumab post-randomisation was 11.0 months on the Lynparza arm and 10.4 months on the placebo arm.

The progression status based on investigator assessment at the time of PFS analysis is presented below.

Table 14: Progression status at the time of PFS analysis based on investigator assessment (FAS) (DCO 22 March 2019)

Progression status	Type of event	Number (%) of patients	
		Olaparib/bevacizumab (N=537)	Placebo/bevacizumab (N=269)
Progression	Total	280 (52.1)	194 (72.1)
	RECIST progression[a]	274 (51.0)	188 (69.9)
	Target lesions[b]	8 (1.5)	6 (2.2)
	Non-target lesions[b]	47 (8.8)	22 (8.2)
	New lesions[b]	250 (46.6)	172 (63.9)
	Death[c]	6 (1.1)	6 (2.2)
No progression	Total	257 (47.9)	75 (27.9)
	Censored RECIST progression[d]	3 (0.6)	0
	Censored death[e]	2 (0.4)	1 (0.4)
	Progression free at time of analysis[f]	240 (44.7)	69 (25.7)
	Lost to follow-up[g]	2 (0.4)	0
	Withdrawn consent[g]	10 (1.9)	5 (1.9)
	Discontinued study[g]	0	0

[a] Does not include RECIST progression events that occurred after 2 or more missed visits or within 2 visits of baseline where the patient had no evaluable visits or did not have a baseline assessment.
[b] Not necessarily mutually exclusive categories.
[c] Death in the absence of RECIST progression or death that occurred within 2 visits of baseline where the patient had no evaluable visits or did not have a baseline assessment. Does not include deaths that occurred after 2 or more missed visits.
[d] RECIST progression event occurred after 2 or more missed visits or within 2 visits of baseline where the patient had no evaluable visits or did not have a baseline assessment.
[e] Death which occurred after 2 or more missed visits in the absence of RECIST progression.
[f] Patients known to be alive and without RECIST progression.
[g] Patients at last evaluable RECIST assessment.

Table 15: Summary of analysis of progression-free survival by investigator (FAS) (DCO 22 March 2019)

	Olaparib/bevacizumab (N=537)	Placebo/bevacizumab (N=269)
n (%) of events[a]	280 (52.1)	194 (72.1)
Treatment effect		
Median PFS (95% CI), months[b]	22.1 (21.8, 24.1)	16.6 (15.4, 18.6)
HR[c]	0.59	
95% CI[c]	0.49, 0.72	
2-sided p-value[d]	<0.0001	
Progression free at 6 months (%)[b]	88.8	85.3
Progression free at 12 months (%)[b]	78.0	65.6
Progression free at 18 months (%)[b]	62.3	45.8
Progression free at 24 months (%)[b]	46.0	27.7
Median (IQR) follow-up for PFS, months[e]	22.7 (18.0, 27.7)	24.0 (18.7, 27.7)

[a] PFS was defined as time from randomisation until the date of objective radiological disease progression according to modified RECIST 1.1 or death.
[b] Calculated using KM techniques
[c] Estimated from a stratified Cox proportional hazards model stratified by first line treatment outcome and *tBRCA* status.
[d] Determined using log-rank test stratified by first line treatment outcome and *tBRCA* status.
[e] Time from randomisation to date of censoring.

CI confidence interval; FAS Full Analysis Set; HR hazard ratio; IQR interquartile range; KM Kaplan-Meier; PFS progression-free survival; RECIST Response Evaluation Criteria in Solid Tumours.
Data derived from Table 14.2.1.2.

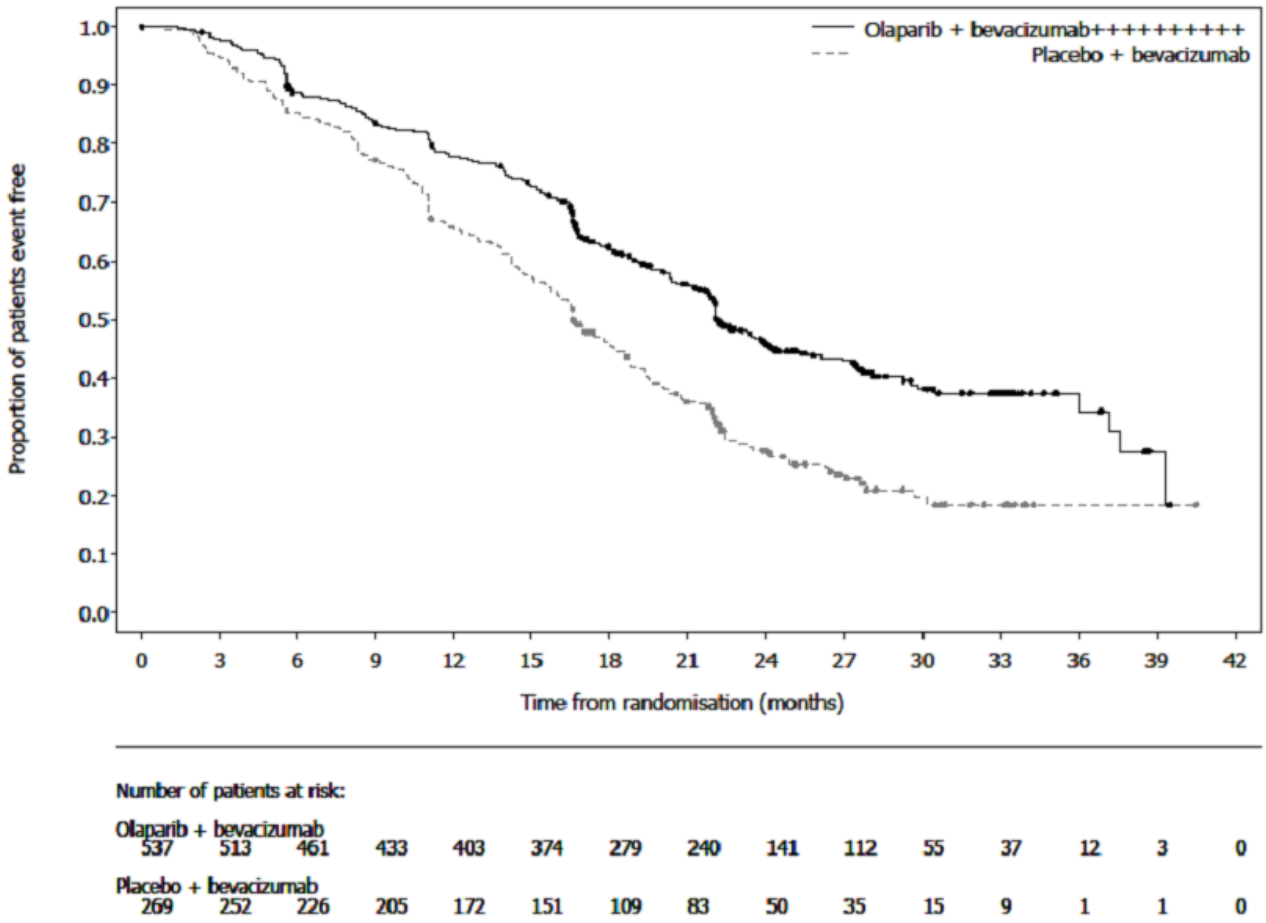


Figure 7: Progression-free survival by investigator, Kaplan-Meier plot (FAS) (DCO 22 March 2019)

Secondary endpoints

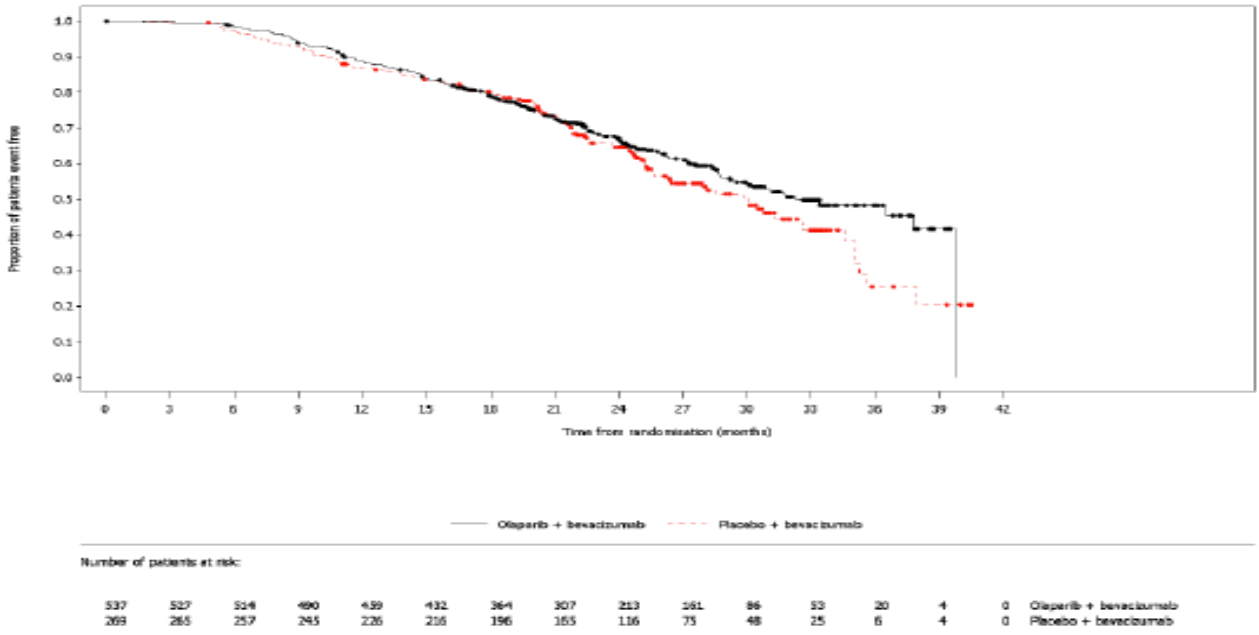
Time from randomisation to second progression or death

PFS2 events were based on radiological, CA-125 or symptomatic progression as assessed by the investigator or death. At the time of the PFS analysis, the interim PFS2 data were 39.1% mature (315 events/806 patients).

Table 16: Second Progression-free survival (FAS) (DCO 22 March 2019)

	Olaparib/bevacizumab (N=537)	Placebo/bevacizumab (N=269)
n (%) of events[a]	196 (36.5)	119 (44.2)
Treatment effect		
Median PFS2 (95% CI), months[b]	32.3 (29.2, 39.8)	30.1 (25.7, 32.6)
HR[c]	0.86	
95% CI[c]	0.69, 1.09	
2-sided p-value[d]	0.2097	
Second progression free at 6 months (%)[b]	98.3	97.3
Second progression free at 12 months (%)[b]	88.7	86.7
Second progression free at 18 months (%)[b]	79.0	80.1
Second progression free at 24 months (%)[b]	67.0	64.6
Median (IQR) follow-up for second progression-free survival (months)[e]	24.0 (19.8, 28.3)	24.8 (21.6, 28.2)

[a] PFS2 was defined as time from randomisation to second progression or death.
[b] Calculated using KM techniques.
[c] Estimated from a stratified Cox proportional hazards model stratified by first line treatment outcome and *tBRCA* status.
[d] Determined using log-rank test stratified by first line treatment outcome and *tBRCA* status.
[e] Time from randomisation to date of censoring.
The 2-sided significance level at the interim PFS2 analysis was 0.02092 based on an information fraction of 0.766.
CI confidence interval; FAS Full Analysis Set; HR hazard ratio; IQR interquartile range; KM Kaplan-Meier; RECIST Response Evaluation Criteria in Solid Tumours.
Data derived from Table 14.2.2.2.



FAS Full Analysis Set; PFS2 time from randomisation to second progression or death.

Figure 8: Second progression-free survival, Kaplan-Meier plot (FAS) (DCO 22 March 2019)

Overall survival

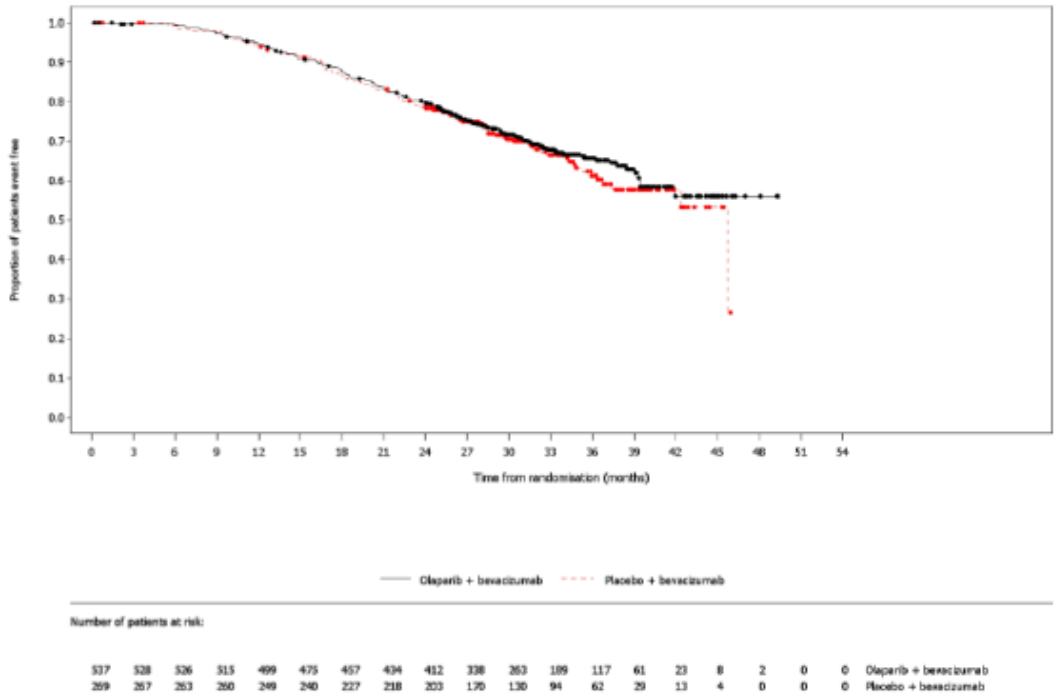
At the time of the primary analysis (DCO 22 March 2019), the interim OS data were immature (25.9% mature [209 events/806 patients]; HR 1.01; 95% CI 0.76 to 1.36) with similar proportions of deaths reported on each arm.

At the time of the DCO for the updated OS analysis (30 September 2019), six months after the primary DCO (22 March 2019), the OS data maturity increased to 32% with 259 events (168 patients had died in the olaparib/bevacizumab arm and 91 patients in the placebo/bevacizumab arm).

Table 17: Summary of overall survival status (FAS)

	DCO 22 March 2019		DCO 30 September 2019	
	Olaparib/ bevacizumab (n=537)	Placebo/ bevacizumab (n=269)	Olaparib/ bevacizumab (n=537)	Placebo/ bevacizumab (n=269)
n (%) of events	139 (25.9)	70 (26.0)	168 (31.3)	91 (33.8)
Treatment effect				
Median OS (95% CI), months	39.4 (38.4, Not reached)	Not reached	Not reached	45.7 (37.4, Not reached)
HR (95% CI)	1.01 (0.76, 1.36)		0.94 (0.73, 1.21)	
p-value (2-sided)	0.9270		Not calculated	
Alive at 6 months (%)	99.4	99.2	99.4	99.2
Alive at 12 months (%)	94.7	94.0	94.7	94.0
Alive at 18 months (%)	87.6	86.7	87.6	86.7
Alive at 24 months (%)	79.1	78.0	79.8	78.7

CI = confidence interval; CSR = clinical study report; DCO =data cut-off; FAS = full Analysis Set; HR = hazard ratio; OS = overall survival.
Source: Table 14.2.3.2, PAOLA-1 CSR (DCO 22 March 2019); Table 14.2.3.2 (DCO 30 September 2019).



DCO = data cut-off; FAS = full Analysis Set; KM = Kaplan-Meier.
Source: Figure 14.2.3.1 (DCO 30 September 2019).

Figure 9: Overall survival, Kaplan-Meier plot (FAS), DCO 30 September 2019

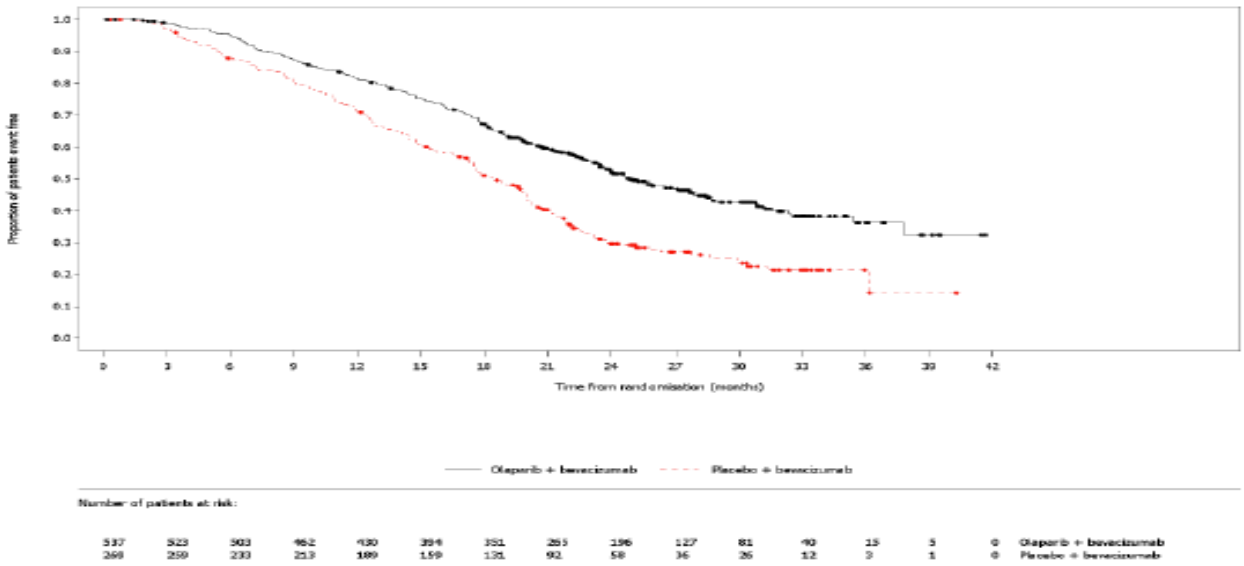
Time from randomisation to the earlier of first subsequent therapy start date following study treatment discontinuation, or death

Table 18: Summary of TFST (FAS), DCO 22 March 2019

	Olaparib/bevacizumab (N=537)	Placebo/bevacizumab (N=269)
n (%) of events[a]	275 (51.2)	190 (70.6)
Treatment effect		
Median TFST (95% CI), months[b]	24.8 (23.4, 27.9)	18.5 (17.2, 20.1)
HR[c]	0.58	
95% CI[c]	0.48, 0.70	
2-sided p-value[d]	<0.0001	
Median follow-up for TFST, months[e]	25.1	25.1

[a] TFST was defined as time from randomisation to first subsequent therapy or death.
[b] Calculated using KM techniques.
[c] Estimated from a stratified Cox proportional hazards model stratified by first line treatment outcome and *tBRCA* status.
[d] Determined using log-rank test stratified by first line treatment outcome and *tBRCA* status and not controlled for multiplicity.
[e] Time from randomisation to date of censoring.

BRCA breast cancer susceptibility gene; CI confidence interval; FAS Full Analysis Set; HR hazard ratio; KM Kaplan-Meier; *tBRCA* tumour *BRCA*.
Data derived from Table 14.2.4.1.



FAS Full Analysis Set; TFST time from randomisation to first subsequent therapy or death.
Data derived from Figure 14.2.4.1.

Figure 10: TFST, Kaplan-Meier plot (FAS), DCO 22 March 2019

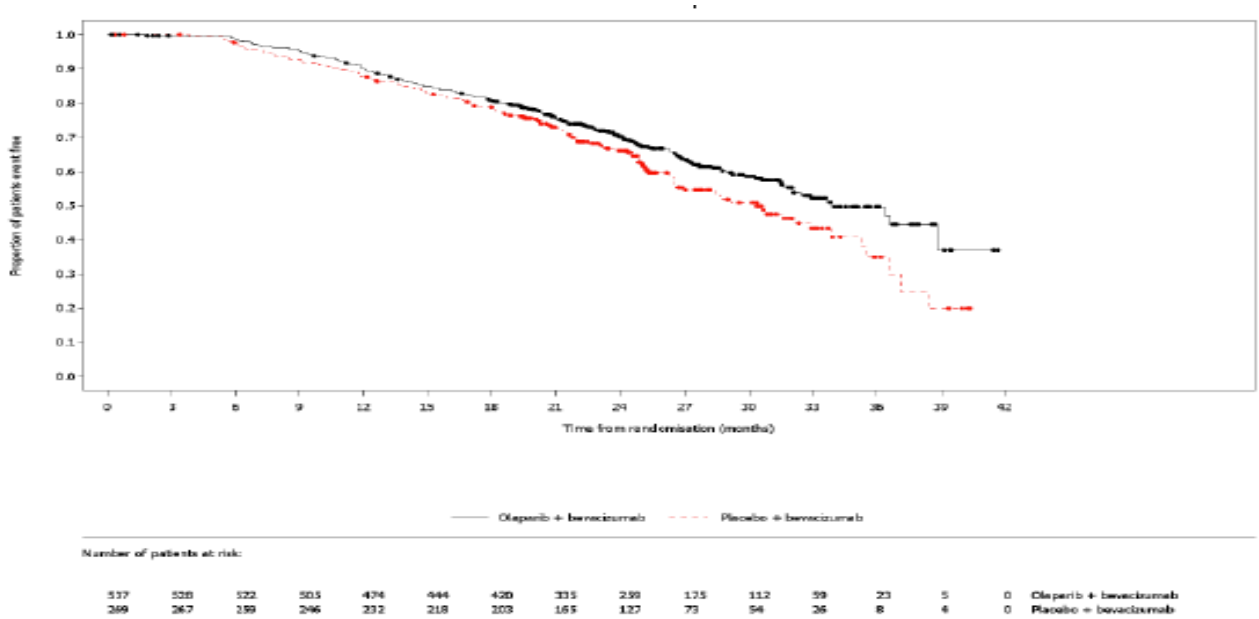
Time from randomisation to the earlier of second subsequent therapy start date following study treatment discontinuation, or death (TSST)

Table 19: Summary of TSST (FAS), DCO 22 March 2019

	Olaparib/bevacizumab (N=537)	Placebo/bevacizumab (N=269)
n (%) of events[a]	194 (36.1)	119 (44.2)
Treatment effect		
Median TSST (95% CI), months[b]	33.8 (31.6, NC)	30.4 (26.5, 33.9)
HR[c]	0.79	
95% CI[c]	0.63, 1.00	
2-sided p-value[d]	0.0444	
Median follow-up for TSST, months[e]	25.2	25.1

[a] TSST was defined as time from randomisation to second subsequent therapy or death.
[b] Calculated using KM techniques.
[c] Estimated from a stratified Cox proportional hazards model stratified by first line treatment outcome and *tBRCA* status.
[d] Determined using log-rank test stratified by first line treatment outcome and *tBRCA* status and not controlled for multiplicity.
[e] Time from randomisation to date of censoring.

BRCA breast cancer susceptibility gene; CI confidence interval; FAS Full Analysis Set; HR hazard ratio; KM Kaplan-Meier; *tBRCA* tumour *BRCA*.
Data derived from Table 14.2.5.1.



FAS Full Analysis Set; TSST time from randomisation to second subsequent therapy or death.
Data derived from Figure 14.2.5.1.

Figure 11: TSST, Kaplan-Meier plot (FAS), DCO 22 March 2019

Time from randomisation to discontinuation of treatment or death (TDT)

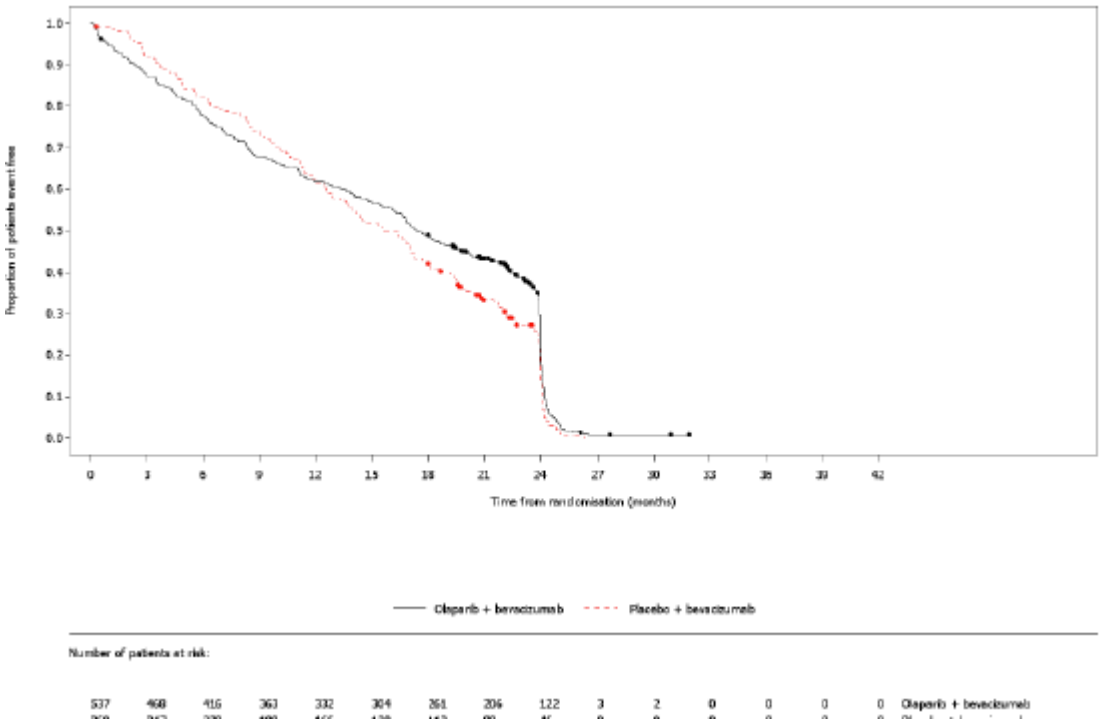


Figure 12: TDT, Kaplan-Meier plot (FAS), DCO 22 March 2019

Table 20: Analysis of time to study treatment discontinuation or death (TDT), FAS, DCO 22 March 2019

	Olaparib + bevacizumab (N=537)		Placebo + bevacizumab (N=269)
Total number of events (%) [a]	479 (89.2)		247 (91.8)
Median (IQR) follow-up for time to study treatment discontinuation (months) [c]	21.1 (20.0,22.4)		21.5 (19.6,22.5)
Discontinuation free at 6 months (%) [b]	77.6		82.1
95% Confidence Interval	73.8,80.9		77.0,86.2
Discontinuation free at 12 months (%) [b]	61.9		61.9
95% Confidence Interval	57.7,65.9		55.8,67.5
Discontinuation free at 18 months (%) [b]	48.9		42.2
95% Confidence Interval	44.6,53.0		36.2,48.0
Discontinuation free at 24 months (%) [b]	29.7		22.8
95% Confidence Interval	25.6,33.8		17.7,28.2
Discontinuation free at 30 months (%) [b]	0.9		0.0
95% Confidence Interval	0.3,2.3		0.0,0.0
Discontinuation free at 36 months (%) [b]	-		0.0
95% Confidence Interval	-,-		0.0,0.0
Discontinuation free at 42 months (%) [b]	-		0.0
95% Confidence Interval	-,-		0.0,0.0
Median time to study treatment discontinuation (months) [b]	17.4		16.3
95% Confidence Interval	16.3,19.5		13.8,17.3
25th percentile	6.9		8.6
75th percentile	24.0		23.9
Hazard ratio [d]		0.83	
95% Confidence Interval [d]		0.71,0.98	
2-sided p-value [e]		0.0232	

Best objective response (BoR)

Table 21: BoR (FAS – patients with evidence of disease at baseline) (DCO 22 March 2019)

Response status	Best objective response	Number (%) of patients	
		Olaparib/ bevacizumab (N=129)	Placebo/ bevacizumab (N=72)
Response	Total	39 (30.2)	18 (25.0)
	CR[a]	32 (24.8)	13 (18.1)
	PR[a]	7 (5.4)	5 (6.9)
Non-response	Total	90 (69.8)	54 (75.0)
	Stable disease ≥24 weeks	54 (41.9)	33 (45.8)
	Progression	34 (26.4)	21 (29.2)
	RECIST progression	34 (26.4)	21 (29.2)
	NE	2 (1.6)	0
	No evaluable follow-up assessments	2 (1.6)	0

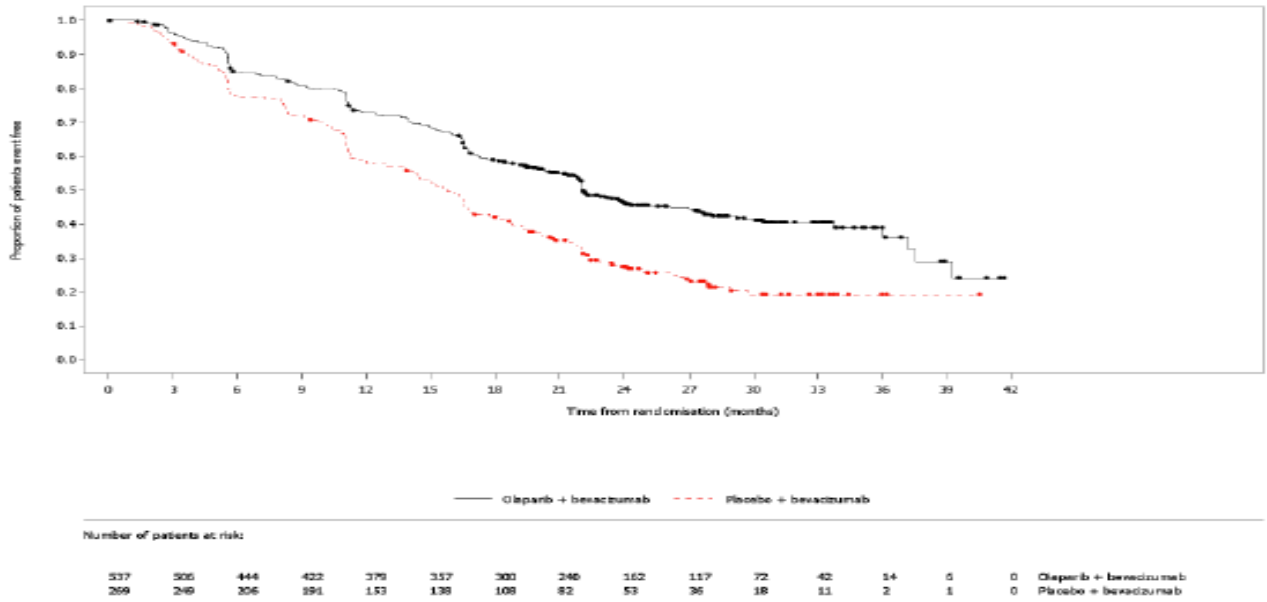
[a] Response did not require confirmation.
Patients with evidence of disease at baseline were considered evaluable for response.
This analysis is based on investigator RECIST assessment. Modified RECIST Version 1.1.
CR complete response; FAS Full Analysis Set; PR partial response; NE non evaluable; RECIST Response Evaluation Criteria in Solid Tumours.
Data derived from Table 14.2.8.3.1.

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

Table 22: Summary of time to earliest progression by modified RECIST 1.1, CA-125 or death (FAS) DCO 22 March 2019

	Olaparib/bevacizumab (N=537)	Placebo/bevacizumab (N=269)
n (%) of events[a]	287 (53.4)	198 (73.6)
Treatment effect		
Median (95% CI), months[b]	22.1 (21.4, 25.1)	15.8 (13.8, 16.8)
HR[c]	0.58	
95% CI[c]	0.48, 0.69	
2-sided p-value[d]	<0.0001	
Median follow-up, months[e]	24.2	24.4

[a] Time to event was defined as time from randomisation to time of earliest progression by modified RECIST 1.1, CA-125 or death.
[b] Calculated using KM techniques.
[c] Estimated from a stratified Cox proportional hazards model stratified by first line treatment outcome and *tBRCA* status.
[d] Determined using log-rank test stratified by first line treatment outcome and *tBRCA* status and not controlled for multiplicity.
[e] Time from randomisation to date of censoring.
BRCA breast cancer susceptibility gene; CA-125 cancer antigen-125; CI confidence interval; FAS Full Analysis Set; HR hazard ratio; KM Kaplan-Meier; RECIST Response Evaluation Criteria in Solid Tumours; *tBRCA* tumour *BRCA*.
Data derived from Table 14.2.7.1.



CA-125 cancer antigen-125; FAS Full Analysis Set; RECIST Response Evaluation Criteria in Solid Tumours.
Data derived from Figure 14.2.7.1.

Figure 13: Time to earliest progression by modified RECIST 1.1, CA-125 or death, Kaplan-Meier plot (FAS)

Health-related quality of life: EORTC QLQ-C30 and EORTC QLQ-OV28

Table 23: Change from baseline in QLQ-C30 global health status/QoL score, MMRM (FAS) (DCO 22 March 2019)

	Olaparib/bevacizumab (N=537)	Placebo/bevacizumab (N=269)
Average over 24 months		
n	446	229
Adjusted mean	0.13	-0.46
Standard error	0.583	0.824
95% CI	-1.020, 1.271	-2.078, 1.159
Estimated difference	0.59	
95% CI for difference	-1.399, 2.570	
p-value[a]	0.5626	

[a] Not adjusted for multiplicity.
Baseline was defined as the last evaluable assessment prior to dosing with olaparib or placebo.
The analysis was performed using an MMRM analysis of the change from baseline QLQ-C30 QoL score for all post-baseline visits (up to study treatment discontinuation) with treatment, visit and treatment by visit interaction included as explanatory variables and the baseline QLQ-C30 QoL score included as a covariate along with the baseline QLQ-C30 QoL score by visit interaction. Treatment, visit and treatment by visit interaction were fixed effects in the model, patient was included as a random effect.
CI confidence interval; FAS Full Analysis Set; MMRM mixed models for repeated measures;
QLQ-C30 quality of life questionnaire Core 30 item module; QoL quality of life.
Data derived from Table 14.2.9.1.

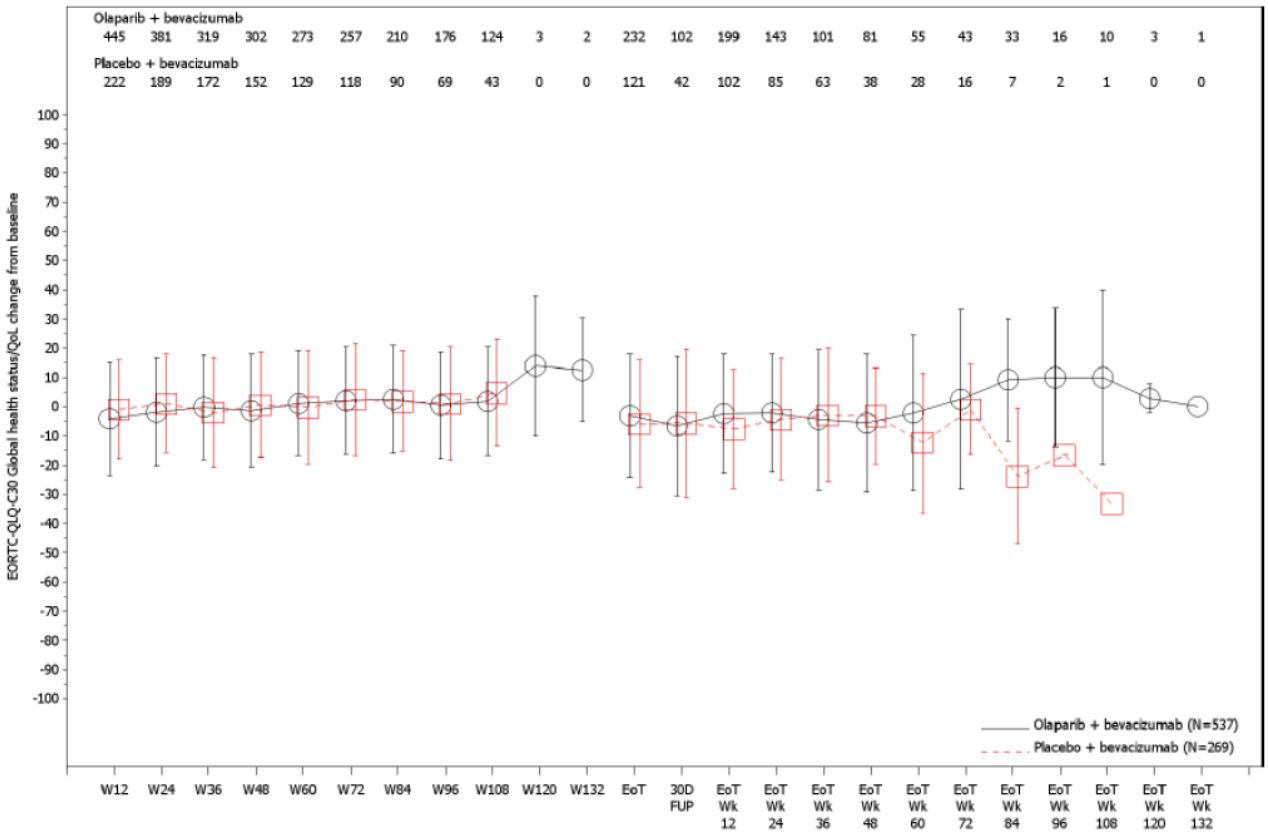


Figure 14: Mean (±SD) EORTC QLQ-C30 global health status/QoL score change from baseline across time points, by treatment group (FAS)

Ancillary analyses

Subsequent therapy

Of patients who received any subsequent therapy, PARP inhibitors were received by 49 (16.4%) of the 298 olaparib/bevacizumab-treated patients and 83 (43.0%) of the 193 placebo/bevacizumab-treated patients (DCO Sept 2019). Out of the 36 patients in the olaparib/bevacizumab arm who received a subsequent PARPi treatment, 34 patients receive it as maintenance treatment and 2 patients as a first subsequent treatment (DCO 22 March 2019).

Table 24: Summary of subsequent therapies received (FAS)

	Number of patients (%)					
	DCO 22 March 2019			DCO 30 September 2019		
	Olaparib/ bevacizumab n=537	Placebo/ bevacizumab n=269	Total n=806	Olaparib/ bevacizumab n=537	Placebo/ bevacizumab n=269	Total n=806
Received subsequent therapy	261 (48.6)	181 (67.3)	442 (54.8)	298 (55.5)	193 (71.7)	491 (60.9)
Type of subsequent therapy[a]						
Platinum chemotherapy	241 (44.9)	160 (59.5)	401 (49.8)	272 (50.7)	172 (63.9)	444 (55.1)
Non-platinum cytotoxic drug	253 (47.1)	175 (65.1)	428 (53.1)	289 (53.8)	188 (69.9)	477 (59.2)
Other	15 (2.8)	11 (4.1)	26 (3.2)	19 (3.5)	12 (4.5)	31 (3.8)
Targeted therapy	96 (17.9)	103 (38.3)	199 (24.7)	117 (21.8)	122 (45.4)	239 (29.7)
PARP inhibitor	36 (6.7)	65 (24.2)	101 (12.5)	49 (9.1)	83 (30.9)	132 (16.4)
Antiangiogenic	48 (8.9)	33 (12.3)	81 (10.0)	54 (10.1)	40 (14.9)	94 (11.7)
Number of subsequent regimes						
0	276 (51.4)	88 (32.7)	364 (45.2)	239 (44.5)	76 (28.3)	315 (39.1)
1	119 (22.2)	90 (33.5)	209 (25.9)	116 (21.6)	77 (28.6)	193 (23.9)
2	79 (14.7)	49 (18.2)	128 (15.9)	91 (16.9)	57 (21.2)	148 (18.4)
3	43 (8.0)	28 (10.4)	71 (8.8)	60 (11.2)	36 (13.4)	96 (11.9)
4	13 (2.4)	12 (4.5)	25 (3.1)	19 (3.5)	16 (5.9)	35 (4.3)
5	7 (1.3)	2 (0.7)	9 (1.1)	12 (2.2)	7 (2.6)	19 (2.4)

[a] According to the AstraZeneca medical review.
CSR = clinical study report; DCO = data cut-off; FAS = full analysis set; PARP = polyadenosine 5'diphosphoribose polymerase.

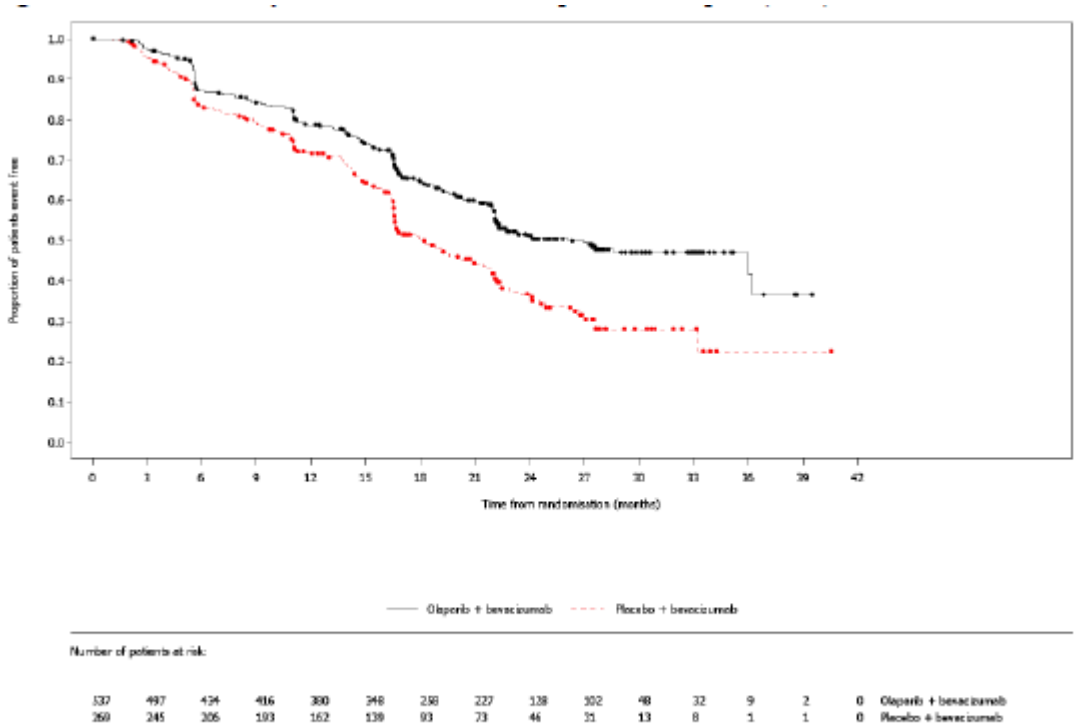
Sensitivity analyses

Table 25: Sensitivity analysis of progression-free survival (FAS, DCO 22 March 2019)

	Number of events:total number of patients (%)	Median PFS (months)	HR	95% CI
PFS by BICR	Olaparib/bev: 226:537 (42.1)	26.1	0.63	0.51, 0.77
	Placebo/bev: 146:269 (54.3)	18.3		
Evaluation time bias	Olaparib/bev: 280:537 (52.1)	20.5	0.59	0.49, 0.71
	Placebo/bev: 194:269 (72.1)	14.9		
Attrition bias	Olaparib/bev: 279:537 (52.0)	22.2	0.60	0.50, 0.72
	Placebo/bev: 189:269 (70.3)	16.6		
eCRF stratification variables	Olaparib/bev: 280:537 (52.1)	22.1	0.58	0.48, 0.70
	Placebo/bev: 194:269 (72.1)	16.6		
Informative censoring (using BICR)	Olaparib/bev: 293:537 (54.6)	22.1	0.61	0.51, 0.74
	Placebo/bev: 203:269 (75.5)	16.6		
Estimating HR using the stratified log rank test	Olaparib/bev: 280:537 (52.1)	22.1	0.57	0.47, 0.69
	Placebo/bev: 194:269 (72.1)	16.6		
Programmatically derived RECIST visit response (using investigator data)	Olaparib/bev: 285:537 (53.1)	22.1	0.60	0.50, 0.72
	Placebo/bev: 194:269 (72.1)	16.6		

	Number of events:total number of patients (%)	Median PFS (months)	HR	95% CI
Earliest of investigator/BICR assessment of progression	Olaparib/bev: 293:537 (54.6)	22.0	0.58	0.49, 0.70
	Placebo/bev: 203:269 (75.5)	16.0		
Deviation bias	Analysis not performed as ≤10% patients with specified deviations			

Bev= Bevacizumab; BICR Blinded Independent Central Review; *BRCA* Breast cancer susceptibility gene; CI Confidence interval; CSR Clinical study report; DCO Data cut-off; eCRF Electronic case report form; FAS Full Analysis Set; HR Hazard ratio; PFS Progression-free survival; RECIST Response Evaluation Criteria in Solid Tumours; *tBRCA* Tumour *BRCA.* Source: Table 14.2.1.3, Table 14.2.1.4, Table 14.2.1.5, Table 14.2.1.6, Table 14.2.1.7, Table 14.2.1.16, Table 14.2.1.17, Table 14.2.1.18 and Table 14.2.1.19, PAOLA-1 CSR, Module 5.3.5.1.



BICR blinded independent central review; FAS Full Analysis Set; PFS progression-free survival.
Data derived from Figure 14.2.1.6.

Figure 15: Progression-free survival by BICR, Kaplan-Meier plot (FAS) (DCO 22 March 2019)

Table 26: Disagreement between investigator and central reviews of RECIST progression (FAS) (DCO 22 March 2019)

	Number (%) of patients		Difference
	Olaparib/ bevacizumab (N=537)	Placebo/ bevacizumab (N=269)	Olaparib/ bevacizumab - Placebo/ bevacizumab
RECIST progression[a] declared by:			
Investigator and central review	213 (39.7)	137 (50.9)	NA
Progression date agreement (within 2 weeks)[b]	123 (57.7)	85 (62.0)	NA
Progression date ≥2 weeks earlier by central review than by investigator[b]	71 (33.3)	44 (32.1)	NA
Progression date ≥2 weeks earlier by investigator than by central review[b]	19 (8.9)	8 (5.8)	NA
Investigator but not central review	67 (12.5)	57 (21.2)	NA
Central review but not investigator	13 (2.4)	9 (3.3)	NA
No progression by both	244 (45.4)	66 (24.5)	NA
Early discrepancy rate[c]	0.31	0.34	-0.03
Late discrepancy rate[d]	0.49	0.45	0.04

[a] Progression events that occurred after 2 or more missed visits, were censored at the latest evaluable RECIST assessment, or Day 1 if there were no evaluable visits. Patients with a RECIST progression within 2 visits of baseline who did not have any evaluable visits or did not have a baseline assessment were censored at Day 1.

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

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

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

FAS Full Analysis Set; RECIST Response Evaluation Criteria in Solid Tumours.
Data derived from Table 14.2.1.12.

PFS subgroup analyses

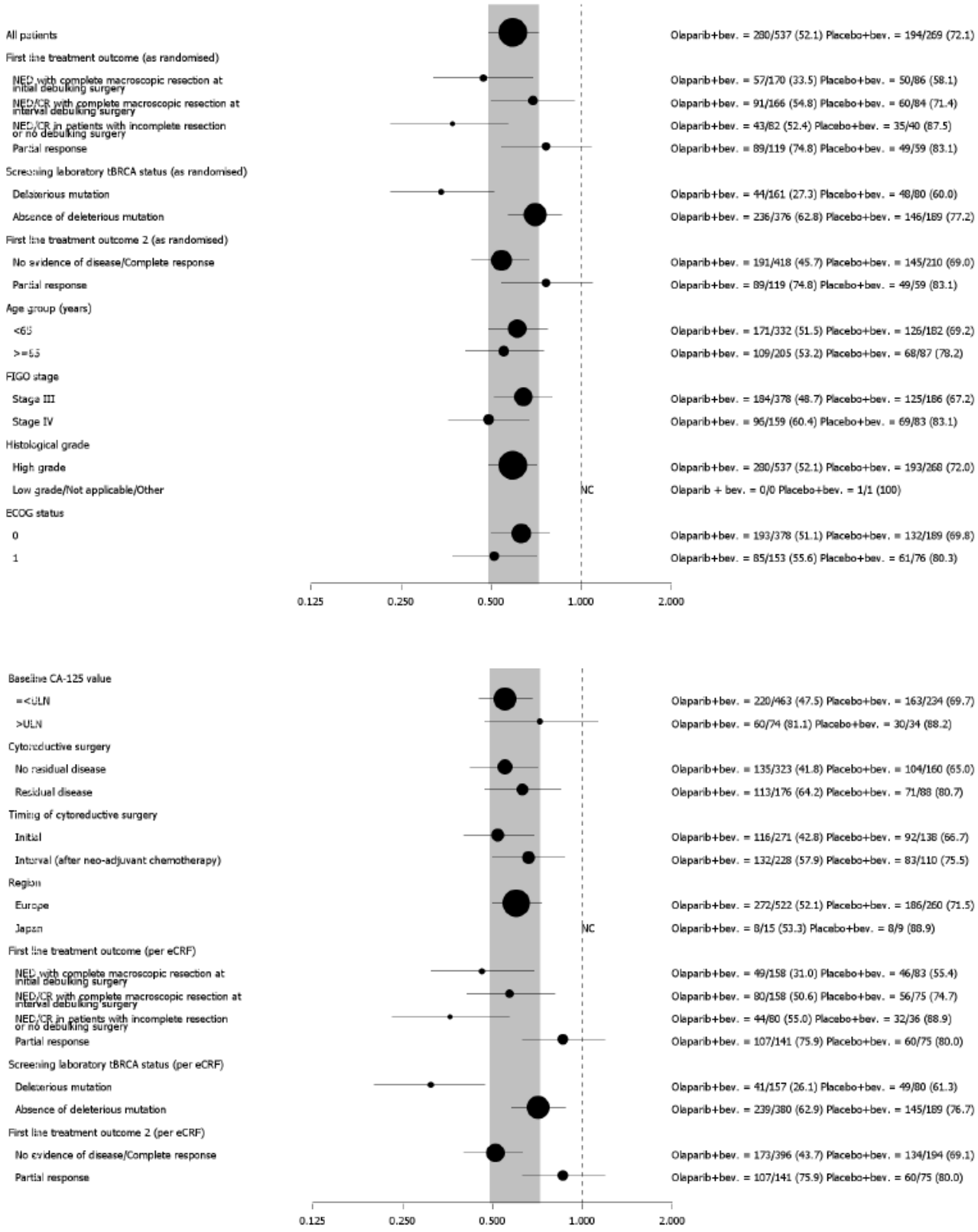


Figure 16: Forest plot of progression-free survival subgroup analysis (FAS), (DCO 22 March 2019)

Table 27: PFS subgroup analyses (FAS): Stratification factors (DCO 22 March 2019)

Subgroup	Olaparib/ bevacizumab (N=537)	Placebo/ bevacizumab (N=269)
First line treatment outcome at screening (as randomised)		
NED with complete macroscopic resection at initial debulking surgery		
Number of events/total number of patients (%)	57/170 (33.5)	50/86 (58.1)
Median PFS (months)	39.3	20.7
HR (95% CI)	**0.47 (0.32, 0.69)**	
NED/CR with complete macroscopic resection at interval debulking surgery		
Number of events/total number of patients (%)	91/166 (54.8)	60/84 (71.4)
Median PFS (months)	22.1	18.2
HR (95% CI)	**0.69 (0.50, 0.95)**	
NED/CR in patients with incomplete resection or no debulking surgery		
Number of events/total number of patients (%)	43/82 (52.4)	35/40 (87.5)
Median PFS (months)	21.8	12.3
HR (95% CI)	**0.37 (0.23, 0.57)**	
PR		
Number of events/total number of patients (%)	89/119 (74.8)	49/59 (83.1)
Median PFS (months)	16.4	11.2
HR (95% CI)	**0.76 (0.54, 1.08)**	
Screening *tBRCA* status (as randomised)		
Deleterious mutation		
Number of events/total number of patients (%)	44/161 (27.3)	48/80 (60.0)
Median PFS (months)	37.2	22.0
HR (95% CI)	**0.34 (0.23, 0.51)**	
Absence of deleterious mutation		
Number of events/total number of patients (%)	236/376 (62.8)	146/189 (77.2)
Median PFS (months)	18.9	16.0
HR (95% CI)	**0.70 (0.57, 0.86)**	
Screening *tBRCA* status (per eCRF)		
Deleterious mutation		
Number of events/total number of patients (%)	41/157 (26.1)	49/80 (61.3)
Median PFS (months)	37.2	21.7
HR (95% CI)	**0.31 (0.20, 0.47)**	
Absence of deleterious mutation		
Number of events/total number of patients (%)	239/380 (62.9)	145/189 (76.7)
Median PFS (months)	18.9	16.0
HR (95% CI)	**0.71 (0.58, 0.88)**	

CI Confidence interval; CR Complete response; CSR Clinical study report; DCO Data cut-off; FAS Full Analysis Set; HR Hazard ratio; NED No evidence of disease; PFS Progression-free survival; PR Partial response; *tBRCA* Tumour *BRCA*.

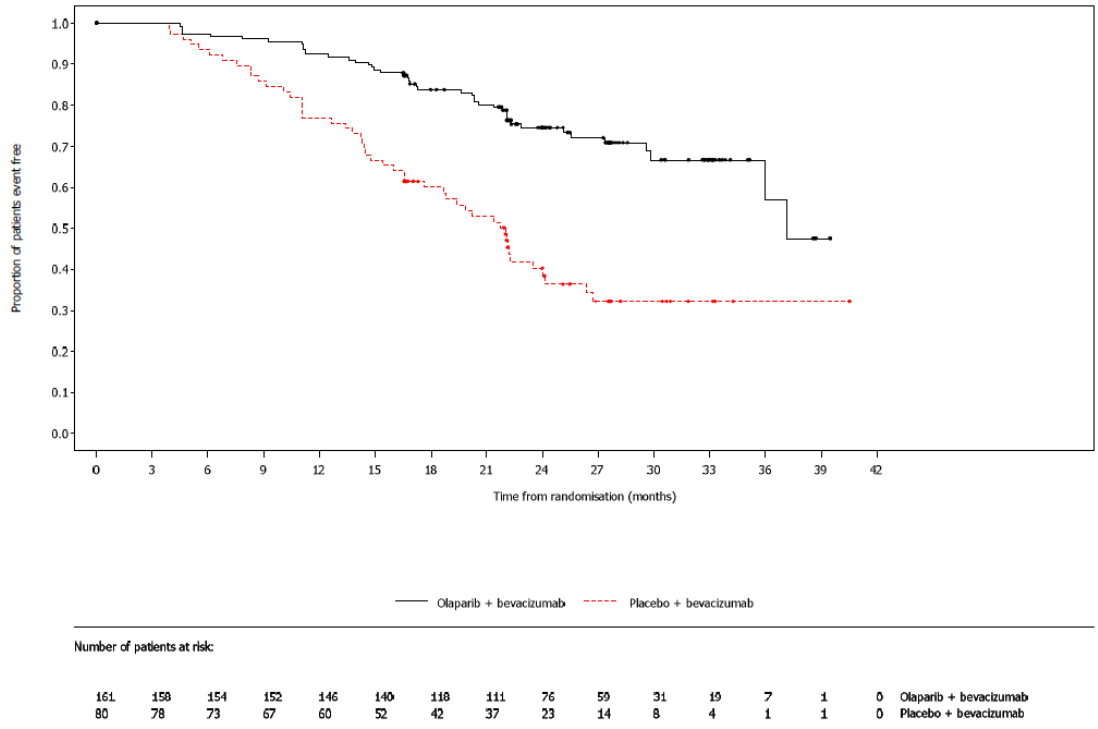
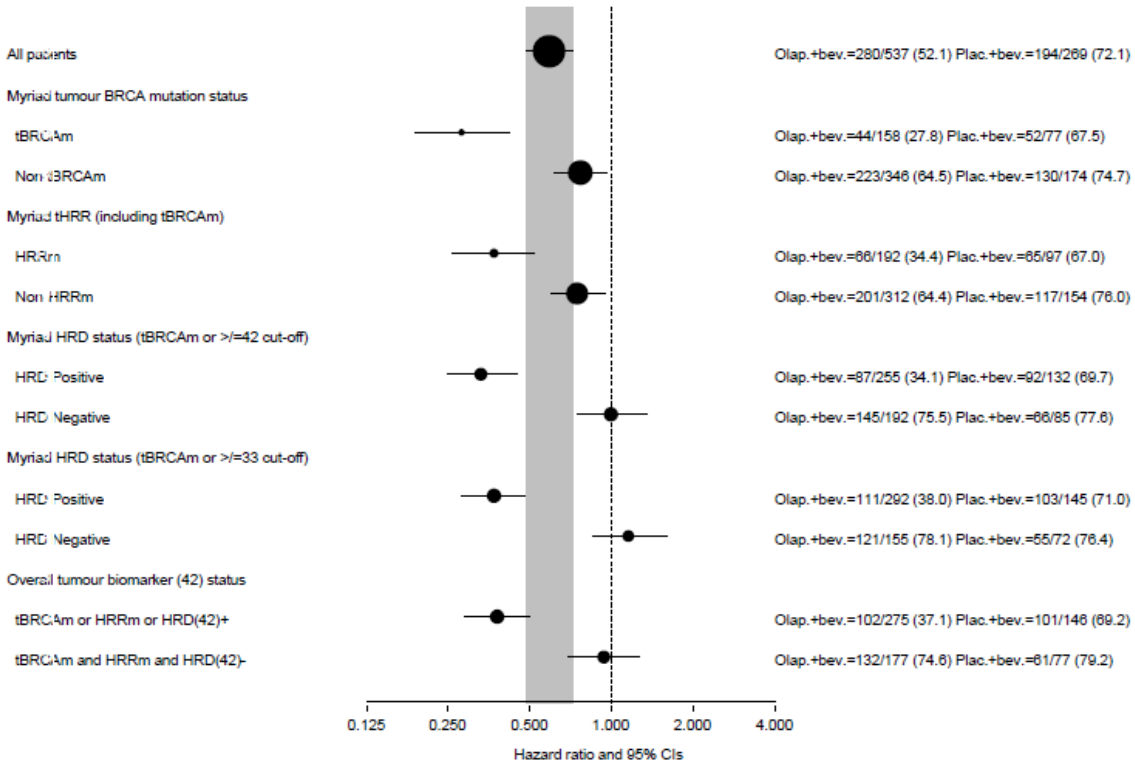


Figure 17: PAOLA-1: Kaplan-Meier plot of PFS for patients with tBRCAm (as randomised) (44% maturity - investigator assessment)

Other PFS exploratory biomarker subgroup analyses per Myriad myChoice HRD Plus



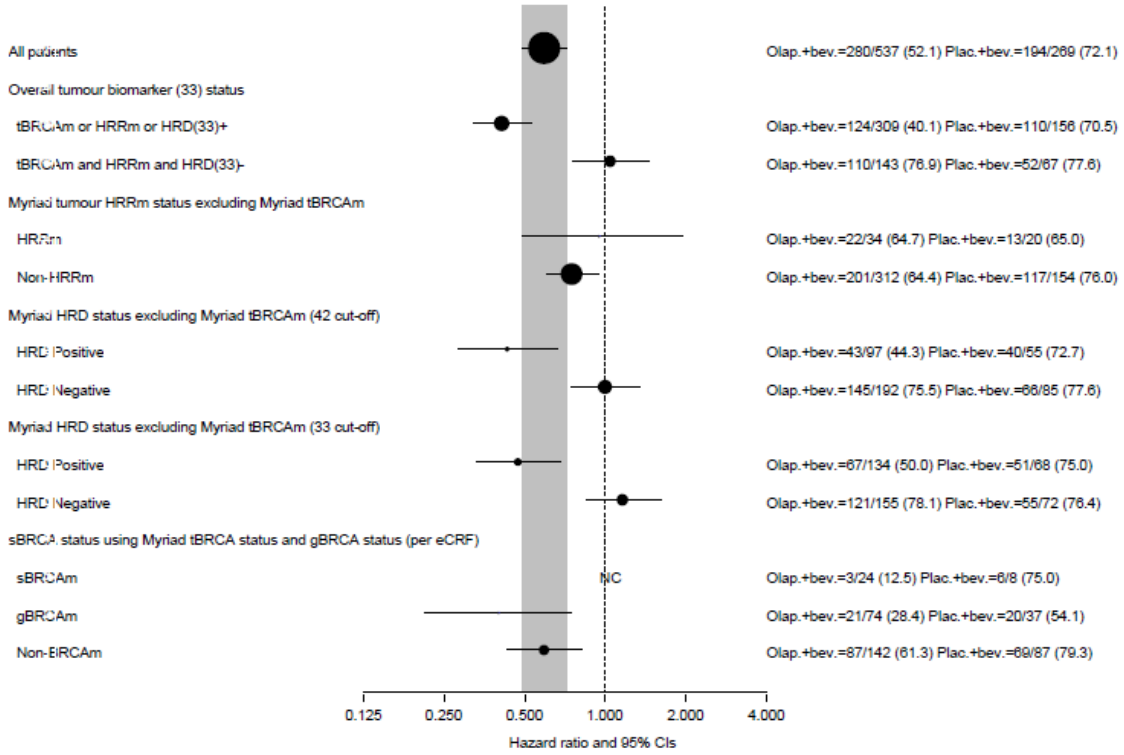


Figure 18 Forest plot of PFS subgroup analysis (FAS), (DCO 22 March 2019) Tumour characteristics as assessed by Myriad myChoice HRD Plus test

Subgroups in the figure and table below (tBRCAm, GIS positive, HRD positive) correspond respectively to subgroups 'Myriad tBRCAm', 'Myriad HRD positive excluding tBRCA' (with genomic instability score ≥42) and Myriad HRD status positive (with genomic instability score ≥42). Analyses only by GIS subgroups in the overall population are described in the section 'Post-hoc analyses in exploratory biomarker subgroups'.

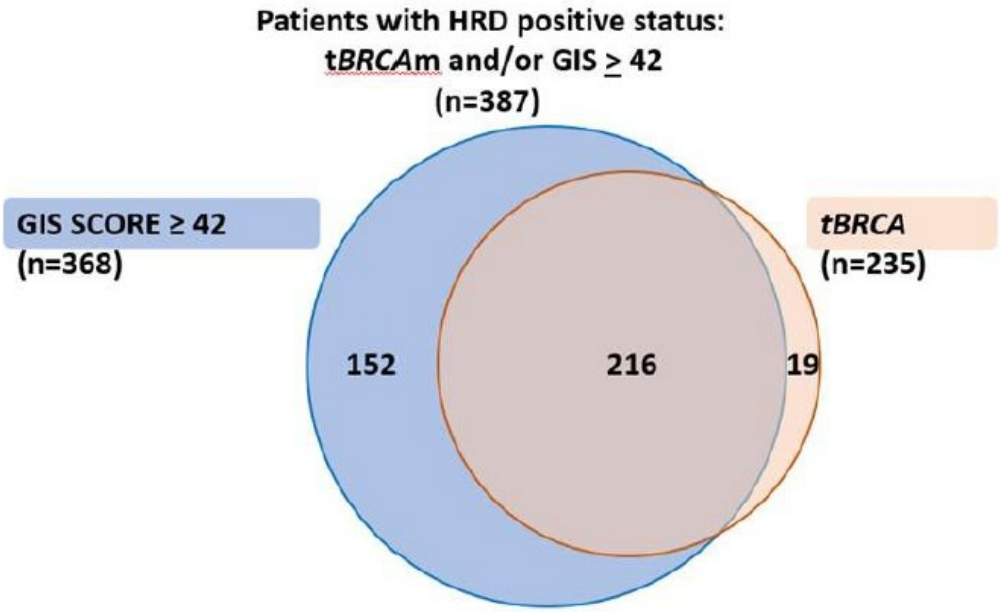


Figure 19 Overlap Between GIS positive (score≥ 42) and tBRCA Mutation positive Within HRD Positive Status (tBRCAm and/or GIS) group of patients in PAOLA-1

Table 28: PFS results for patients with homologous recombination deficiency (HRD) positive status defined by either tBRCAm and/or GIS in advanced ovarian cancer patients in PAOLA-1

	t*BRCAm, c (n=235)**		**GIS positive*, d (n=152)**		**HRD positive* (n=387)**	
	Olaparib/ bevacizumab	**Placebo/ bevacizumab**	**Olaparib/ bevacizumab**	**Placebo/ bevacizumab**	**Olaparib/ bevacizumab**	**Placebo/ bevacizumab**
PFS, investigator assessment (46% maturity) DCO 22 March 2019[a]						
Number of events: Total number of patients (%)	44/158 (28)	52/77 (68)	43/97 (44)	40/55 (73)	87/255 (34)	92/132 (70)
Median time (months)	37.2	18.8	28.1	16.6	37.2	17.7
HR (95%) CI[b]	0.28 (0.19, 0.42)		0.43 (0.28, 0.66)		0.33 (0.25, 0.45)	

* Pre-planned subgroup

[a] Based on Kaplan-Meier estimates, the proportion of patients that were progression free at 12 and 24 months were 89% and 66% for olaparib/bevacizumab versus 71% and 29% for placebo/bevacizumab.

[b] A value <1 favours olaparib. The analysis was performed using a Cox proportional hazards model stratified by first line treatment outcome at screening and screening laboratory t*BRCA* status.

[c] t*BRCA*m status by Myriad

[d] Genomic instability score (GIS) by Myriad ≥42 (pre-specified cut-off)

CI Confidence interval; HR Hazard ratio; NR not reached

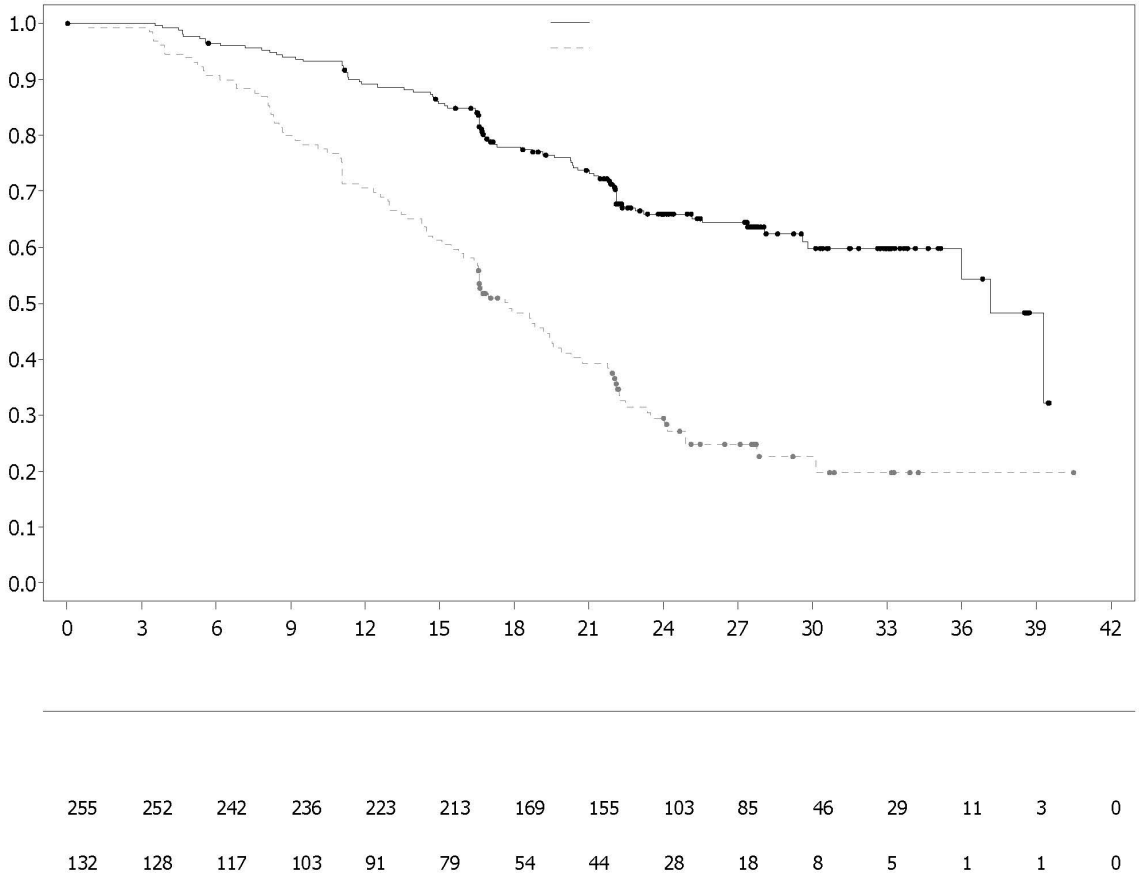


Figure 20: PAOLA-1: Kaplan-Meier plot of PFS for patients with advanced ovarian cancer defined as HRD positive in PAOLA-1 (46% maturity - investigator assessment)

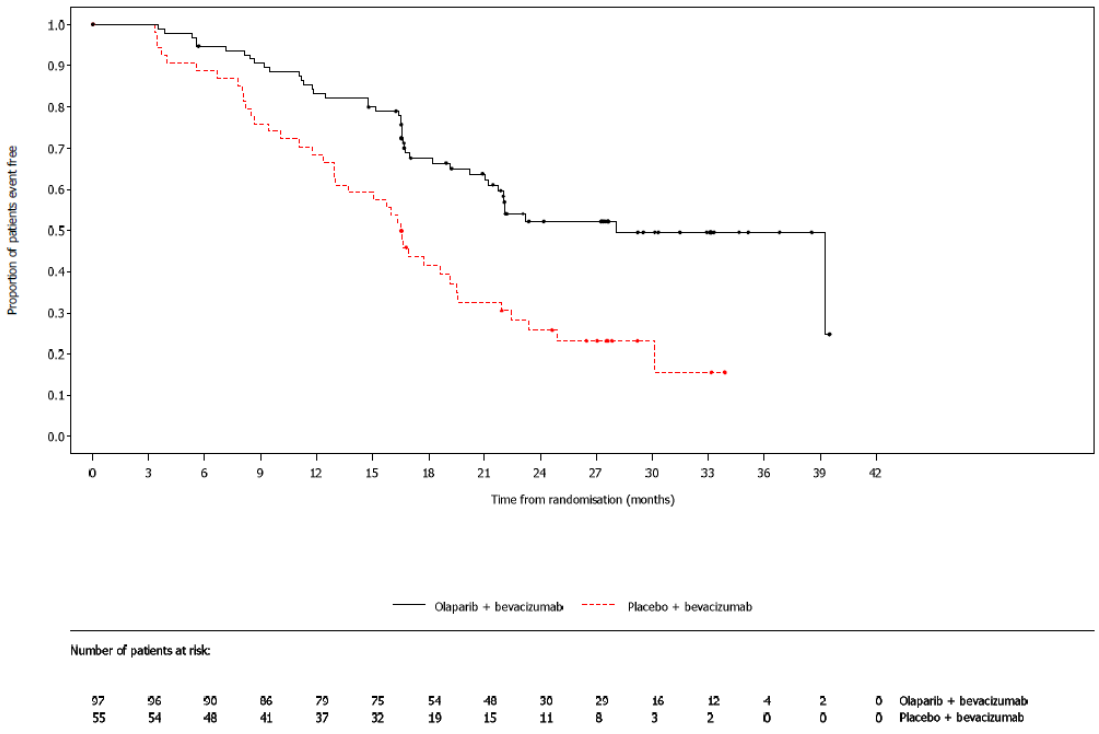


Figure 21: PAOLA-1: Kaplan-Meier plot of PFS for patients with advanced ovarian cancer defined as Myriad HRD positive excluding tBRCA in PAOLA-1

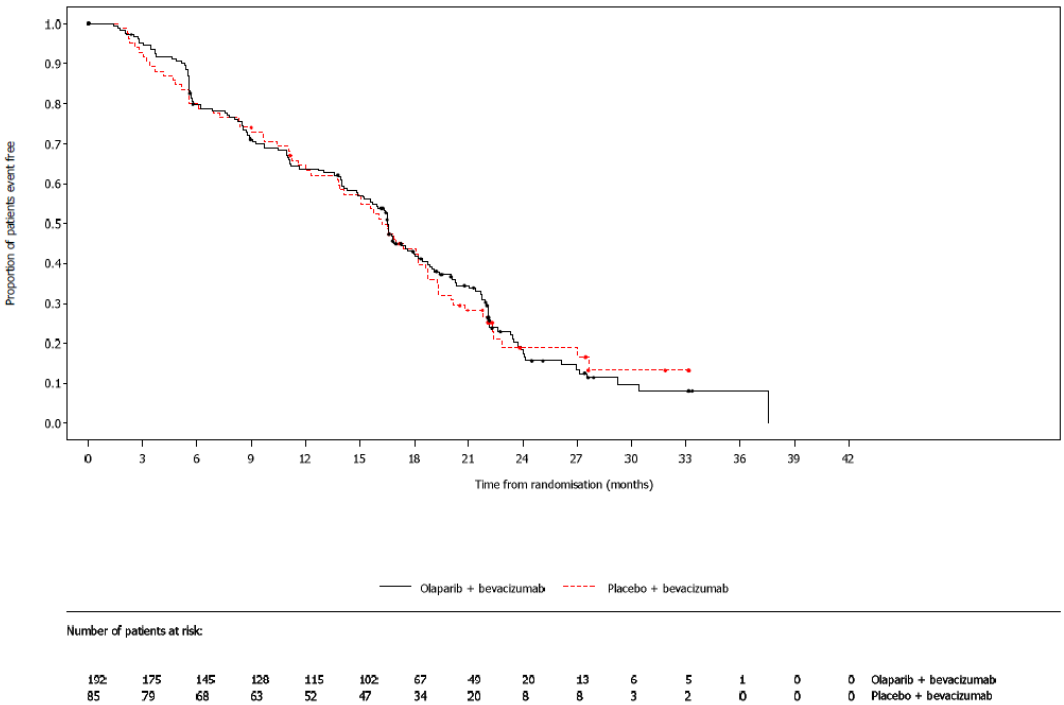


Figure 22: PAOLA-1: Kaplan-Meier plot of PFS for patients with advanced ovarian cancer defined as HRD negative in PAOLA-1

PFS-2 in exploratory biomarker subgroups

Table 29: PFS-2 results for patients with homologous recombination deficiency (HRD) positive status defined by either tBRCAm and/or GIS in advanced ovarian cancer patients in PAOLA-1

	t*BRCAm, c (n=235)**		**GIS positive*, d (n=152)**		**HRD positive* (n=387)**	
	Olaparib/ bevacizumab	**Placebo/ bevacizumab**	**Olaparib/ bevacizumab**	**Placebo/ bevacizumab**	**Olaparib/ bevacizumab**	**Placebo/ bevacizumab**
Interim PFS2, investigator assessment (30% maturity) DCO 22 March 2019						
Number of events: Total number of patients (%)	29/158 (18)	24/77 (31)	31/97 (32)	24/55 (44)	60/255 (24)	48/132 (36)
Median time (months)	NR	NR	37.8	28.6	NR	34.6
HR (95%) CI[b]	0.59 (0.34, 1.02)		0.64 (0.37, 1.10)		0.60 (0.41, 0.88)	

* Pre-planned subgroup

[b] A value <1 favours olaparib. The analysis was performed using a Cox proportional hazards model stratified by first line treatment outcome at screening and screening laboratory t*BRCA* status.
[c] t*BRCA*m status by Myriad
[d] Genomic instability score (GIS) by Myriad ≥42 (pre-specified cut-off)
CI Confidence interval; HR Hazard ratio; NR not reached

Overall survival in exploratory biomarker subgroups

Exploratory OS analyses in HRD subgroups as defined by the Myriad myChoice HRD plus assay were performed. OS analyses by subgroups have been pre-specified as such, but an update has been with DCO 30 September 2019, in addition to the analysis with primary endpoint analysis DCO, has been submitted during procedure. Analyses for main subgroups (tBRCAm at randomisation, tBRAm by Myriad analysis and HRD status as defined in PAOLA-1) are presented below.

Table 30: Updated OS analyses in exploratory subgroups (DCO 30 September 2019)

	Olaparib/ bevacizumab (N=537)	**Placebo/ bevacizumab (N=269)**
FAS (n=806) (31.3-33.8% maturity)		
HR (95% CI)	0.59 (0.49, 0.72)	
tBRCA status based on test at randomisation		
tBRCAm (n=241) (16.8-23.8% maturity)		
HR (95% CI)	0.66 (0.37, 1.21)	
Non-tBRCAm (n=565) (37.5-38.1% maturity)		
HR (95% CI)	1.02 (0.77, 1.36)	
Myriad tBRCA status		
tBRCAm (n=235) (17.1-26.0% maturity)		
HR (95% CI)	0.61 (0.34, 1.09)	
Non-tBRCAm (n=520) (37.9-39.9% maturity)		
HR (95% CI)	1.04 (0.77, 1.40)	
Myriad tBRCA test cancelled/failed/missing (n=51) (30.3-27.8% maturity)		
HR (95% CI)	1.02 (0.77, 1.36)	
Myriad HRD status (tBRCAm and/or GIS cut-off 42)		
HRD positive (tBRCAm or GIS ≥42) (n=387) (21.1-27.3% maturity)		
HR (95% CI)	0.71 (0.47, 1.10)	
HRD negative (GIS <42) (n=277) (43.2.1-43.5% maturity)		
HR (95% CI)	1.11 (0.76, 1.65)	
HRD status unknown (test cancelled/failed/missing) (n=142) (34.4-34.6% maturity)		
HR (95% CI)	1.03 (0.58, 1.88)	

[a] Non-tBRCAm = tBRCAwt/VUS
BRCA = breast cancer susceptibility gene; BRCAm = BRCA mutated; CI = confidence interval; CSR = clinical study report; DCO = data cut-off; FAS = full analysis set; HR = hazard ratio; HRD = homologous recombination deficiency; OS = overall survival; tBRCAm = tumour BRCA mutated.
Source: Table 14.2.3.2 PAOLA-1 CSR, Table 2160.1 (DCO 30 September 2019).

Subjects who are either lost to follow-up or who withdrew consent from further participation from the study were censored.

The KM plots for the HRD positive and HRD negative subgroups are shown in the Figures below.

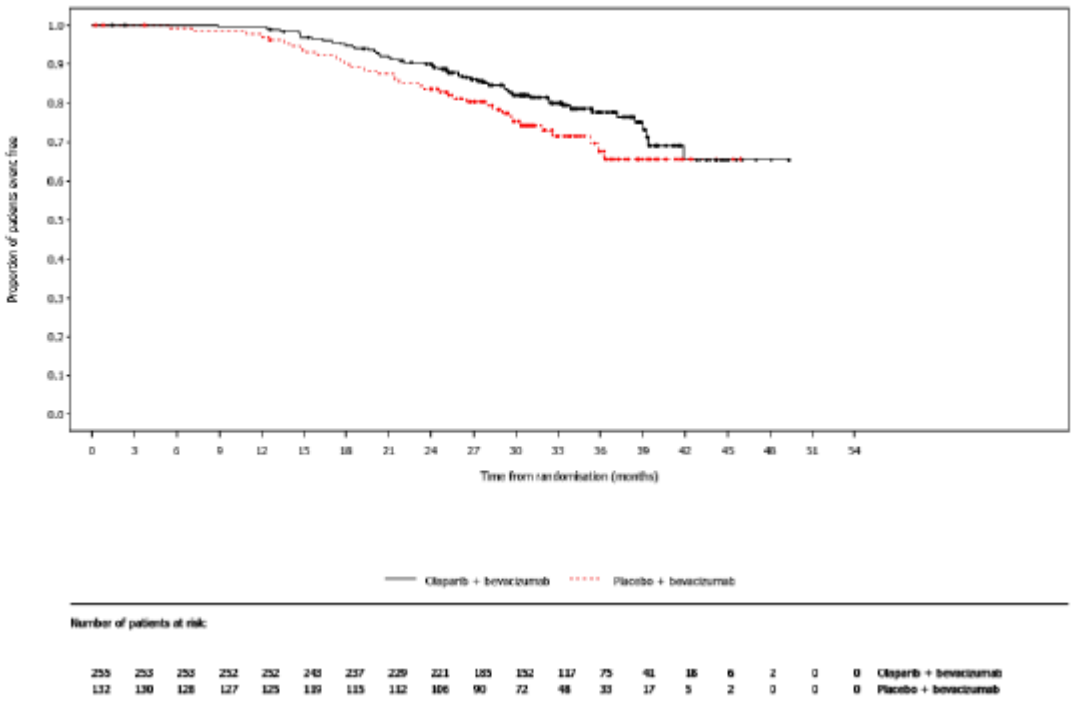


Figure 23: Overall survival, HRD positive subgroup (DCO 30 September 2019)

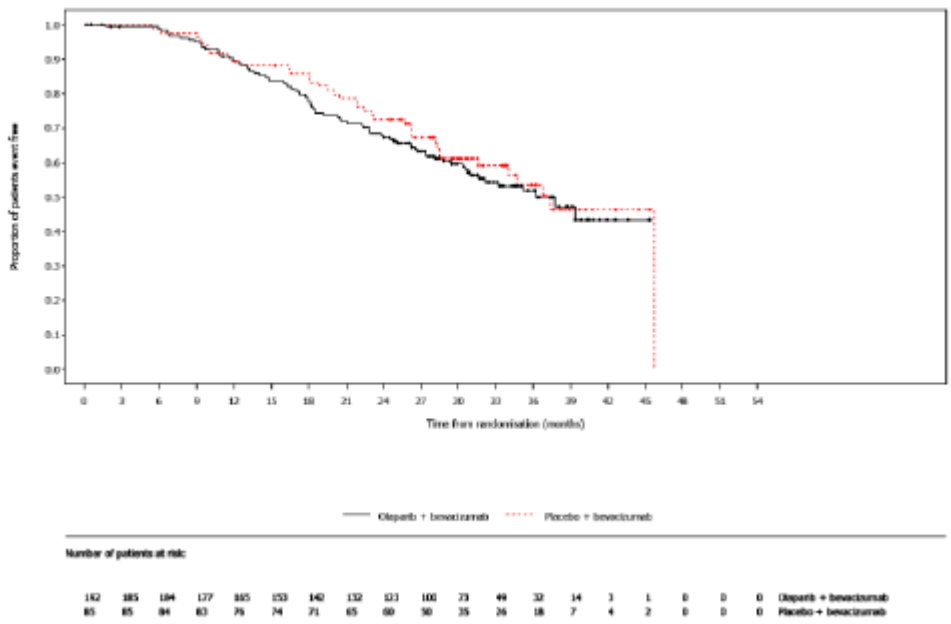


Figure 24: Overall survival, HRD negative subgroup (30 September 2019)

Table 31: OS results for patients with homologous recombination deficiency (HRD) positive status defined by either tBRCAm and/or GIS in advanced ovarian cancer patients in PAOLA-1

	t*BRCAm*[*, c] (n=235)		**GIS positive[*, d] (n=152)**		**HRD positive[*] (n=387)**	
	Olaparib/ bevacizumab	**Placebo/ bevacizumab**	**Olaparib/ bevacizumab**	**Placebo/ bevacizumab**	**Olaparib/ bevacizumab**	**Placebo/ bevacizumab**
Interim OS (23% maturity) DCO 30 September 2019						
Number of events: Total number of patients (%)	27/158 (17)	20/77 (26)	27/97 (28)	16/55 (29)	54/255 (21)	36/132 (27)
Median time (months)	NR	NR	NR	NR	NR	NR
HR (95%) CI[b]	0.61 (0.34, 1.09)		0.88 (0.48, 1.67)		0.71 (0.47, 1.10)	

* Pre-planned subgroup
[b] A value <1 favours olaparib. The analysis was performed using a Cox proportional hazards model stratified by first line treatment outcome at screening and screening laboratory t*BRCA* status.
[c] t*BRCA*m status by Myriad
[d] Genomic instability score (GIS) by Myriad ≥42 (pre-specified cut-off)
CI Confidence interval; HR Hazard ratio; NR not reached

Post-hoc analyses in exploratory biomarker subgroups

Analyses for GIS subgroups

Subgroups defined only by GIS have not been pre-specified and subgroup analyses in GIS positive (score ≥42), GIS negative (score <42) and unknown GIS subgroups has been requested during procedure.

At cut-off 42, the GIS positive subgroup contains 60 fewer patients than the HRD positive subgroup:

- 19 tBRCAm patients that had a GIS score <42 (these patients moved into the GIS score negative group)

- 41 tBRCAm patients that failed GIS score testing (these patients moved into the unknown group)

Table 32: Summary of Key Efficacy Outcome Variables Using Only GIS at Cut off 42

	myChoice® CDx GIS positive		myChoice® CDx GIS negative		myChoice® CDx GIS unknown [a]	
	Olaparib/ bevacizumab (n=216)	Placebo/ bevacizumab (n=111)	Olaparib/ bevacizumab (n=204)	Placebo/ bevacizumab (n=92)	Olaparib/ bevacizumab (n=117)	Placebo/ bevacizumab (n=66)
PFS (by investigator assessment)						
Number of events/total number of patients (%)	70/216 (32.4)	77/111 (69.4)	153/204 (75.0)	72/92 (78.3)	57/117 (54.7)	45/66 (68.2)
Median PFS (months)	39.3	16.7	16.6	16.6	24.0	16.0
HR (95% CI)	0.30 (0.22-0.42)		1.01 (0.76-1.34)		0.63 (0.43-0.94)	
PFS2						
Number of events/total number of patients (%)	46/216 (21.3)	40/111 (36.0)	89/158 (56.3)	38/73 (78.2)	43/117 (36.8)	28/66 (42.4)
Median PFS (months)	Not reached	34.6	22.5	26.4	32.3	35.1
HR (95% CI)	0.55 (0.36-0.84)		1.10 (0.79-1.55)		0.91 (0.57-1.47)	
Updated OS (DCO 30 September 2019)						
Number of events/total number of patients (%)	41/216 (19.0)	28/111 (25.2)	89/204 (43.6)	40/92 (43.5)	38/117 (32.5)	23/66 (34.8)
Median PFS (months)	Not reached	Not reached	37.8	36.8	Not reached	42.3
HR (95% CI)	0.69 (0.43-1.12)		1.13 (0.78-1.65)		0.93 (0.56-1.59)	

[a] Analyses presented for GIS unknown patients to cover the totality of the ITT.
CDx = companion diagnostic; CI = confidence interval; DCO = data cut-off; HR = hazard ratio; GIS = genomic instability score; ITT = intention-to-treat; PFS = progression-free survival; PFS2 = time from randomisation to second progression or death; OS = overall survival.

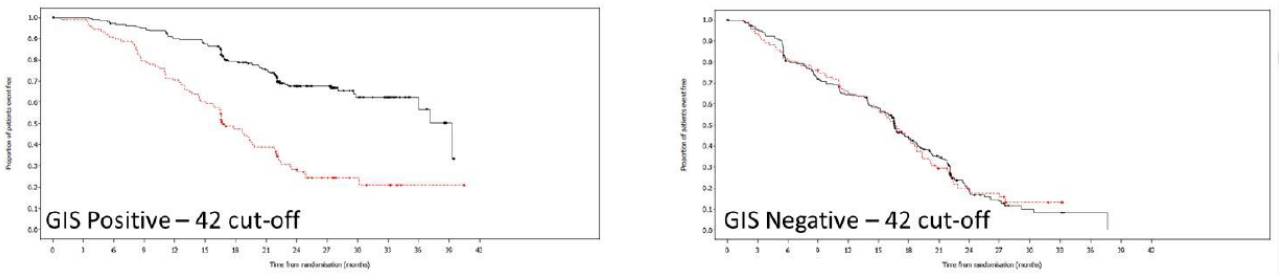


Figure 25: KM Plots for PFS at GIS Cut-offs 42 (DCO 22 March 2019)

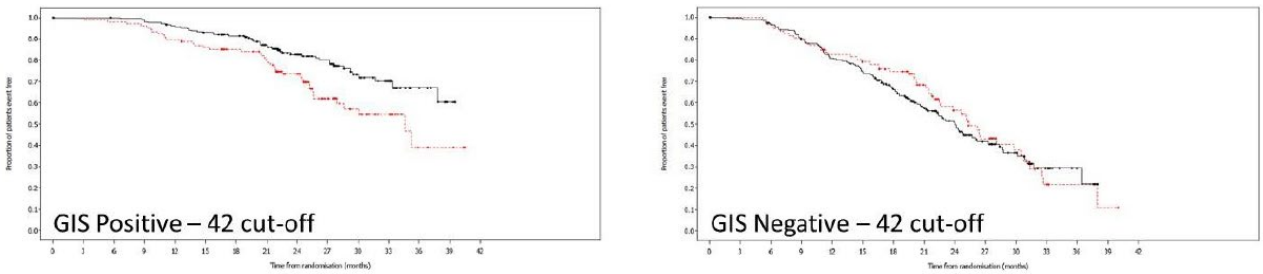


Figure 26: KM Plots for PFS2 at GIS Cut-offs 42 (DCO 22 March 2019)

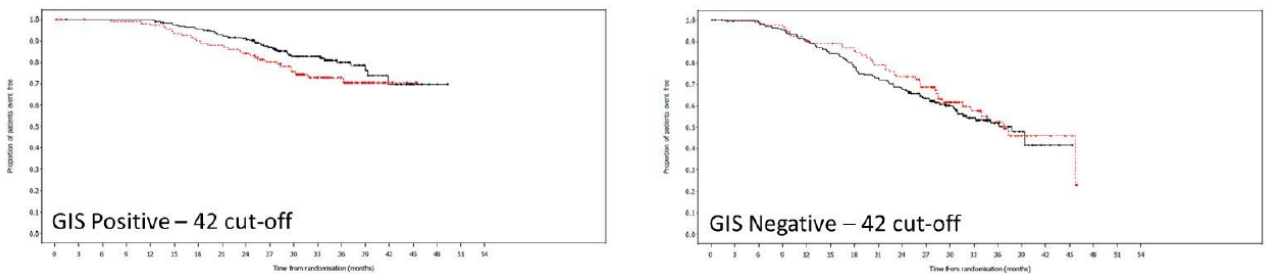


Figure 27: KM Plots for OS at GIS Cut-offs 42 (DCO 30 September 2019)

Baseline characteristics by Myriad HRD status

Table 33: **Baseline Patient characteristics by Myriad HRD status**

	FAS		HRD positive		HRD negative		HRD unknown	
	Olaparib/ bevacizumab (n=537)	Placebo/ bevacizumab (n=269)	Olaparib/ bevacizumab (n=255)	Placebo/ bevacizumab (n=132)	Olaparib/ bevacizumab (n=192)	Placebo/ bevacizumab (n=85)	Olaparib/ bevacizumab (n=90)	Placebo/ bevacizumab (n=52)
First line treatment outcome at screening (obtained from the eCRF)								
NED with complete macroscopic resection at initial debulking surgery	158 (29.4)	83 (30.9)	88 (34.5)	47 (35.6)	57 (29.7)	27 (31.8)	13 (14.4)	9 (17.3)
NED/CR with complete macroscopic resection at interval debulking surgery	158 (29.4)	75 (27.9)	75 (29.4)	32 (24.2)	36 (18.8)	18 (21.2)	47 (52.2)	25 (48.1)
NED/CR at screening, in patient who had either incomplete resection (at initial or interval debulking surgery) or no debulking surgery	80 (14.9)	36 (13.4)	39 (15.3)	18 (13.6)	35 (18.2)	14 (16.5)	6 (6.7)	4 (7.7)
Partial response	134 (25.0)	73 (27.1)	50 (19.6)	33 (25.0)	60 (31.3)	26 (30.6)	24 (26.7)	14 (26.9)
Not applicable as per eCRF[b]	7 (1.3)	2 (0.7)	3 (1.2)	2 (1.5)	4 (2.1)	0	0	0

[a] Stage III combined.

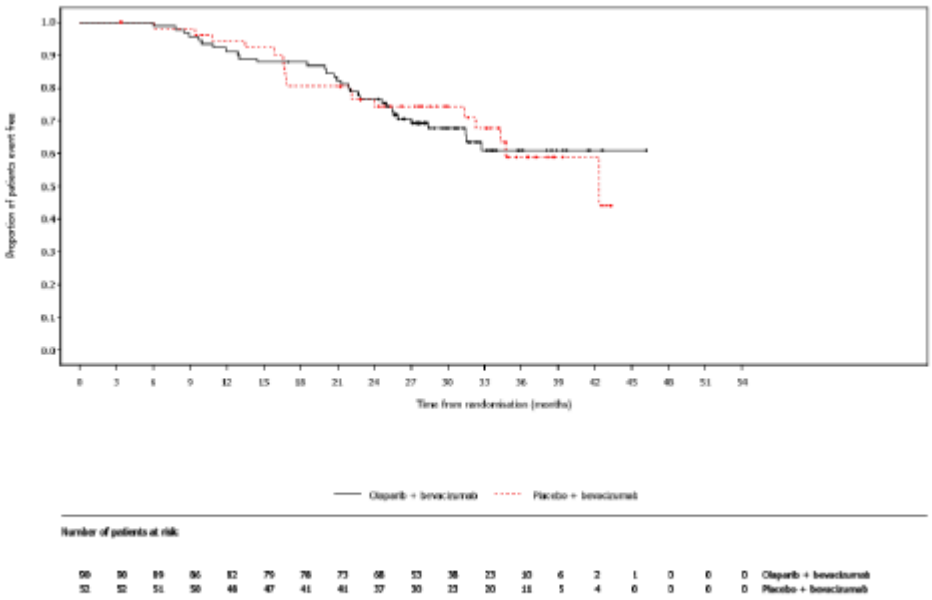
[b] Not applicable as unable to assign to one of detailed categories.

BRCA = breast cancer susceptibility gene; CR = complete response; CSR = clinical study report; ECOG = eastern cooperative oncology group; eCRF = electronic case report form; FAS = full analysis set; FIGO = international federation of gynaecology and obstetrics; HRD = homologous recombination deficiency; NED = no evidence of disease.
Source: Tables 14.1.8.1, 14.1.12.1, PAOLA-1 CSR; Table 1860.2, 1860.3 (DCO 22 March 2019).

Myriad HRD status "unknown" subgroup

Although not a protocol-specified subgroup, to account for the remaining patients in the FAS, a post-hoc analysis of OS was conducted in the subgroup of patients with Myriad HRD unknown status (see table with updated OS analysis at DCO 30 September 2019 above).

The HRD biomarker positive and negative subgroups considered the Myriad testing results only, and therefore the HRD unknown subgroup included a subset of patients that were tBRCAm by screening laboratory testing. In total, there were 21 Myriad HRD status unknown patients who were tBRCAm at randomisation with 9 (10%) on the olaparib arm and 12 (23.1%) on the placebo arm. The KM plot for the HRD unknown subgroup is shown in Figure below.



DCO = data cut off; HRD = homologous recombination deficiency.
Source: Figure 2181.8 (DCO 30 September 2019).

Figure 28: Overall Survival, HRD unknown subgroup (DCO 30 September 2019)

Subsequent therapies for HRD subgroups

Subsequent PARP inhibitor treatment was generally balanced within arms across the HRD positive, HRD negative, and HRD status unknown subgroups (

Table 34). Cross over to a PARP inhibitor in the placebo arm as subsequent treatment varied between 24.7% and 36.4%.

Table 34: Summary of subsequent therapies received by subgroup (DCO 30 September 2019)

Subgroup		Number of patients (%)		
HRD positive				
Subsequent Regimen	Category Type	Olaparib/ bevacizumab	Placebo/ bevacizumab	Total
		n=255	n=132	n=387
Any	Total	96 (37.6)	93 (70.5)	189 (48.8)
	Platinum chemotherapy	90 (35.3)	84 (63.6)	174 (45.0)
	Non-platinum cytotoxic drug	92 (36.1)	92 (69.7)	184 (47.5)
	PARP inhibitor	14 (5.5)	48 (36.4)	62 (16.0)
HRD negative				
		n=192	n=85	n=277
Any	Total	149 (77.6)	66 (77.6)	215 (77.6)
	Platinum chemotherapy	134 (69.8)	58 (68.2)	192 (69.3)
	Non-platinum cytotoxic drug	146 (76.0)	64 (75.3)	210 (75.8)
	PARP inhibitor	25 (13.0)	21 (24.7)	46 (16.6)
HRD unknown				
		n=90	n=52	n=142
Any	Total	53 (58.9)	34 (65.4)	87 (61.3)
	Platinum chemotherapy	48 (53.3)	30 (57.7)	78 (54.9)
	Non-platinum cytotoxic drug	51 (56.7)	32 (61.5)	83 (58.5)
	PARP inhibitor	10 (11.1)	14 (26.9)	24 (16.9)

[a] According to the AstraZeneca medical review.
DCO = data cut-off; HRD = homologous recombination deficiency; PARP = polyadenosine 5'diphosphoribose

Subgroup OS analysis by disease evaluation

Table 35: OS subgroup analyses by overall disease evaluation (DCO 30 September 2019)

Subgroup	Olaparib/ bevacizumab (N=537)	Placebo/ bevacizumab (N=269)
Overall Disease Evaluation (eCRF)		
NED		
Number of events/total number of patients (%)	60/290 (20.7)	38/141 (27.0)
Median OS (months) [a]	NR	45.7
HR (95% CI) [b]	0.76 (0.51,1.15)	
CR		
Number of events/total number of patients (%)	33/106 (31.1)	18/53 (34.0)
Median OS (months) [a]	NR	42.3
HR (95% CI) [b]	0.87 (0.50, 1.58)	
PR		
Number of events/total number of patients (%)	75/141 (53.2)	35/75 (46.7)
Median OS (months)[a]	31.6	36.8
HR (95% CI) [b]	1.23 (0.83, 1.86)	

[a] Calculated using KM techniques.
[b] Estimated from a Cox proportional hazards model including treatment, subgroup of interest and subgroup of interest by treatment interaction terms.
CI = confidence interval; CR = complete response; DCO = data cut-off; eCRF = electronic case report form; HR = hazard ratio; NED = no evidence of disease; OS = overall survival; PR = partial response.
Source: Table 2322.1.

Summary of main study(ies)

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 36: Summary of Efficacy for trial PAOLA-1

Title: A Randomized, Double-Blind, Phase III Trial of Olaparib vs. Placebo in Patients with Advanced FIGO Stage IIIB – IV High Grade Serous or Endometrioid Ovarian, Fallopian Tube, or Peritoneal Cancer treated with standard First Line Treatment, Combining Platinum-Taxane Chemotherapy and Bevacizumab Concurrent with Chemotherapy and in Maintenance.		
Study identifier	PAOLA-1 D0817C00003	
Design	Randomized, double-blind, phase III study, placebo controlled	
	Duration of main phase:	Until objective radiological disease progression, or up to 2 years if patient had NED.

	Duration of Extension phase:		Patients who in the opinion of the treating physician could derive further benefit from continuous treatment, could be treated beyond 2 years.
Hypothesis	Superiority		
Treatments groups	Olaparib/bevacizumab		Olaparib 300 mg BID 2 years, N=537 Bevacizumab 15mg/kg q3weeks, in the maintenance phase up to a total of 15 months.
	Placebo/bevacizumab		Pb 300 mg BID 2 years, N=269 Bevacizumab 15mg/kg q3weeks, in the maintenance phase up to a total of 15 months.
Endpoints and definitions	Primary endpoint	PFS	the time from randomisation until the date of objective radiological disease progression according to modified RECIST 1.1 or death (by any cause in the absence of progression) regardless of whether the patient discontinued randomised therapy or received another anticancer therapy prior to progression.
	Secondary endpoint	PFS2	time from the date of randomisation to the earliest of the progression event subsequent to that used for the primary variable PFS or death.
	Secondary endpoint	OS	time from the date of randomisation until death due to any cause.
	Secondary endpoint	TFST	time from randomisation to the earlier of first subsequent therapy start date following study treatment discontinuation, or death.
	Secondary endpoint	TSST	Time from randomisation to the earlier of the second subsequent therapy start date following study treatment discontinuation, or death.
	Secondary endpoint	TDT	Time from randomisation to study treatment discontinuation or death.
Database lock	22 March 2019; 30 September 2019 (OS analyses)		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat: FAS All patients who were randomized		
Descriptive statistics and estimate variability	Treatment group	Olaparib/bevacizumab	Placebo/bevacizumab
	Number of subject	537	269
	Median PFS (months)	22.1	16.6
	95% CI	21.8; 24.1	15.4; 18.6
	Median PFS2 (months)	32.3	30.1
	95% CI	29.2; 39.8	25.7; 32.6
	Median OS (months) 95% CI	NR	45.7 (37.4, NR)
	Median TFST 95% CI	24.8 23.4; 27.9	18.5 17.2; 20.1

	Median TSST 95% CI	33.8 31.6; NC	30.4 26.5; 33.9
	Median TDT 95% CI	17.4 16.3; 19.5	16.3 13.8; 17.3
Effect estimate per comparison	Primary endpoint PFS	Comparison groups	Olaparib vs placebo added to bevacizumab
		HR	0.59
		95% CI	0.49; 0.72
		P-value	<0.0001
	Secondary endpoint PFS2	Comparison groups	Olaparib vs placebo added to bevacizumab
		HR	0.86
		95% CI	0.69; 1.09
		P-value	0.2097
	Secondary endpoint OS	Comparison groups	Olaparib vs placebo added to bevacizumab
		HR	0.94
		95% CI	(0.73, 1.21)
		P-value	Not calculated
	Secondary endpoint TFST	Comparison groups	Olaparib vs placebo added to bevacizumab
		HR	0.58
		95% CI	0.48; 0.70
		P-value	<0.0001
	Secondary endpoint TSST	Comparison groups	Olaparib vs placebo added to bevacizumab
		HR	0.79
		95% CI	0.63; 1.00
		P-value	0.0444
	Secondary endpoint TDT	Comparison groups	Olaparib vs placebo added to bevacizumab
		HR	0.83
		95% CI	0.71; 0.98
		P-value	0.0232
Notes	NR: Not reached		

Analysis description	**Subgroup analysis**		
	PFS, investigator assessment (46% maturity) DCO 22 March 2019 [a]		
	tBRCAm by Myriad* (n= 235)	Olaparib/bevacizumab	Olaparib/placebo
	Number of events/total number of patients	44/158 (28)	52/77 (68)
	Median PFS (months)	37.2	18.8
	HR (95% CI)	0.28 (0.19, 0.42)	
	GIS positive* [b] (n=152)	Olaparib/bevacizumab	Olaparib/placebo
	Number of events/total number of patients	43/97 (44)	40/55 (73)
	Median PFS (months)	28.1	16.6
	HR (95% CI)	0.43 (0.28, 0.66)	
	HRD positive* (n=387)	Olaparib/bevacizumab	Olaparib/placebo
	Number of events/total number of patients	87/255 (34)	92/132 (70)
	Median PFS (months)	37.2	17.7

	HR (95% CI)	0.33 (0.25, 0.45)	
	Interim PFS2, investigator assessment (30% maturity) DCO 22 March 2019		
	tBRCAm by Myriad* (n= 235)	Olaparib/bevacizumab	Olaparib/placebo
	Number of events/total number of patients	29/158 (18)	24/77 (31)
	Median PFS (months)	NR	NR
	HR (95% CI)	0.59 (0.34, 1.02)	
	GIS positive* [b] (n=152)	Olaparib/bevacizumab	Olaparib/placebo
	Number of events/total number of patients	31/97 (32)	24/55 (44)
	Median PFS (months)	37.8	28.6
	HR (95% CI)	0.64 (0.37, 1.10)	
	HRD positive*	Olaparib/bevacizumab	Olaparib/placebo
	Number of events/total number of patients	60/255 (24)	48/132 (36)
	Median PFS (months)	NR	34.6
	HR (95% CI)	0.60 (0.41, 0.88)	
	Interim OS (23% maturity) DCO 30 September 2019		
	tBRCAm by Myriad* (n= 235)	Olaparib/bevacizumab	Olaparib/placebo
	Number of events/total number of patients	27/158 (17)	20/77 (26)
	Median PFS (months)	NR	NR
	HR (95% CI)	0.61 (0.34, 1.09)	
	GIS positive* [b] (n=152)	Olaparib/bevacizumab	Olaparib/placebo
	Number of events/total number of patients	27/97 (28)	16/55 (29)
	Median PFS (months)	NR	NR
	HR (95% CI)	0.88 (0.48, 1.67)	
	HRD positive*	Olaparib/bevacizumab	Olaparib/placebo
	Number of events/total number of patients	54/255 (21)	36/132 (27)
	Median PFS (months)	NR	NR
	HR (95% CI)	0.71 (0.47, 1.10)	

* Pre-planned subgroup; [b] Genomic instability score (GIS) by Myriad ≥42 (pre-specified cut-off)
Note: HRD positive status was defined in this study by a combination of both biomarkers; tBRCAm (prospectively and retrospectively defined), GIS.

In the tBRCAm as randomised subgroup (241/806 patients) median PFS for the olaparib/bevacizumab arm was 37.2 months vs 22.0 months for the placebo/bevacizumab arm (HR=0.34, 95% CI 0.23,0.51) and for OS the HR was 0.66 (95% CI 0.37, 1.21).

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

In support of the submitted application, the MAH provided the results of PAOLA-1 study which is an institutional sponsored, pivotal Phase III, randomised, double blind, placebo controlled, multicentre study investigating the efficacy and safety of olaparib vs placebo when added to bevacizumab as maintenance treatment for patients with newly diagnosed advanced (FIGO stage IIIB-IV) high-grade serous or endometrioid ovarian, fallopian tube, or primary peritoneal cancer who were in response following first line treatment with platinum-taxane chemotherapy and bevacizumab.

The study was designed to investigate a potential synergistic clinical benefit or at least additive benefit when combining bevacizumab (VEGF inhibitor) and olaparib (PARP inhibitor) in the maintenance setting in patients who are not selected by biomarker status.

No PK/PD modelling was performed in order to investigate the PK/PD relationship of olaparib and bevacizumab in the claimed indication. Empirically, the currently approved doses of each drug in solid tumours were implemented in the development of the combination (Study PAOLA-1).

Olaparib was approved on 12 June 2019 for maintenance treatment of newly diagnosed advanced BRCAm ovarian cancer patients (EPAR Lynparza). The results from SOLO1 demonstrated a substantial 70% reduction in risk of disease progression or death (HR 0.30; 95% CI 0.23 to 0.41; p<0.0001) with olaparib compared to placebo with an improvement in median PFS for olaparib over placebo estimated to be in the region of 3 years.

In a population not selected on the basis on BRCA mutations, according to the results from study GOG-218, a phase III multicentre, randomised, double-blind, placebo-controlled, three arm study evaluating the effect of adding bevacizumab to an approved chemotherapy regimen in patients with advanced ovarian cancer, a maintenance treatment with bevacizumab produced a significant benefit in PFS (15 months compared with 12 months without maintenance and with 11 months without bevacizumab at all (Avastin SmPC). Bevacizumab could not show a clear benefit for BRCAm patients. In the subgroup of patients with HRR mutations (n=228) the HR for PFS was 0.95 (95% CI 0.71-1.26) for bevacizumab + carboplatin/paclitaxel vs carboplatin/paclitaxel while the HR 0.71 (95% CI 0.60-0.85) in the subgroup of patients with no HRR mutation (n=581) (Norquist et al. 2018). In patients with BRCA mutations, HR was 0.82 (95% CI 0.55-1.21) and 1.10 (95% CI 0.61-2.0) in the BRCA1 (n=114) and BRCA2 subgroups (n=59) respectively.

Due to the absence of olaparib monotherapy arm and suboptimal stratification factor (tBRCAm) to distinguish patients with or without the sensitive degree of HRD, it remains currently unknown what is the contribution of components of such VEGFi-PARPi combination therapy in maintenance phase. Bevacizumab is indicated in the first-line maintenance setting only after prior concomitant treatment with platinum-based chemotherapy, whereas olaparib is indicated in first-line maintenance after platinum-based chemotherapy in the subgroup of BRCA1/2-mutated (germline and/or somatic) patients. Only, the contribution of olaparib could be assessed as add-on therapy to bevacizumab used in both arms concurrently with chemotherapy and in maintenance setting for the total duration of treatment up to 15 months.

Inclusion and exclusion criteria are overall considered acceptable. Nevertheless, they define a heterogeneous population as patients were included regardless of their HRD status (mutations in HRR genes/ HRD genomic scar/unknown Pt sensitivity status). There is *a priori* biological rational and evidence indicating that biomarkers associated with homologous recombination deficiency can be a plausible predictive factor of therapeutic response for olaparib in ovarian cancer, more particularly in the context of

first line maintenance treatment when, in contrast to relapsed setting, platinum sensitivity has not yet been established according to usually used criteria (Pt treatment-free-interval>6 months).

Eligible patients were those with newly diagnosed advanced (FIGO Stage IIIB, IIIC or IV) ovarian cancer, primary peritoneal cancer and/or fallopian tube cancer that was histologically confirmed as high-grade serous, or high-grade endometrioid, or other epithelial non mucinous ovarian cancer in a patient with gBRCA1 or 2 deleterious mutation. Prior to randomisation, patients must have had NED or be in CR or PR following first line treatment. There should have been no clinical evidence of disease progression (physical exam, imaging, or CA-125) throughout the first line treatment and prior to study randomisation. Any occurrence of discrepancy between investigator tumour assessment and BICR assessment at baseline in term of deviation from eligibility criteria (NED, CR and PR) and incorrect stratification by first line treatment outcome was requested to be discussed. The MAH argued that the eligibility criteria with regards to first line treatment outcome was assessed only by the investigator. The baseline overall response status was not a requirement for the BICR assessment. Patients were randomised at least 3 weeks and no more than 9 weeks after the last dose of chemotherapy and during this time bevacizumab could be continued as a single agent.

Bevacizumab was administered for up to 15 months/22 cycles in total (including the period of pre-randomisation given with chemotherapy and post-randomisation given with olaparib or placebo) in line with the SmPC recommendations (SmPC Avastin). Patients were to receive olaparib or placebo 300 mg BID for up to 2 years or until objective radiological disease progression or unacceptable toxicity in line with the recently approved recommendations in the SmPC for maintenance treatment in newly diagnosed advanced BRCAm ovarian cancer (SmPC Lynparza). Patients who in the opinion of the treating physician could derive further benefit from continuous treatment, could be treated beyond 2 years. Upon progression, patients were able to access PARP inhibitors including olaparib outside of the study. OS and PFS2 analysis are thus diluted by cross-over and multiple subsequent lines of therapy. This is likely to hamper comparisons in terms of OS and PFS2.

PFS by investigator is the primary endpoint in PAOLA-1 study, supported by PFS2, OS (adjusted for multiplicity), TFST, TSST, TDT, BOR, PRO as secondary endpoints. The assessment of PFS2 is considered crucial in this setting in order to assess any possible negative effect on next line therapy and to outbalance tolerability and toxicity concerns related to maintenance therapy.

The primary analysis of PFS was based on site or investigator assessment of scans according to modified RECIST 1.1 criteria. The study was double-blinded, but investigator bias cannot be ruled out due to the known toxicity profile of olaparib. A blinded independent central review (BICR) of progression data was thus conducted. Nevertheless, after investigators confirmed progression, no further scans were sent for central review. In this regard, bias due to informative censoring (patients had progressed according to investigator but not according to BICR) may be likely. PFS2 events were defined by investigator according to local standard clinical practice, without considering scheduled visits, and could involve radiological, CA-125 or symptomatic progression. The variability in the methods and frequency of tumour assessments between treatment arms and different centres were discussed. There is no impact on the reliability and the accuracy of results.

Sample size calculation was driven by number of PFS events. 762 patients were planned to be randomised (2:1 ratio) so that maturity of the PFS data was approximately 60%, considering a recruitment duration of 24 months and a 21-month follow-up for the last included patient (estimated total duration from first randomized patient to PFS1 assessment: 45months) and assuming a common exponential dropout rate of 1%. In addition, approximately 24 patients were to be randomised in Japan. The patients randomised in Japan were included in the FAS provided that there were no clinical data derived from the ongoing olaparib programme that suggested a different efficacy or safety profile for olaparib tablets in Japanese patients with high-grade epithelial ovarian cancer. It is noted that the sample size was increased by protocol

amendment (Version 4) from 612 to 762 patients. The assumption of treatment effect was reduced for the calculation of the new sample size (from HR of 0.7 to HR of 0.75).

Patients were randomized in a 2:1 ratio. The randomisation was stratified by 2 prognostic factors: first line treatment outcome including 4 strata (NED with complete resection at initial surgery, CR with complete resection at IDS, CR with incomplete resection or no surgery and PR) and local tBRCA status with 2 strata (deleterious mutation, and absence of deleterious mutation) at screening.

A multiple testing procedure was employed across PFS and key secondary endpoints (PFS2 and OS). An interim OS analysis was planned to be performed when statistical significance was shown for PFS and PFS2 (interim or final PFS2 analysis). Accordingly, only a descriptive OS interim analysis (25.9% maturity) was performed at the primary analysis of PFS (DCO 22 March 2019). An updated descriptive interim OS analysis (33% maturity) has been provided during procedure (DCO 30 September 2019).

Seven amendments to the original study protocol version were made. Most of the amendments and changes to the design of the study were for administrative or clarification purposes. In the protocol version 3, the amendment allowed patients having IDS to have only 2 cycles of bevacizumab in combination with the last 3 cycles of Platinum-based chemotherapy, in line with standard clinical practices for patients having IDS.

Under protocol amendment 6, additional PFS and OS subgroup analyses have been pre-specified, including analyses in biomarker-defined subgroups defined based on retrospective post-randomisation analysis of tumour tissue samples by Myriad myChoice HRD Plus test.

Important protocol deviations have been reported in 6% of patients. These were generally balanced between treatment arms (6.5% for the olaparib/bevacizumab arm and 4.8% for the placebo/bevacizumab arm) and no patient have had more than 1 important protocol deviation.

The applicant reported that the sponsor of the study, one CRO and 10 investigator centres (France 1 site, Germany 1 site, Italy 1 site and Japan 7 sites) were independently audited by a third party, on behalf of the MAH and no critical findings were identified across the five audits conducted. However, one outcome of the sponsor audit was that the process for assessing, documenting and managing protocol violations was not considered robust to ensure compliance with GCP and integrity of trial results. In fact, sponsor grading and assessment of the majority of protocol violations has not been completed (violations dated from 2015 and included violations to eligibility criteria, dispensing errors and incorrect randomisation). This was a serious concern that could have substantially affected the integrity and the robustness of the study data. Accordingly, a retrospective re-review and formal grading of all the protocol non-compliance prior to June 2018 has been undertaken. Feedback from the Sponsor with regards to the non-compliance review is that there are 20 additional major deviations. The number of patients with at least one major protocol deviations has thus increased from 6% to 8.4%. The newly identified major deviations are considered unlikely to have influenced the overall efficacy and safety conclusions of the study.

Efficacy data and additional analyses

Of the 1222 patients enrolled into the study, 416 patients were not randomised, with 324 patients not meeting the eligibility criteria; the most common reason being that patients had not received a minimum of 3 cycles of bevacizumab in combination with the 3 last cycles of platinum-based therapy. 806 patients were randomised in 137 study centres in 11 countries worldwide (97% in Europe and 3% in Japan). 24 patients were randomised in Japan centers and are included in the FAS. The DCO date for the primary analysis was 22 March 2019.

Of the 806 patients randomised into the study, 535 olaparib patients and 267 placebo patients received study treatment in addition to bevacizumab; 2 patients randomised to the olaparib/bevacizumab arm and

2 patients randomised to the placebo/bevacizumab arm did not receive olaparib or placebo. A higher proportion of patients in the olaparib/bevacizumab arm (27.7%) completed the protocol-specified 2 years of treatment than in the placebo/bevacizumab arm (19.9%). 61.9% patients in the olaparib/bevacizumab arm discontinued olaparib, and 72.7% patients in the placebo/bevacizumab arm discontinued placebo. The most common reason for discontinuation of olaparib or placebo was disease progression as per RECIST criteria; this was lower in the olaparib/bevacizumab arm (34.0%) than in the placebo/bevacizumab arm (58.1%). A higher proportion of patients discontinued olaparib due to AEs (20.4%) than placebo (4.9%). A similar and low proportion of patients in both arms discontinued olaparib or placebo for any other reason: for most of these patients in the olaparib/bevacizumab arm (13/19 patients) and all of the patients in the placebo bevacizumab arm (6/6 patients), the reason was patient decision.

Patients randomised were overall representative of the intended target population. Demographic and baseline characteristics were balanced between both arms in the ITT population and in the biomarker-defined sub-groups by t*BRCA*m (prospectively and retrospectively defined), GIS and HRD status (defined in this study by a combination of both biomarkers).

Median age overall was 61 years, which is consistent with the expected median age of an advanced ovarian cancer patient population not selected for gBRCA mutation. The majority of patients were FIGO Stage IIIC, had high-grade serous histology, and had an ECOG performance status of 0 across both treatment arms. 30% of patients were Stage IV. The majority of patients had normal CA-125 at study entry.

In total, 747 patients (92.7%) underwent debulking surgery prior to randomisation. The timing and outcome of debulking surgery was well balanced across both treatment arms. Stratification factors, as randomised or per eCRF (occurrence of some discrepancies), were well balanced between treatment arms.

All randomised patients had a prior platinum-based chemotherapy and bevacizumab regimen at baseline. The majority of patients had received between 4 and 9 cycles of platinum/taxane-based chemotherapy, with 62.8% of patients having received 6 cycles. All patients received a minimum of 5 cycles of platinum chemotherapy; 1 patient received >9 cycles of platinum chemotherapy. All patients had received a minimum of 2 cycles of bevacizumab prior to randomisation.

At study entry, approximately 29.4% of patients had local tBRCAm status and 70.6% of patients had non-BRCAm status (wild type or variant of uncertain significance or inconclusive/unknown status). Demographic and baseline characteristics in the biomarker sub-groups were consistent with those in the ITT population.

Post randomisation testing using the Myriad myChoice HRD Plus test was performed to determine Myriad tBRCAm status, HRRm status and Myriad HRD status. Genomic instability score (GIS) was also determined and considered with tBRCAm for determination of the positive Myriad HRD status (tBRCAm and/or positive GIS). In accordance with two GIS cut-offs (≥42 or ≥33), two different cut-offs (≥42 or ≥33) were used to assign HRD positive status in PAOLA-1 (Myriad HRD status 42 and 33 cut-offs). Myriad biomarker status was available for 97% of randomised patients (782/806 patients, for 24 patients no sample sent). 93.7% of patients (755/806 patients) had a Myriad tBRCA and HRR results available (for 27 patients test failed) and 82.4% (664/806 patients) had an available Myriad HRD status. The proportion of Myriad tBRCA mutations, HRR mutations and Myriad HRD status was well balanced between treatment arms. The overall agreement between screening tBRCA and Myriad tBRCA was 96.3% (701/728 patients). 29.2% of patients (235/806) were tBRCAm and 64.5% of patients (520/806) were non-tBRCAm by Myriad testing. Only a low proportion of patients (6.7% or 54/806) were Myriad HRRm excluding tBRCAm.

Using the Myriad HRD status 42 and 33 cut-offs, 48.0% and 54.2% of overall patient population, respectively, were considered Myriad HRD positive. In addition to tBRCAm patients within these groups, measuring of GIS by Myriad test allowed to include patients with positive GIS (≥42 or ≥33). Therefore, 18.9% of overall patient population were defined as Myriad HRD (42) positive excluding Myriad tBRCAm patients (also called 'GIS positive' within 'HRD positive' group) and 25.1% were Myriad HRD (33) positive excluding Myriad tBRCAm patients. Hence, biomarkers of homologous recombination deficiency (tBRCAm and HR-associated genomic instability) can both define HRD status, which in PAOLA-1 was defined as by combining both detection of tBRCAm and positive GIS, resulting in about half of patient population defined as HRD-positive.

Central gBRCA testing was performed only for patients at study sites in France. gBRCA status was available for half of the patients (404/806 [50.1%]). Of these, 120/404 (29.7%) patients were gBRCAm. The proportion of sBRCAm (8.6%) is in line with that expected in first line ovarian cancer.

All efficacy and HRQoL data were analysed using the FAS on an ITT basis (FAS=806).

Primary endpoint

The study met its primary objective. The investigator assessed PFS showed a statistically significant improvement in patients treated with olaparib compared with placebo when added to bevacizumab with a 41% reduction in the risk of disease progression or death (58.8% maturity, HR 0.59; 95%CI (0.49;0.72) p-value <0.0001). The median PFS showed a difference of 5.5 months favouring olaparib/bevacizumab arm (22.1 months vs 16.6 months). Based on KM analysis estimations, 46.0% of the patients in the olaparib/bevacizumab arm remained progression free at 2 years compared with 27.7% of the patients in the placebo/bevacizumab arm. The majority of patients in both arms progressed due to developing new lesions.

The results of the BICR PFS analysis were consistent with the primary analysis. The estimates of median PFS were longer by BICR than by investigator (26 vs 22 months, respectively, for olaparib/bevacizumab; 18.3 vs 16.6 months, respectively, for placebo/ bevacizumab). However, HR and p values were similar (HR = 0.63, 95% CI: 0.51–0.77; p <0.0001).

Overall, there was 82% concordance between investigator and central reviews in progression. Nevertheless, there was a difference in the rate of patients who had progressed by investigator but not according to BICR (67 patients (12.5%) in olaparib arm and 57 patients (21.2%) in placebo arm) between treatment arms (informative censoring). The potential impact of informative censoring was assessed through a sensitivity analysis based on BICR where informatively censored patients were assumed to have an event 24 weeks after time of censoring. Results were consistent with those of the investigator assessed PFS analysis.

Of note, differences in early discrepancy rate (-0.03) and late discrepancy rate (0.04) were observed between treatment arms. The negative discordance in EDR and positive discordance in LDR may indicate investigator bias in favour of olaparib/bevacizumab arm, however they did not reach the threshold of 0.075.

Evaluation-time bias analysis results for PFS were in line with those of the primary analysis. A descriptive analysis about compliance with scheduled evaluations by treatment arm was provided. The proportion of patients with at least one visit off-schedule was higher in the olaparib arm than in the placebo arm (difference of 9%). The MAH have provided a detailed analysis of the timing of RECIST assessments to explain this difference (data not shown). This is likely due to the fact that the number of assessments per patient in the olaparib arm was higher than on the placebo arm due to longer PFS (19% difference).
The MAH also provided a sensitivity analysis censoring patients who missed at least one RECIST assessment at the time of the latest evaluable RECIST assessment without previous missed visits (data not shown). Results were consistent with the primary analysis.

Secondary endpoints

At DCO of 22 March 2019, the investigator assessed PFS2 data were 39.1% mature (315 events/806 patients) with 63.5% of patients in the olaparib/bevacizumab arm vs 55.8% of patients in the placebo/bevacizumab arm not having had second progression. Median PFS2 was 32.3 months in the olaparib/bevacizumab arm and 30.1 months in the placebo/bevacizumab arm (HR=0.86 [0.69; 1.09], p-value=0.2). In both treatment arms, the majority of progression events were based on radiological assessment. Symptomatic progression and progression by CA-125 events were a minority. The interim analysis of PFS2 indicates a slightly better outcome, not statistically significant, favouring olaparib/ bevacizumab arm. Nevertheless, PFS2 analysis is considered immature, and results are not conclusive.

The interim OS analysis is considered extremely immature (209 events; 25.9% mature) with a similar proportion of patients in the olaparib/bevacizumab arm and in the placebo/bevacizumab arm (70.8% vs 71.4% respectively) in survival follow-up. The median OS was 39.4 months in the olaparib/bevacizumab arm and was not reached in the placebo/bevacizumab arm with a HR of 1.01 (95%CI 0.76, 1.36) p=0.9270. At the DCO of 30 September 2019, the updated OS analysis shows a HR of 0.94 (95% CI 0.73 to 1.21) in the ITT population.

PFS2 and OS were key secondary endpoints. The next planned analysis of PFS2 and OS was to be performed when the PFS2 data were approximately 53% mature (approximately 427 events) or after a maximum duration of one year post primary analysis PFS DCO, whichever occurs first. The DCO was set as 22 March 2020 which is one year post PFS analysis. The MAH is recommended to submit the updated data for PFS2 and OS estimated to be in December 2020 and the final OS data when available (planned in March 2022) (REC).

In the placebo/bevacizumab arm, 20.4% of patients received PARPi as a first subsequent therapy compared to 5.2% in the olaparib/bevacizumab arm. This may have a confounding effect on OS and PFS2 analysis. Additional analysis adjusting for impact of subsequent PARP inhibitor treatment will be provided with the updated and final analyses (REC).

No multiplicity adjustment was applied on secondary exploratory efficacy endpoints including TFST, TSST, and TDT. There was a delay in TFST in favour of olaparib/bevacizumab arm in line with the benefit observed in PFS (HR: 0.58, 95%CI: 0.48; 0.7, 2-sided p-value<0.0001). The median value was 24.8 months in the olaparib/bevacizumab arm compared with 18.5 months in the placebo/bevacizumab arm. The numerical improvement obtained in TSST and TDT is considered limited. The 95% interval confidence of median values overlapped. It should be noted that, at the beginning of the treatment (up to 9 months), there was a higher rate of treatment discontinuation in the olaparib/bevacizumab arm compared to placebo/bevacizumab.

The main endpoint for HRQoL analysis in the study was EORTC QLQ-C30. Overall, there was no meaningful difference between the treatment arms in average change over the 24-month treatment period in QLQ-C30 global health status/QoL score using MMRM (estimated difference: 0.59, 95% CI-1.399, 2.57, p=0.5626). Although PRO assessment was a secondary endpoint, there was no multiplicity adjustment and this analysis is considered as exploratory. Therefore, the inclusion of PRO data in the SmPC is not accepted.

Patients have been stratified by tBRCAm status, based on the prospectively conducted tumour tissue testing. As expected, the magnitude of treatment effect was notable in the subgroup of patients with deleterious BRCA1/2 mutations, with HR (95% CI) of 0.34 (0.23, 0.51) and clinically relevant difference in median PFS: 37.2 months and 22 months in olaparib/bevacizumab and placebo/bevacizumab arms, respectively. The extent of treatment effect was much lower in the non-tBRCAm patients compared to tBRCAm patients with median PFS of 19 months and 16 months (HR (95% CI) 0.7 (0.57, 0.86)) in olaparib/bevacizumab and placebo/bevacizumab arms respectively. The subgroup analysis by tBRCA status by Myriad was consistent with this analysis.

In the tBRCAm subgroup based on test result at randomisation, the OS HR point estimate was reported as 0.66 (95% CI 0.37 to 1.21), while in non-tBRCAm subgroup it was 1.02 (95% CI 0.77 to 1.36) (DCO 30 September 2019). In line with analysis in these prospectively defined subgroups, in exploratory subgroups by mutation status determined retrospectively by Myriad test, the OS HR point estimate was 0.61 (95% CI 0.34 to 1.09) in the Myriad tBRCAm subgroup while it was 1.04 (95% CI 0.77 to 1.4) in non-tBRCAm subgroup (DCO 30 September 2019).

Similarly, an inconsistency in treatment effect was observed in subgroup analysis based on retrospectively analysed samples to determine tumour Myriad HRD status combining tBRCAm status and HRD score (GIS, genomic instability score). This analysis is however pre-specified in the SAP. Patients were classified as having Myriad HRD positive or Myriad HRD negative tumours using a combination of positive or negative BRCAm status and Myriad GIS/HRD score (≥ 42/ 33 for positive, <42/33 for negative). For the remaining patients, such combined HRD status was considered unknown. A large differential benefit in PFS was observed in the following subgroups: (1) Subgroup of patients classified as Myriad HRD positive at two cut-offs 42 and 33 (either tBRCAm or GIS/HRD score ≥ cut-off). With the GIS score cut-off 42, HR was 0.33 [0.25, 0.45]; median PFS 37 months in olaparib vs 17 months in placebo arm; (2) Subgroup of patients classified as overall tumour biomarker status positive (patients identified by biomarkers associated with HRD: tBRCAm or HRRm or Myriad HRD (≥ 42 or 33) tumours): HR of 0.38 [0.29, 0.50].

However, absence of effect on PFS was reported in the following subgroups: (1) Subgroup of patients classified as Myriad HRD negative at two cut-offs (HRD score<cut-off in absence of tBRCAm): HR=1.00 [0.75; 1.35], median PFS 16.4 months in olaparib vs 16.5 months in placebo arm; (2) Subgroup of patients classified as overall tumour biomarker status negative (negative status for biomarkers associated with HRD: absence of tBRCAm and HRRm and Myriad HRD (≥ 42 or 33) tumours): HR of 0.94 [0.69, 1.27] median PFS 16.6 months in olaparib vs 16.2 months in placebo arm.

Consistently with data observed in patients without determined tBRCAm and supported by biological plausibility, the updated OS analysis do not allow to exclude a detrimental effect in the HRD-negative subgroup. In the 30 September 2019 DCO analysis, the OS HR point estimate was 0.71 (95% CI 0.47 to 1.10) in the HRD-positive subgroup and 1.11 (95% CI 0.76 to 1.65) in the HRD-negative subgroup. KM plots separate late in the HRD-negative subgroup in favour of bevacizumab/placebo arm. Though acknowledging limitations related to data immaturity, it cannot be excluded that treatment with the combination bevacizumab+olaparib in the first line setting in ovarian cancer patients whose tumours are defined as HRD-negative may be associated with poorer OS.

Post-hoc analyses using only the Genomic Instability Score (GIS)/HRD score at cut-off 42, have shown results in the GIS positive subgroup consistent to those in the HRD positive subgroup.

It is noted that a GIS or HRD test is not available to date in Europe and different cut-offs are used across different PARPi studies. However, a greater treatment effect was consistently observed across several trials using predefined cut-off for GIS (42) as used for Myriad HRD test. There is also a biological rational supporting genomic instability as a biomarker predicting magnitude of PARPi activity.

Overall, efficacy can only be considered established in patients identified as HR deficient based on biomarkers associated with HRD (BRCAm, HR deficiency-associated genomic instability and combination thereof). In patients without defined positivity for combined biomarker (HRD-negative patients), the overall efficacy data do not support that benefits outweigh risks. The indication has been restricted to patient population whose tumour are associated with HR deficiency defined by biomarkers (tBRCAm and/or genomic instability).

2.4.4. Conclusions on the clinical efficacy

PAOLA-1 met its primary objective, demonstrating a statistically significant improvement in PFS (HR 0.59 [0.49; 0.72] p<0.0001) in the ITT population for olaparib vs placebo when added to bevacizumab in the maintenance setting in patients with newly-diagnosed ovarian cancer who are not selected by HRD biomarker status. However, patients defined as biomarker-positive (t*BRCA*m, GIS, HRD status positive defined as t*BRCA*m and/or GIS positive) derived most of the benefit.

The magnitude of treatment effect was large in the subgroup of patients with deleterious BRCA1/2 mutations and higher genomic instability scores with pre-defined cut-off (HRD-positive), with HR (95% CI) of 0.33 (0.25, 0.45); with a clinically relevant difference in median PFS: 37.2 months vs 17 months in olaparib/bevacizumab and placebo/bevacizumab arms, respectively. However, the treatment effect was absent in the HRD-negative patients with median PFS of 16.4 months and 16.5 months in olaparib/bevacizumab and placebo/bevacizumab arms respectively (HR (95% CI) 1.00 [0.75; 1.35]). Furthermore, there is an indication of detrimental effect on OS, observed in subgroups without defined positivity for biomarkers associated with homologous recombination deficiency, including HR deficiency-associated genomic instability as a biomarker for predicting PARPi activity. It is noted that an HRD test is not available to date in Europe and different cut-offs are used across different PARPi studies for genomic instability score. However, a greater treatment effect in BRCAm and HRD-positive patients, was consistently observed across these trials using Myriad HRD test when considering a pre-defined cut-off (42).

Overall, efficacy can only be considered established in patients whose cancer is associated with HR deficiency defined by biomarkers (tBRCAm and/or genomic instability) and identified as biomarker-positive.

Data for PFS2 and OS are still immature with no clear benefit reported in interim analysis. The MAH is recommended to provide updated and final analyses as soon as available (REC).

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 PAOLA-1 study, where olaparib 300 mg (or placebo) bd was given in addition to bevacizumab as a maintenance treatment for patients with newly-diagnosed advanced (FIGO Stage IIIB-IV) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer and were in response following first line treatment, with platinum-taxane chemotherapy and bevacizumab.

Supportive safety data were provided from a pool of patients who were intended to receive olaparib 300 mg bd as a monotherapy in the MAH-sponsored studies.

Table 37: Number of patients in the 300 mg bd pool (as of DCO 15 June 2019)

Study/pooled dataset	Number of patients intended for the 300 mg bd cohort and received olaparib (all tumour types)
Total exposed	**1585**
D0818C00001 (SOLO1): Phase III FIGO Stage III-IV ovarian cancer SOLO1 China cohort[a]	260 40
D0816C00002 (SOLO2): Phase III platinum-sensitive serous ovarian cancer SOLO2: China cohort[a]	195 22
Study D0816C00010 (SOLO3): Phase III *gBRCAm* ≥third line ovarian cancer patients	178
D0819C00003 (OlympiAD): Phase III HER2-negative breast cancer patients with *gBRCA1/2* mutation	205
Study D081DC00007 (PROfound): Phase III HRRm metastatic castration-resistant prostate cancer (mCRPC)	256
Study D081FC00001 (POLO): Phase III *gBRCAm* metastatic pancreatic adenocarcinoma patients whose disease has not progressed on first-line platinum-based chemotherapy.	91
Study 24: Phase I Relative Bioavailability (300 mg tablet bd patients only, Groups 4 and 6)	24
Study 04: Phase I Food interaction & QT	57
Study 06: Phase I Renal impairment study	43
Study 07: Phase I CYP3A4 inhibition and QT	56
Study 08: Phase I CYP induction	19
Study D081CC00001: Phase I anti-hormonal PK study	69
Study D081BC00001: Phase I Japan Monotherapy study	19
D0816C00005: Phase I hepatic impairment study	31
D081BC00002: China PK study	20

[a] The patients in the China cohorts of SOLO1 and SOLO2 were reported separately to the main CSRs for these studies.

Patient exposure

Overall extent of exposure: PAOLA-1

All except 4 of the 806 randomised patients in PAOLA-1 received study treatment (2 patients in the olaparib/bevacizumab arm and 2 patients in the placebo/bevacizumab arm). At the DCO, the majority of

patients in the safety analysis set (SAS) had discontinued olaparib or placebo treatment (331 [61.9%] of 535 olaparib/bevacizumab-treated patients and 194 [72.7%] of 267 placebo/bevacizumab-treated patients). It should be noted that study treatment discontinuation reasons were only collected for olaparib or placebo and not for bevacizumab.

As per protocol, olaparib or placebo treatment was stopped after 2 years of exposure. The proportion of patients who had completed the maximum 2 year treatment period was higher in the olaparib/bevacizumab arm (148 [27.7%] of 535 patients) compared with the placebo/bevacizumab arm (53 [19.9%] of 267 patients). At the time of DCO, 56 (10.5%) patients in the olaparib/bevacizumab arm and 20 (7.5%) patients in the placebo/bevacizumab arm remained on (olaparib or placebo) study treatment.

The most common reason for discontinuation in both treatment arms was disease progression, although the proportion of patients discontinuing due to disease progression was lower in the olaparib/bevacizumab arm (182 [34.0%] of 535 patients) compared with the placebo/bevacizumab arm (155 [58.1%] of 267 patients).

A higher proportion of patients in the olaparib/bevacizumab arm had discontinued for an AE, compared with the placebo/bevacizumab arm (109 [20.4%] of 535 patients versus 153 [5.6%] of 267 patients, respectively).

Table 38: PAOLA-1: overall extend of olaparib or placebo exposure (SAS)

Month (approximate)	Number (%) of patients	
	Overall study duration	
	Olaparib/ bevacizumab N=535	Placebo/ bevacizumab N=267
≥Day 1	535 (100)	267 (100)
≥1 month (30.4 days)	506 (94.6)	265 (99.3)
≥3 months (91.3 days)	467 (87.3)	246 (92.1)
≥6 months (182.6 days)	415 (77.6)	219 (82.0)
≥9 months (273.9 days)	362 (67.7)	196 (73.4)
≥12 months (365.3 days)	331 (61.9)	165 (61.8)
≥18 months (547.9 days)	259 (48.4)	110 (41.2)
≥24 months (730.5 days)	109 (20.4)	37 (13.9)
≥25 months	11 (2.1)	2 (0.7)
≥30 months	2 (0.4)	0
≥33 months	1 (0.2)	0

Table 39: PAOLA-1: duration of olaparib or placebo exposure (SAS)

	Number (%) of patients					
	Overall study duration		Combination treatment phase only		Post combination treatment phase	
	Olaparib/ bevacizumab N=535	Placebo/ bevacizumab N=267	Olaparib/ bevacizumab N=534	Placebo/ bevacizumab N=267	Olaparib N=388	Placebo N=214
Total treatment duration (months)[a]						
Mean (Std)	15.2 (8.7)	14.9 (7.6)	9.1 (4.1)	9.5 (3.7)	8.5 (5.2)	6.8 (5.4)
Median (range)	17.3 (0.0 – 33.0)	15.6 (0.1 – 26.2)	10.6 (0.3 – 20.2)	10.6 (0.7 – 17.1)	9.9 (0.0 – 20.5)	6.6 (0.0 – 23.0)
Total treatment days	8144.7	3981.3	4882.0	2543.9	3288.8	1448.2
Actual treatment duration (months)[b]						
Mean (Std)	14.6 (8.6)	14.7 (7.6)	8.7 (4.1)	9.4 (3.7)	8.3 (5.1)	6.7 (5.3)
Median (range)	16.8 (0.0 – 32.1)	15.0 (0.1 – 26.2)	10.2 (0.3 – 20.1)	10.4 (0.5 – 17.1)	9.6 (0.0 – 20.5)	6.6 (0.0 – 22.7)
Total treatment days	7815.6	3924.9	4647.9	2509.8	3201.3	1424.9

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.

For patients who were able to stay on treatment (i.e., did not discontinue due to progression or other reasons), the majority received the 300 mg bd dose (throughout the duration of the study). For the majority of patients in the olaparib/bevacizumab treatment arm, olaparib dose reductions were not required (first dose reduction was to 250 mg bd [i.e., 500 mg total daily dose]; second dose reduction was to 200 mg bd [i.e., 400 mg total daily dose]) with AEs in most patients being managed through dose interruptions. The majority of dose reductions occurred in the first 3 months of treatment.

Table 40: PAOLA-1: dose reductions of olaparib by time period (SAS)

	Number (%) of patients by time period				
	Up to 3 months (N=535)	>3 to ≤6 months (N=460)	>6 to ≤9 months (N=402)	>9 to ≤12 months (N=356)	>12 months (N=324)
First dose reduction	183 (34.2)	40 (8.7)	4 (1.0)	2 (0.6)	1 (0.3)
Second dose reduction	72 (13.5)	56 (12.2)	11 (2.7)	10 (2.8)	11 (3.4)

Overall extent of exposure: Olaparib 300 mg bd pool

Table 41: 300 mg bd pool: overall extend of exposure (SAS)

Month (days)	Number (%) of patients
	Olaparib 300 mg bd N=1585
≥Day 1	1585 (100.0)
≥1 month (30.4 days)	1495 (94.3)
≥3 months (91.3 days)	1246 (78.6)
≥6 months (182.6 days)	977 (61.6)
≥12 months (365.3 days)	599 (37.8)
≥18 months (547.9 days)	417 (26.3)
≥24 months (730.5 days)	285 (18.0)
≥36 months (1095.8 days)	22 (1.4)
≥48 months (1461.1 days)	6 (0.4)

Compared with the olaparib/bevacizumab arm of PAOLA-1, treatment duration in the 300 mg bd pool was generally shorter. Of note, 27.6% of patients in this pool were recruited to Phase I studies.

Demographic

PAOLA-1

Key demographic and baseline characteristics are described in Table 6.

Olaparib 300 mg bd pool

Summaries of the key demographic and baseline patient characteristics for the 15 studies contributing to the pooled dataset are provided in the Table below.

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

Study Number of Subjects randomised/ treated	Age/sex/race	Performance status	Tumour type	Prior anticancer treatment	Gene mutation status
SOLO1 N=391/390 (260 n the pooled dataset)	29 to 84 years (mean age 53.5 years) All Female 320 (81.8%) White, 59 (15.1%) Asian 12 (3.1%) Black, African American and Other	ECOG PS ≤1 305 (78.0%) PS0 85 (21.7%) PS1	Advanced (FIGO Stage III-IV) Ovarian Cancer	All pre-treated Median number of prior chemotherapies was 1.0	389 *gBRCAm* 2 *sBRCAm*
SOLO1 China cohort N=64/64 (44[4] 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*
SOLO2 N=295/294 (195 in pooled dataset)	28 to 83 years (mean age 57.0 years) All female 173 (88.3%) White 22 (11.2%) Asian 1 (0.5%) Black or African American	ECOG PS ≤1 239 (81.0%) PS0 54 (18.3%) PS1	PSR ovarian cancer	All treated patients had prior chemotherapy Median number of prior regimens = 2.0 (range 2 – 7)	All *gBRCAm*
SOLO2 China Cohort N=32/32 (22 in pooled dataset)	33 to 67 years (mean age 49.6 years) All female 32 (100%) Asian	ECOG PS ≤1	PSR ovarian cancer	All treated patients had prior chemotherapy Median number of prior regimens = 2.0 (range 2 – 4)	All *gBRCAm*
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*
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*

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*
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, African American, 23 (5.9%) Missing and 3 (0.8%) Other.	ECOG PS ≤2 186 (48.1%) PS0 183 (47.3%) PS1 17 (4.4%) PS2 (data were missing for 1 patient).	HRRm metastatic castration-resistant prostate cancer	All pre-treated	All HRRm
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

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

AE category[a]	Number (%) of patients			
	Overall study duration		Combination treatment phase only	
	Olaparib/ bevacizumab N=535	Placebo/ bevacizumab N=267	Olaparib/ bevacizumab N=534[b]	Placebo/ bevacizumab N=267
Any AE	531 (99.3)	256 (95.9)	523 (97.9)	255 (95.5)
Any AE of CTCAE Grade 3 or higher	308 (57.6)	136 (50.9)	267 (50.0)	116 (43.4)
Any AE with outcome = death	1 (0.2)	4 (1.5)	0	2 (0.7)
Any SAE (including events with outcome = death)	167 (31.2)	83 (31.1)	130 (24.3)	67 (25.1)
Any AE leading to discontinuation of olaparib or placebo	109 (20.4)	15 (5.6)	86 (16.1)	10 (3.7)
Any AE leading to dose reduction of olaparib or placebo	220 (41.1)	20 (7.5)	210 (39.3)	16 (6.0)
Any AE leading to dose interruption of olaparib or placebo	291 (54.4)	65 (24.3)	272 (50.9)	51 (19.1)

The majority of AE were reported during the combination period, with most events occurring early in treatment. In the olaparib/bevacizumab arm, 531 (99.3%) patients reported a total of 5970 AEs across the overall study duration, 4719 of these 5970 (79.0%) AEs were reported during the combination period. For the placebo/bevacizumab arm, 256 (95.9%) patients reported a total of 2304 AEs, with 1812 of 2304 (78.6%) AEs reported during the combination period.

The safety profile of olaparib/bevacizumab in non-tBRCAm and tBRCAm patients was similar to that of the SAS (data not shown).

Comparison with olaparib 300mg bd pool

As shown in the table below, the proportions of patients with SAEs, AEs leading to treatment (olaparib) discontinuation, CTCAE Grade ≥3 AEs, DAEs, AEs leading to dose reduction and AEs leading to treatment interruption were higher for the olaparib/bevacizumab arm of PAOLA-1 compared with the 300 mg bd pool.

Table 44: Number (%) of patients who had at least 1 AE in any category (olaparib treatment groups) in PAOLA-1 and the 300 mg bd pool

AE category[a]	Number (%) of patients		
	PAOLA-1 SAS, overall study duration		Olaparib 300 mg bd pool (N=1585)
	Olaparib/ bevacizumab N=535	Placebo/ bevacizumab N=267	
Any AE	531 (99.3)	256 (95.9)	1542 (97.3)
Any AE of CTCAE Grade 3 or higher	308 (57.6)	136 (50.9)	659 (41.6)
Any AE with outcome = Death	1 (0.2)	4 (1.5)	19 (1.2)
Any SAE (including events with outcome = death)	167 (31.2)	83 (31.1)	365 (23.0)
Any AE leading to discontinuation of olaparib or placebo	109 (20.4)	15 (5.6)	148 (9.3)
Any AE leading to dose reduction of olaparib or placebo	220 (41.1)	20 (7.5)	339 (21.4)
Any AE leading to interruption of olaparib or placebo	291 (54.4)	65 (24.3)	630 (39.7)

Table 45: PAOLA-1: Most commonly reported AEs (occurring in >10%) of patients in either treatment group (SAS)

MedDRA preferred term[b]	Number (%) of patients			
	Overall study duration		Combination treatment phase only	
	Olaparib/ bevacizumab N=535	Placebo/ bevacizumab N=267	Olaparib/ bevacizumab N=534	Placebo/ bevacizumab N=267
Patients with any AE	531 (99.3)	256 (95.9)	523 (97.9)	255 (95.5)
Nausea	285 (53.3)	58 (21.7)	277 (51.9)	51 (19.1)
Fatigue	283 (52.9)	86 (32.2)	264 (49.4)	80 (30.0)
Hypertension	245 (45.8)	160 (59.9)	223 (41.8)	153 (57.3)
Anaemia	219 (40.9)	27 (10.1)	193 (36.1)	16 (6.0)
Lymphopenia	120 (22.4)	24 (9.0)	97 (18.2)	20 (7.5)
Vomiting	117 (21.9)	29 (10.9)	105 (19.7)	26 (9.7)
Arthralgia	116 (21.7)	64 (24.0)	99 (18.5)	58 (21.7)
Abdominal pain	103 (19.3)	53 (19.9)	89 (16.7)	39 (14.6)
Diarrhoea	98 (18.3)	45 (16.9)	93 (17.4)	39 (14.6)
Leukopenia	87 (16.3)	26 (9.7)	75 (14.0)	24 (9.0)
Urinary tract infection	79 (14.8)	27 (10.1)	65 (12.2)	24 (9.0)
Headache	73 (13.6)	36 (13.5)	68 (12.7)	34 (12.7)
Neutropenia	62 (11.6)	33 (12.4)	55 (10.3)	28 (10.5)
Constipation	53 (9.9)	28 (10.5)	34 (6.4)	22 (8.2)
Proteinuria	31 (5.8)	40 (15.0)	26 (4.9)	36 (13.5)

The largest differences in incidence between the two arms for the overall study duration were for the AEs of nausea and anaemia (incidence difference of 31.6 and 30.8 percentage points respectively). AEs of fatigue, lymphopenia and vomiting were also reported at a higher incidence (an incidence difference of ≥10 percentage points) for patients in the olaparib/bevacizumab arm compared with the placebo/bevacizumab arm. All of the AEs reported with a higher incidence of ≥10% for patients in the olaparib/bevacizumab arm, compared with the placebo/bevacizumab arm are known ADRs for olaparib.

Other AEs which occurred more frequently in the olaparib/bevacizumab arm (a higher incidence of ≥5 to 10 percentage points in the olaparib/bevacizumab arm compared with the placebo/bevacizumab arm; overall study duration) were: dysgeusia and leukopenia. Dysgeusia is a known ADR for olaparib and leukopenia is a known ADR for both olaparib and bevacizumab. There were no AEs which occurred more frequently (a higher incidence of ≥5 percentage points) in the olaparib/bevacizumab arm that are not currently listed as ADRs for either olaparib alone or both olaparib and bevacizumab.

AEs which occurred less frequently in the olaparib/bevacizumab arm (a lower incidence of ≥5 percentage points in the olaparib/bevacizumab arm compared with the placebo/bevacizumab arm) were proteinuria and hypertension (both listed as ADRs for bevacizumab).

Comparison with olaparib 300mg bd pool

Table 46: Most commonly reported AEs (occurring in >10% of patients) in PAOLA-1 or the 300 mg bd pool

Preferred term	Number (%) of patients[a]		
	PAOLA-1 SAS, overall study duration		Olaparib 300 mg bd pool N=1585
	Olaparib/ bevacizumab N=535	Placebo/ bevacizumab N=267	
Patients with any AE	531 (99.3)	256 (95.9)	1542 (97.3)
Nausea	285 (53.3)	58 (21.7)	944 (59.6)
Fatigue	283 (52.9)	86 (32.2)	589 (37.2)
Hypertension	245 (45.8)	160 (59.9)	42 (2.6)
Anaemia	219 (40.9)	27 (10.1)	632 (39.9)
Lymphopenia	120 (22.4)	24 (9.0)	53 (3.3)
Vomiting	117 (21.9)	29 (10.9)	514 (32.4)
Arthralgia	116 (21.7)	64 (24.0)	201 (12.7)
Abdominal pain	103 (19.3)	53 (19.9)	246 (15.5)
Diarrhoea	98 (18.3)	45 (16.9)	412 (26.0)
Leukopenia	87 (16.3)	26 (9.7)	114 (7.2)
Urinary tract infection	79 (14.8)	27 (10.1)	132 (8.3)
Headache	73 (13.6)	36 (13.5)	243 (15.3)
Neutropenia	62 (11.6)	33 (12.4)	200 (12.6)
Constipation	53 (9.9)	28 (10.5)	288 (18.2)
Dysgeusia	42 (7.9)	3 (1.1)	173 (10.9)
Decreased appetite	42 (7.9)	10 (3.7)	371 (23.4)
Dyspnoea	39 (7.3)	8 (3.0)	197 (12.4)
Back pain	33 (6.2)	9 (3.4)	196 (12.4)
Proteinuria	31 (5.8)	40 (15.0)	4 (0.3)
Pyrexia	28 (5.2)	10 (3.7)	175 (11.0)
Cough	23 (4.3)	11 (4.1)	207 (13.1)
Dizzinesss	14 (2.6)	5 (1.9)	181 (11.4)
Asthenia	1 (0.2)	1 (0.4)	262 (16.5)

The only common (≥30% of patients) AE reported in PAOLA-1 but not consistently reported in the 300 mg bd pool was hypertension (45.8% of olaparib/bevacizumab patients in PAOLA-1 compared with 2.6% of patients in the 300 mg bd pool); hypertension is a known ADR for bevacizumab.

Of the AEs reported with an incidence of ≥10% in the olaparib/bevacizumab arm of PAOLA-1 or the 300 mg bd pool, AEs of hypertension, lymphopenia, fatigue, leukopenia, arthralgia and urinary tract infection were reported at a higher incidence (≥5 percentage points difference) in the

olaparib/bevacizumab arm of PAOLA-1 compared with the 300 mg bd pool. All of these terms are either known ADRs for bevacizumab, or are symptoms commonly reported in an ovarian cancer population.

Adverse events by treatment period

The majority of AEs first occurred within the first 3 months of treatment. Data for the most common (≥10% of patients) in the olaparib/bevacizumab arm are presented in the table below.

Table 47: PAOLA-1: onset of AE by months of study treatment (up to D360) for the most common AEs (reported in ≥10% of patients in the olaparib/bevacizumab arm, overall); SAS, overall study duration

Preferred term	Number (%) of patients							
	Onset Day 1-90		Onset Day 91-180		Onset Day 181-270		Onset Day 271-360	
	Olap/ bev N=535	Pbo/ bev N=267	Olap/ bev N=486	Pbo/ bev N=261	Olap/ bev N=435	Pbo/ bev N=224	Olap/ bev N=382	Pbo/ bev N=207
Nausea	259 (48.4)	36 (13.5)	54 (11.1)	12 (4.6)	28 (6.4)	7 (3.1)	28 (7.3)	10 (4.8)
Fatigue	217 (40.6)	52 (19.5)	61 (12.6)	24 (9.2)	37 (8.5)	15 (6.7)	22 (5.8)	11 (5.3)
Hypertension	160 (29.9)	105 (39.3)	98 (20.2)	68 (26.1)	56 (12.9)	41 (18.3)	52 (13.6)	44 (21.3)
Anaemia	163 (30.5)	12 (4.5)	67 (13.8)	3 (1.1)	29 (6.7)	2 (0.9)	20 (5.2)	2 (1.0)
Lymphopenia	72 (13.5)	14 (5.2)	36 (7.4)	5 (1.9)	27 (6.2)	3 (1.3)	23 (6.0)	3 (1.4)
Vomiting	81 (15.1)	14 (5.2)	33 (6.8)	4 (1.5)	15 (3.4)	5 (2.2)	15 (3.9)	8 (3.9)
Arthralgia	64 (12.0)	42 (15.7)	23 (4.7)	21 (8.0)	20 (4.6)	10 (4.5)	13 (3.4)	4 (1.9)
Abdominal pain	56 (10.5)	26 (9.7)	26 (5.3)	8 (3.1)	15 (3.4)	10 (4.5)	13 (3.4)	10 (4.8)
Diarrhoea	59 (11.0)	24 (9.0)	27 (5.6)	8 (3.1)	13 (3.0)	6 (2.7)	15 (3.9)	8 (3.9)
Leukopenia	57 (10.7)	19 (7.1)	24 (4.9)	4 (1.5)	15 (3.4)	3 (1.3)	10 (2.6)	2 (1.0)
Urinary tract infection	33 (6.2)	8 (3.0)	25 (5.1)	12 (4.6)	15 (3.4)	4 (1.8)	12 (3.1)	5 (2.4)
Headache	48 (9.0)	24 (9.0)	14 (2.9)	10 (3.8)	15 (3.4)	8 (3.6)	7 (1.8)	6 (2.9)

CTCAE Grade >3 or higher

Adverse events of CTCAE Grade ≥3 (version 4.0) were most commonly reported in the SOC of Blood and lymphatic system disorders. The majority of CTCAE Grade ≥3 AEs were reported during the combination period.

Table 48: PAOLA-1: CTCAE Grade≥3 AEs occurring in ≥1% patients in either treatment arm (SAS)

MedDRA SOC preferred term[b]	Number (%) of patients[a]			
	Overall study duration		Combination treatment phase only	
	Olaparib/ bevacizumab N=535	Placebo/ bevacizumab N=267	Olaparib/ bevacizumab N=534	Placebo/ bevacizumab N=267
Patients with any CTCAE Grade ≥3 AE	**308 (57.6)**	**136 (50.9)**	**267 (50.0)**	**116 (43.4)**
Blood and lymphatic system disorders	**140 (26.2)**	**13 (4.9)**	**125 (23.4)**	**9 (3.4)**
Anaemia	93 (17.4)	1 (0.4)	87 (16.3)	1 (0.4)
Lymphopenia	37 (6.9)	3 (1.1)	31 (5.8)	2 (0.7)
Neutropenia	21 (3.9)	6 (2.2)	19 (3.6)	4 (1.5)
Leukopenia	9 (1.7)	3 (1.1)	6 (1.1)	2 (0.7)
Thrombocytopenia	7 (1.3)	1 (0.4)	6 (1.1)	0
Vascular disorders	**108 (20.2)**	**81 (30.3)**	**89 (16.7)**	**74 (27.7)**
Hypertension	100 (18.7)	81 (30.3)	83 (15.5)	73 (27.3)
Gastrointestinal disorders	**63 (11.8)**	**25 (9.4)**	**52 (9.7)**	**17 (6.4)**
Nausea	13 (2.4)	2 (0.7)	12 (2.2)	0
Diarrhoea	12 (2.2)	5 (1.9)	12 (2.2)	3 (1.1)
Vomiting	9 (1.7)	5 (1.9)	8 (1.5)	1 (0.4)
Abdominal pain	8 (1.5)	5 (1.9)	7 (1.3)	3 (1.1)
Subileus	7 (1.3)	4 (1.5)	6 (1.1)	2 (0.7)
Ileus	4 (0.7)	3 (1.1)	2 (0.4)	3 (1.1)
General disorders and administration site conditions	**34 (6.4)**	**8 (3.0)**	**31 (5.8)**	**4 (1.5)**
Fatigue	28 (5.2)	4 (1.5)	27 (5.1)	2 (0.7)
Mucosal inflammation	6 (1.1)	0	4 (0.7)	0
Investigations	**29 (5.4)**	**10 (3.7)**	**22 (4.1)**	**9 (3.4)**
Neutrophil count decreased	10 (1.9)	3 (1.1)	8 (1.5)	3 (1.1)
Weight increased	4 (0.7)	4 (1.5)	2 (0.4)	4 (1.5)
Respiratory, thoracic and mediastinal disorders	**15 (2.8)**	**4 (1.5)**	**5 (0.9)**	**2 (0.7)**
Pulmonary embolism	7 (1.3)	1 (0.4)	2 (0.4)	0
Musculoskeletal and connective tissue disorders	**8 (1.5)**	**7 (2.6)**	**7 (1.3)**	**6 (2.2)**
Arthralgia	3 (0.6)	4 (1.5)	3 (0.6)	4 (1.5)
Cardiac disorders	**2 (0.4)**	**7 (2.6)**	**1 (0.2)**	**2 (0.7)**
Myocardial infarction	0	4 (1.5)	0	2 (0.7)

Comparison with olaparib 300mg bd pool

Table 49: Most common AEs of CTCAE Grade≥3 (reported in ≥1% patients in the olaparib/bevacizumab arm of PAOLA-1 or ≥2% patients in the 300 mg bd pool)

System organ class Preferred term	Number (%) of patients[a]		
	PAOLA-1 SAS, overall study duration		Olaparib 300 mg bd pool (N=1585)
	Olaparib/ bevacizumab N=535	Placebo/ bevacizumab N=267	
Patients with any CTCAE Grade ≥3 AE	**308 (57.6)**	**136 (50.9)**	**659 (41.6)**
Blood and lymphatic system disorders	**140 (26.2)**	**13 (4.9)**	**347 (21.9)**
Anaemia	93 (17.4)	1 (0.4)	284 (17.9)
Lymphopenia	37 (6.9)	3 (1.1)	12 (0.8)
Neutropenia	21 (3.9)	6 (2.2)	72 (4.5)
Leukopenia	9 (1.7)	3 (1.1)	23 (1.5)
Thrombocytopenia	7 (1.3)	1 (0.4)	29 (1.8)
Vascular disorders	**108 (20.2)**	**81 (30.3)**	**24 (1.5)**
Hypertension	100 (18.7)	81 (30.3)	8 (0.5)
Gastrointestinal disorders	**63 (11.8)**	**25 (9.4)**	**102 (6.4)**
Nausea	13 (2.4)	2 (0.7)	16 (1.0)
Diarrhoea	12 (2.2)	5 (1.9)	17 (1.1)
Vomiting	9 (1.7)	5 (1.9)	22 (1.4)
Abdominal pain	8 (1.5)	5 (1.9)	20 (1.3)
Subileus	7 (1.3)	4 (1.5)	0
General disorders and administration site conditions	**34 (6.4)**	**8 (3.0)**	**83 (5.2)**
Fatigue	28 (5.2)	4 (1.5)	41 (2.6)
Investigations	**29 (5.4)**	**10 (3.7)**	**103 (6.5)**
Neutrophil count decreased	10 (1.9)	3 (1.1)	42 (2.6)
Respiratory and mediastinal disorders	**15 (2.8)**	**4 (1.5)**	**52 (3.3)**
Pulmonary embolism	7 (1.3)	1 0.4)	18 (1.1)

Serious adverse event/deaths/other significant events

Deaths

Table 50: PAOLA-1: all deaths (FAS)

Category	Number (%) of patients	
	Overall study duration	
	Olaparib/ bevacizumab N=537	Placebo/ bevacizumab N=269
Total number of deaths	139 (25.9)	70 (26.0)
Death related to disease under investigation only[a]	127 (23.6)	61 (22.7)
AE with outcome of death only	1 (0.2)	4 (1.5)
AE with outcome of death (AE start date falling >30 days after last treatment dose)[b]	3 (0.6)	2 (0.7)
Other deaths[c]	7 (1.3)	2 (0.7)
Patients with unknown reason for death	1 (0.2)	1 (0.4)

[a] Deaths on or after the date of first dose and up to 30 days following the last dose of study medication.
[b] After the 30-day safety follow-up period, only events that are AESIs were reported as AEs
[c] Patients who died and are not captured in the earlier categories.

Two of the 4 patients in the placebo/bevacizumab arm who died as a result of an AE were in the combination phase of the study. The remaining 2 patients in the placebo/bevacizumab arm, and the patient in the olaparib/bevacizumab arm who died as a result of an AE were in the monotherapy phase of the study (i.e., after discontinuation of bevacizumab treatment).

For twelve patients in the olaparib/bevacizumab arm, death was not considered due to disease progression only. There was one additional case in the olaparib/bevacizumab arm, the primary cause of death was first reported by the investigator as disease progression due to pancreas carcinoma (second primary tumour), and not due to her underlying cancer.

Comparison with olaparib 300mg bd pool

Table 51: Patients who died in PAOLA-1 and the 300 mg pool

Category	Number (%) of patients		
	PAOLA-1 FAS, overall study duration		Olaparib 300 mg bd pool (N=1585)
	Olaparib/ bevacizumab N=537	Placebo/ bevacizumab N=269	
Total number of deaths	139 (25.9)	70 (26.0)	462 (29.1)
Death related to disease under investigation only	127 (23.6)	61 (22.7)	419 (26.4)
AE with outcome = death only	1 (0.2)	4 (1.5)	11 (0.7)
Death related to disease and an AE with outcome = death	0	0	8 (0.5)
AE with outcome of death ≥30 days after last treatment dose	3 (0.6)	2 (0.7)	2 (0.1)
Other deaths[a,b]	7 (1.3)	2 (0.7)	22 (1.4)
Patients with unknown reason for death	1 (0.2)	1 (0.4)	0

Serious adverse event

Table 52: PAOLA-1: SAEs occurring in ≥1% patients in either treatment group (SAS)

Category	Number (%) of patients			
	Overall study duration		Combination treatment phase only	
	Olaparib/ bevacizumab N=535	Placebo/ bevacizumab N=267	Olaparib/ bevacizumab N=534	Placebo/ bevacizumab N=267
Patients with any SAE	167 (31.2)	83 (31.1)	130 (24.3)	67 (25.1)
Vascular disorders				
Hypertension	48 (9.0)	35 (13.1)	38 (7.1)	32 (12.0)
Blood and lymphatic system disorders				
Anaemia	34 (6.4)	1 (0.4)	30 (5.6)	1 (0.4)
Gastrointestinal disorders				
Subileus	8 (1.5)	3 (1.1)	6 (1.1)	2 (0.7)
Intestinal obstruction	8 (1.5)	2 (0.7)	4 (0.7)	1 (0.4)
Ileus	3 (0.6)	3 (1.1)	3 (0.6)	3 (1.1)
Cardiac disorders				
Myocardial infarction	0	4 (1.5)	0	2 (0.7)

Comparison with olaparib 300mg bd pool

There was an increased incidence of SAEs in the olaparib/bevacizumab arm of PAOLA-1, compared with the 300 mg bd pool. This increased incidence appeared to be largely caused by an increased incidence of SAEs of hypertension (which occurred at a frequency of 9.0% in the olaparib/bevacizumab arm of PAOLA-1, compared with no SAEs in the 300 mg bd pool). The most common (≥2% of patients) SAE of anaemia in the olaparib 300 mg bd pool was reported at a similar frequency in the olaparib/bevacizumab arm of PAOLA- Most other SAEs were reported in fewer than 2 patients in each arm of PAOLA-1.

Table 53: Most comment SAEs (reported by ≥1% patients in PAOLA-1 and/or reported by ≥2% patients in the 300 mg bd pool)

System organ class Preferred term	Number (%) of patients		
	PAOLA-1 SAS, overall study duration		Olaparib 300 mg bd pool (N=1585)
	Olaparib/ bevacizumab N=535	Placebo/ bevacizumab N=267	
Patients with any SAE	**167 (31.2)**	**83 (31.1)**	**365 (23.0)**
Vascular disorders	**56 (10.5)**	**35 (13.1)**	**13 (0.8)**
Hypertension	48 (9.0)	35 (13.1)	0
Blood and lymphatic system disorders	**40 (7.5)**	**4 (1.5)**	**110 (6.9)**
Anaemia	34 (6.4)	1 (0.4)	89 (5.6)
Gastrointestinal disorders	**31 (5.8)**	**19 (7.1)**	**66 (4.2)**
Subileus	8 (1.5)	3 (1.1)	1 (0.1)
Intestinal obstruction	8 (1.5)	2 (0.7)	6 (0.4)
Ileus	3 (0.6)	3 (1.1)	5 (0.3)
Cardiac disorders	**4 (0.7)**	**7 (2.6)**	**14 (0.9)**
Myocardial infarction	0	4 (1.5)	1 (0.1)

Adverse drug reactions

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

The Grade ≥ 3 adverse reactions occurring in > 2% of patients were anaemia (17%), neutropenia (6%), fatigue/asthenia (5%), leukopenia (3%), thrombocytopenia (3%) and vomiting (2%).

Adverse reactions that most commonly led to dose interruptions and/ or reductions in monotherapy were anaemia (16.2%), vomiting (6.8%), nausea (6.2%), neutropenia (6.2%) and fatigue/asthenia (6.0%). Adverse reactions that most commonly led to permanent discontinuation were anaemia (1.8%), fatigue/asthenia (0.7%), nausea (0.7%) and thrombocytopenia (0.7%).

When Lynparza is used in combination with bevacizumab the safety profile is generally consistent with that of the individual therapies.

Adverse events led to dose interruption and/ or reduction of olaparib in 57.4% of patients when used in combination with bevacizumab and led to permanent discontinuation of treatment with olaparib/bevacizumab and placebo/bevacizumab in 20.4% and 5.6% of patients, respectively. The adverse reactions that most commonly led to dose interruption and/or reduction were anaemia (20.6%) and nausea (7.5%). The adverse reactions that most commonly led to permanent discontinuation were anaemia (3.6%), nausea (3.4%) and fatigue/asthenia (1.5%).

The safety profile is based on pooled data from 2351 patients with solid tumours treated with Lynparza monotherapy in clinical trials at the recommended dose.

Table 54: Tabulated list of adverse reactions in clinical trials with Lynparza

	Adverse reactions	
MedDRA System Organ Class	**Frequency of All CTCAE grades**	**Frequency of CTCAE grade 3 and above**
Blood and lymphatic system disorders	**Very common** Anaemia[a], Neutropenia[a], Thrombocytopenia[a], Leukopenia[a] **Common** Lymphopenia[a]	**Very common** Anaemia[a] **Common** Neutropenia[a], Thrombocytopenia[a], Leukopenia[a] **Uncommon** Lymphopenia[a]
Immune system disorders	**Common** Rash[a] **Uncommon** Hypersensitivity[a], Dermatitis[a]	**Rare** Rash[a], Hypersensitivity[a]
Metabolism and nutrition disorders	**Very common** Decreased appetite	**Uncommon** Decreased appetite
Nervous system disorders	**Very common** Dizziness, Headache, Dysgeusia	**Uncommon** Dizziness, Headache

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

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

Haematological toxicity

In clinical studies with the tablet formulation, the incidence of anaemia adverse reactions was 40.8% (CTCAE grade ≥3 18.1%) and the incidences of dose interruptions, reductions and discontinuations for anaemia were 17.7%, 12.2% and 2.5%, respectively; 22.6% of patients treated with olaparib needed one or more blood transfusions. An exposure-response relationship between olaparib and decreases in haemoglobin has been demonstrated. In clinical studies with Lynparza the incidence of CTCAE grade ≥ 2 shifts (decreases) from baseline in haemoglobin was 23%, absolute neutrophils 19%, platelets 6%, lymphocytes 29% and leucocytes 20% (all % approximate).

The incidence of elevations in mean corpuscular volume from low or normal at baseline to above the ULN was approximately 58%.

Anaemia

Table 55: PAOLA-1 and the 300 mg bd pool: patients who had at least one AE of anaemia (grouped term) reported in any category

AE category[a]	Number (%) of patients		
	PAOLA-1 SAS, overall study duration		
	Olaparib/ bevacizumab N=535	Placebo/ bevacizumab N=267	Olaparib 300 mg bd pool (N=1585)
Any AE	219 (40.9)	27 (10.1)	646 (40.8)
Any AE of CTCAE Grade 3 or higher	93 (17.4)	1 (0.4)	287 (18.1)
Any AE with outcome = death	0	0	0
Any SAE	34 (6.4)	1 (0.4)	93 (5.9)
AEs leading to dose reduction of olaparib or placebo	99 (18.5)	0	194 (12.2)
AEs leading to treatment interruption of olaparib or placebo	110 (20.6)	1 (0.4)	285 (18.0)
Any AE leading to discontinuation of olaparib or placebo	19 (3.6)	0	40 (2.5)

In more than half of cases, anaemia events were Grade 1 or 2 in severity. Events rarely led to permanent discontinuation of treatment. In the olaparib/bevacizumab arm, 28 of the 93 patients with CTCAE Grade ≥ 3 AEs of anaemia (single PT) were SAEs and 3 patients had a CTCAE Grade 4 AE that were SAEs. Olaparib treatment was interrupted and the dose subsequently reduced in 2 of the 3 patients with CTCAE Grade 4 AEs of anaemia, treatment was permanently discontinued in the remaining patient. All 3 patients with CTCAE Grade 4 AE received treatment for the AEs, and AEs in all 3 patients were reported as recovered, with durations ranging from 7 days to 48 days.

Onset of anaemia was early, generally in the first 3 months of starting olaparib (median time to first onset was 1.54 months), although the risk of developing anaemia remained fairly constant throughout exposure with no evidence of cumulative effect.

The majority (209 of 219 patients) of first events with olaparib/bevacizumab resolved (median time to resolution 1.41 months for first event.)

Regarding laboratory abnormalities for haemoglobin, no patients in PAOLA-1 had CTCAE Grade 4 haemoglobin values during the study; 12.5% of olaparib/bevacizumab-treated patients had reductions to CTCAE Grade 3 haemoglobin values.

In the olaparib/bevacizumab arm, 112 (51.1%) of 219 patients with AEs of anaemia (grouped term) were treated for the AE compared with 3 (11.1%) of 27 patients in the placebo/bevacizumab arm.

In the olaparib/bevacizumab arm of PAOLA-1, 94 (17.6%) patients received a blood transfusion. A total of 26 (4.9%) patients in the olaparib/bevacizumab arm had more than 1 transfusion of either whole blood or packed red blood cells (PRBCs) after the start of study treatment; the majority of these occurred in the first 4 months on study treatment. Thirty (5.6%) olaparib/bevacizumab-treated patients had an erythropoiesis stimulating agent.

Neutropenia

Table 56: PAOLA-1 and the 300 mg bd pool: patients who had at least one AE of neutropenia (grouped term) reported in any category

AE category[a]	Number (%) of patients		
	PAOLA-1 SAS, overall study duration		
	Olaparib/ bevacizumab N=535	Placebo/ bevacizumab N=267	Olaparib 300 mg bd pool (N=1585)
Any AE	97 (18.1)	42 (15.7)	293 (18.5)
Any AE of CTCAE Grade 3 or higher	34 (6.4)	8 (3.0)	114 (7.2)
Any AE with outcome = death	0	0	1 (0.1)
Any SAE	5 (0.9)	1 (0.4)	18 (1.1)
AEs leading to dose reduction of olaparib or placebo	7 (1.3)	1 (0.4)	44 (2.8)
AEs leading to treatment interruption of olaparib or placebo	19 (3.6)	4 (1.5)	117 (7.4)
Any AE leading to discontinuation of olaparib or placebo	3 (0.6)	0	10 (0.6)

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

These events were predominantly Grade 1 or 2 in severity and rarely led to permanent discontinuation of treatment. No patients in either treatment arm had AEs of febrile neutropenia occurring on treatment. In the follow-up period, 4 (0.7%) patients in the olaparib/bevacizumab arm had AEs of febrile neutropenia 3 of the 4 patients had CTCAE Grade 3 AEs, 1 patient had a CTCAE Grade 4 AE. All 4 patients were treated for the event.

Onset of AEs was 5 to 18 days after the last dose of olaparib. Five patients in the olaparib/bevacizumab arm and 2 patients in the placebo/bevacizumab arm had AEs of febrile neutropenia that occurred in the post follow-up period. There were no patients with AEs of neutropenic infection or neutropenic sepsis in PAOLA-1.

In the olaparib/bevacizumab arm, 5 of the 34 patients with CTCAE Grade ≥3 AEs of neutropenia were SAEs.

There was no association between the development of neutropenia and the length of time on olaparib/bevacizumab treatment; AEs of neutropenia were reported throughout the study period in the olaparib/bevacizumab-treated arm (median time to onset of first event was 1.31 months); the majority (94 of 97 patients) of events with olaparib/bevacizumab resolved (median time to resolution of 0.72 months for first event). A small proportion of patients in each treatment arm received colony stimulating factors (4 patients [0.7%] in the olaparib/bevacizumab arm and 3 patients [1.1%] in the placebo/bevacizumab arm). The AE category table for the 300 mg bd pool showed a consistent pattern of AEs when compared with olaparib/bevacizumab data from PAOLA-1.

Regarding abnormalities data of neutrophils, the majority (534 [93.6 %] patients) of olaparib/bevacizumab-treated patients in PAOLA- 1 had a maximum CTCAE Grade ≤2 reported for absolute neutrophil count (ANC) values; 97.4% (260 of 267 patients) of patients in the placebo/bevacizumab arm also had CTCAE Grade ≤2 ANC during the PAOLA-1 study.

Of the patients in the olaparib/bevacizumab arm with AEs of neutropenia, 8 (8.2%) of 97 patients were treated for the AE compared with 4 (9.5%) of 42 patients in the placebo/bevacizumab arm.

Colony stimulating factor use in the olaparib/bevacizumab arm was rare (4 patients [0.7%] in the olaparib/bevacizumab arm and 3 patients [1.1%] in the placebo/bevacizumab arm received colony stimulating factors.

Thrombocytopenia

AEs of thrombocytopenia were reported for a higher percentage of patients in the olaparib/bevacizumab arm compared with the placebo/bevacizumab arm. These events were predominantly Grade 1 or 2 in severity and none led to permanent discontinuation of treatment. The proportion of patients with AEs in the grouped term of haemorrhagic events and wound healing complications were similar between the 2 treatment arms in PAOLA-1.

A grouped term analysis of haemorrhage events in PAOLA-1 showed that 52 (9.7%) of 535 patients in the olaparib/bevacizumab arm had a total of 65 AEs. In the placebo/bevacizumab arm 28 (10.5%) of 267 patients had a total of 36 AEs. The majority of these AEs were CTCAE Grade ≤2 AEs; only 3 (0.6%) olaparib/bevacizumab-treated patients and 2 (0.7%) placebo/bevacizumab-treated patients had CTCAE Grade ≥3 AEs.

Three (0.6%) patients in the olaparib/bevacizumab arm and 2 (0.7%) patients in the placebo/bevacizumab arm had haemorrhage events that were SAEs. The SAEs in olaparib/bevacizumab arm were all CTCAE Grade 3 and none were considered related to olaparib by the investigator.

There was no association between the development of thrombocytopenia and the length of time on olaparib/bevacizumab treatment. First onset of AEs of thrombocytopenia were reported throughout the first 12 months of study period in the olaparib/bevacizumab-treated arm (median time to first onset was 1.41 months); the majority (42 of 43 patients) of events with olaparib resolved (median time to resolution of first event of 0.82 month).

Table 57: PAOLA-1 and the 300 mg bd pool: patients who had at least one AE of thrombocytopenia (grouped term) reported in any category

AE category[a]	Number (%) of patients		
	PAOLA-1 SAS, overall study duration		Olaparib 300 mg bd pool (N=1585)
	Olaparib/ bevacizumab N=535	Placebo/ bevacizumab N=267	
Any AE	43 (8.0)	9 (3.4)	197 (12.4)
Any AE of CTCAE Grade 3 or higher	10 (1.9)	1 (0.4)	47 (3.0)
Any AE with outcome = death	0	0	0
Any SAE	4 (0.7)	1 (0.4)	14 (0.9)
AEs leading to dose reduction of olaparib or placebo	11 (2.1)	0	22 (1.4)
AEs leading to treatment interruption of olaparib or placebo	16 (3.0)	1 (0.4)	61 (3.8)
Any AE leading to discontinuation of olaparib or placebo	0	0	14 (0.9)

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

Regarding abnormalities data of decreased platelet count, the majority of patients had a maximum CTCAE Grade of ≤2 reported for platelet values throughout treatment. A low proportion of olaparib/bevacizumab-treated patients (12 patients [2.2%]) had CTCAE Grade ≥3 reductions in platelet count during the study; no patients in the placebo/bevacizumab arm had a CTCAE Grade ≥3 reduction in platelet count.

A similar proportion of patients in each arm (5 [11.6%] of 43 olaparib/bevacizumab-treated patients and 1 [11.1%] of 9 placebo/bevacizumab-treated patients) were treated for AEs of thrombocytopenia. Five olaparib/bevacizumab-treated patients (0.9%) received a platelet transfusion, compared with 1 (0.4%) patient in the placebo/bevacizumab arm.

Lymphopenia

Table 58: PAOLA-1 and the 300 mg bd pool: patients who had at least one AE of lymphopenia (grouped term) reported in any category

AE category[a]	Number (%) of patients		
	PAOLA-1 SAS, overall study duration		Olaparib 300 mg bd pool (N=1585)
	Olaparib/ bevacizumab N=535	Placebo/ bevacizumab N=267	
Any AE	126 (23.6)	25 (9.4)	82 (5.2)
Any AE of CTCAE Grade 3 or higher	38 (7.1)	3 (1.1)	21 (1.3)
Any AE with outcome = death	0	0	0
Any SAE	0	0	0
AEs leading to dose reduction of olaparib or placebo	1 (0.2)	0	3 (0.2)
AEs leading to treatment interruption of olaparib or placebo	2 (0.4)	0	11 (0.7)
Any AE leading to discontinuation of olaparib or placebo	0	0	1 (0.1)

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

The incidence of all AEs and CTCAE Grade ≥3 AEs of lymphopenia in the 300 mg bd pool was lower when compared with olaparib/bevacizumab data from PAOLA-1. The proportion of patients with AEs and CTCAE Grade ≥3 AEs of lymphocyte count reductions were higher for the olaparib/bevacizumab arm of PAOLA-1 compared with the 300 mg bd pool; however, the proportion of patients with laboratory values showing grade changes to CTCAE Grade ≥3 in lymphocyte count in the olaparib/bevacizumab arm of PAOLA-1 (9.4%) was lower than that observed in the 300 mg bd pool (261 [16.7%] of 1563 patients and similar to that observed in SOLO1 (15 of 231 patients [6.5%]). When compared with the tablet pool, the incidence of lymphopenia was higher (grouped terms: any AE, 23.6%; any AE of CTCAE, ≥3, 7.1%); however, laboratory values for lymphocytes were consistent between PAOLA-1 and the tablet pool.

There was no association between the development of lymphopenia and the length of time on olaparib/bevacizumab treatment (median time to first onset was 2.64 months); the majority (116 of 126 patients) of events with olaparib/bevacizumab resolved (median time to resolution of first event of 0.9 months). Two (1.6%) of the 126 olaparib/bevacizumab-treated patients with lymphopenia were treated for the AE, compared with 2 (8.0%) of the 25 placebo/bevacizumab-treated patients.

Regarding laboratory data, the majority of patients in PAOLA-1 had a maximum CTCAE Grade of ≤2 reported for low lymphocyte laboratory values throughout treatment. The proportion of patients with CTCAE Grade ≥3 lymphocyte count reductions was higher for olaparib/bevacizumab-treated patients (50 of 533 patients [9.4%]) than for the placebo/bevacizumab arm (6 of 267 patients [2.2%]).

Leukopenia

Table 59: PAOLA-1 and the 300 mg bd pool: patients who had at least one AE of leukopenia (grouped term) reported in any category

AE category[a]	Number (%) of patients		
	PAOLA-1 SAS, overall study duration		Olaparib 300 mg bd pool (N=1585)
	Olaparib/ bevacizumab N=535	Placebo/ bevacizumab N=267	
Any AE	95 (17.8)	26 (9.7)	221 (13.9)
Any AE of CTCAE Grade 3 or higher	10 (1.9)	4 (1.5)	49 (3.1)
Any AE with outcome = death	0	0	0
Any SAE	0	1 (0.4)	4 (0.3)
AEs leading to dose reduction of olaparib or placebo	1 (0.2)	1 (0.4)	25 (1.6)
AEs leading to treatment interruption of olaparib or placebo	2 (0.4)	1 (0.4)	66 (4.2)
Any AE leading to discontinuation of olaparib or placebo	0	0	4 (0.3)

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

There was no association between the development of leukopenia and the length of time on olaparib/bevacizumab treatment (median time to onset was 2.10 months); all (95 of 95 patients) patients with events of leukopenia in the olaparib/bevacizumab arm resolved (median time to resolution of first event was 0.95 months). One patient in each arm with AEs of leukopenia were treated for the AE (1 [1.1%] of 95 patients in the olaparib/bevacizumab arm and 1 [3.8%] of 26 patients in the placebo/bevacizumab arm).

Fatigue/asthenia

Table 60: PAOLA-1 and the 300 mg bd pool: patients who had at least one AE of fatigue or asthenia reported in any category

AE category[a]	Number (%) of patients		
	PAOLA-1 SAS, overall study duration		Olaparib 300 mg bd pool (N=1585)
	Olaparib/ bevacizumab (N=535)	Placebo/ bevacizumab (N=267)	
Any AE	283 (52.9)	86 (32.2)	822 (51.9)
Any AE of CTCAE Grade 3 or higher	28 (5.2)	4 (1.5)	67 (4.2)
Any AE with outcome = death	0	0	0
Any SAE	0	0	10 (0.6)
AEs leading to dose reduction of olaparib or placebo	21 (3.9)	2 (0.7)	58 (3.7)
AEs leading to treatment interruption of olaparib or placebo	17 (3.2)	2 (0.7)	58 (3.7)
Any AE leading to discontinuation of olaparib or placebo	8 (1.5)	0	15 (0.9)

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

Fatigue and asthenia on olaparib/bevacizumab treatment were generally reported early, with the majority of first events with olaparib/bevacizumab reported within the first 3 months of treatment. Median time to

onset was 0.72 months. The incidence plateaued at around 1 month, suggesting that few first instances were reported after these times.

The majority (220 [77.7%] of 283 patients) of events of fatigue and asthenia with olaparib/bevacizumab resolved (median time to resolution of first event of 2.10 months). A low proportion of olaparib/bevacizumab-treated patients with fatigue and asthenia (6 [2.1%] of 283 patients) were reported by the investigator to have received treatment for the event compared with 3 ([3.5%] of 86 patients) in the placebo/bevacizumab arm).

Nausea and vomiting

Table 61: PAOLA-1 and the 300 mg bd pool: patients who had at least one AE of nausea or vomiting reported in any category

AE category[a]	Number (%) of patients					
	Nausea			Vomiting		
	PAOLA-1 SAS, overall study duration		Olaparib 300 mg bd pool (N=1585)	PAOLA-1 SAS, overall study duration		Olaparib 300 mg bd pool (N=1585)
	Olaparib/ bevacizumab (N=535)	Placebo/ bevacizumab (N=267)		Olaparib/ bevacizumab (N=535)	Placebo/ bevacizumab (N=267)	
Any AE	285 (53.3)	58 (21.7)	944 (59.6)	117 (21.9)	29 (10.9)	514 (32.4)
Any AE of CTCAE Grade 3 or higher	13 (2.4)	2 (0.7)	16 (1.0)	9 (1.7)	5 (1.9)	22 (1.4)
Any AE with outcome = death	0	0	0	0	0	0
Any SAE	0	0	6 (0.4)	2 (0.4)	0	12 (0.8)
Any AE leading to a dose reduction of olaparib or placebo	40 (7.5)	2 (0.7)	31 (2.0)	4 (0.7)	0	15 (0.9)
Any AE leading to a dose interruption of olaparib or placebo	39 (7.3)	4 (1.5)	74 (4.7)	18 (3.4)	3 (1.1)	86 (5.4)
Any AE leading to discontinuation of olaparib or placebo	18 (3.4)	1 (0.4)	12 (0.8)	5 (0.9)	0	10 (0.6)

Events of nausea and vomiting were generally reported early in the treatment period (median time to onset was 0.16 months and 1.38 months, respectively). The majority (263 of 285 AEs of nausea and 110 of 117 AEs of vomiting) of events with olaparib/bevacizumab resolved (median time to resolution of first event of 1.28 months and 0.10 months, respectively). First reports of nausea tended to occur early in treatment and prevalence of nausea events reduced from approximately 0.3% to 0.2% in the first 6 months of treatment, to approximately 0.2% to 0.1% from 6 months onwards. The prevalence of vomiting was approximately 0.05% for the duration of the study.

A total of 104 (19.4%) olaparib/bevacizumab-treated patients reported both nausea and vomiting. Approximately half of the olaparib/bevacizumab-treated patients with nausea (158 [55.4%] of 285 patients) were treated for the AE and 58 (49.6%) of 117 patients with vomiting received treatment; lower proportions of patients received treatment for nausea and vomiting in the placebo/bevacizumab arm (24 [41.4%] of 58 patients and 10 [34.5%] of 29 patients, respectively.

Diarrhoea

Table 62: PAOLA-1 and the 300 mg bd pool: patients who had at least one AE of diarrhoea reported in any category

AE category[a]	Number (%) of patients		
	PAOLA-1 SAS, overall study duration		
	Olaparib/ bevacizumab (N=535)	Placebo/ bevacizumab (N=267)	Olaparib 300 mg bd pool (N=1585)
Any AE	98 (18.3)	45 (16.9)	412 (26.0)
Any AE of CTCAE Grade 3 or higher	12 (2.2)	5 (1.9)	17 (1.1)
Any AE with outcome = death	0	0	0
Any SAE	2 (0.4)	2 (0.7)	2 (0.1)
AEs leading to dose reduction of olaparib or placebo	8 (1.5)	4 (1.5)	3 (0.2)
AEs leading to treatment interruption of olaparib or placebo	12 (2.2)	4 (1.5)	39 (2.5)
Any AE leading to discontinuation of olaparib or placebo	3 (0.6)	0	1 (0.1)

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

Events of diarrhoea were generally reported early in the treatment period (median time to onset was 2.25 months) and the majority (83 of 98 patients) of first events with olaparib/bevacizumab resolved (median time to resolution of first event of 0.44 months). A similar proportion of patients in the olaparib/bevacizumab arm with diarrhoea were treated for the AE (44 [44.9%] of 98 patients) compared with the placebo/bevacizumab arm (23 [51.1%] of 45 patients). The AE category table for the 300 mg bd pool showed a consistent pattern of AEs when compared with olaparib/bevacizumab data from PAOLA-1.

Increase in creatinine

The biochemical observations of elevated serum creatinine for olaparib monotherapy treatment were not associated with renal impairment and without any apparent clinical sequelae. The small increases in creatinine observed with olaparib and the rapid onset of the mild changes observed, with a return to baseline after olaparib discontinuation are consistent with the finding that olaparib is known to be an inhibitor of OCT2 and MATE1.

In clinical studies with Lynparza the incidence of CTCAE grade ≥ 2 shifts (elevations) from baseline in blood creatinine was approximately 11%.

Table 63: PAOLA-1 and the 300 mg bd pool: patients who had at least one AE of increased creatinine reported in any category

AE category[a]	Number (%) of patients		
	PAOLA-1 SAS, overall study duration		
	Olaparib/ bevacizumab N=535	Placebo/ bevacizumab N=267	Olaparib 300 mg bd pool (N=1585)
Any AE	25 (4.7)	3 (1.1)	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 of olaparib or placebo	1 (0.2)	0	2 (0.1)
AEs leading to treatment interruption of olaparib or placebo	3 (0.6)	0	5 (0.3)
Any AE leading to discontinuation of olaparib or placebo	3 (0.6)	0	0

Decreased appetite

Table 64:PAOLA-1 and the 300 mg bd pool: Patients who had at least one AE of decreased appetite reported in any category

AE category[a]	Number (%) of patients		
	PAOLA-1 SAS, overall study duration		
	Olaparib/ bevacizumab (N=535)	Placebo/ bevacizumab (N=267)	Olaparib 300 mg bd pool (N=1585)
Any AE	42 (7.9)	10 (3.7)	371 (23.4)
Any AE of CTCAE Grade 3 or higher	2 (0.4)	1 (0.4)	12 (0.8)
Any AE with outcome = death	0	0	0
Any SAE	0	0	4 (0.3)
AEs leading to dose reduction of olaparib or placebo	0	0	6 (0.4)
AEs leading to treatment interruption of olaparib or placebo	0	0	6 (0.4)
Any AE leading to discontinuation of olaparib or placebo	0	0	4 (0.3)

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

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

AE Adverse event; bd Twice daily; CTCAE Common Terminology Criteria for Adverse Events; DCO Data cut-off; N Total number of patients; SAE Serious adverse event; SAS Safety Analysis Set. (DCO: 22 March 2019).

Headache

Table 65: PAOLA-1 and the 300 mg bd pool: Patients who had at least one AE of headache reported in any category

AE category[a]	Number (%) of patients		
	PAOLA-1 SAS, overall study duration		Olaparib 300 mg bd pool (N=1585)
	Olaparib/ bevacizumab N=535	Placebo/ bevacizumab N=267	
Any AE	73 (13.6)	36 (13.5)	243 (15.3)
Any AE of CTCAE Grade 3 or higher	2 (0.4)	2 (0.7)	4 (0.3)
Any AE with outcome = death	0	0	0
Any SAE	0	0	2 (0.1)
AEs leading to dose reduction of olaparib or placebo	3 (0.6)	1 (0.4)	1 (0.1)
AEs leading to treatment interruption of olaparib or placebo	3 (0.6)	5 (1.9)	9 (0.6)
Any AE leading to discontinuation of olaparib or placebo	1 (0.2)	1 (0.4)	0

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

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

AE Adverse event; bd Twice daily; CTCAE Common Terminology Criteria for Adverse Events; DCO Data cut-off; N Total number of patients; SAE Serious adverse event; SAS Safety Analysis Set. (DCO: 22 March 2019).

Dizziness

Table 66: PAOLA-1 and the 300 mg bd pool: Patients who had at least one AE of dizziness reported in any category

AE category[a]	Number (%) of patients		
	PAOLA-1 SAS, overall study duration		Olaparib 300 mg bd pool (N=1585)
	Olaparib/ bevacizumab (N=535)	Placebo/ bevacizumab (N=267)	
Any AE	14 (2.6)	5 (1.9)	181 (11.4)
Any AE of CTCAE Grade 3 or higher	2 (0.4)	1 (0.4)	1 (0.1)
Any AE with outcome = death	0	0	0
Any SAE	0	0	1 (0.1)
AEs leading to dose reduction of olaparib or placebo	0	1 (0.4)	2 (0.1)
AEs leading to treatment interruption of olaparib or placebo	0	1 (0.4)	8 (0.5)
Any AE leading to discontinuation of olaparib or placebo	1 (0.2)	0	1 (0.1)

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

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

AE Adverse event; bd Twice daily; CTCAE Common Terminology Criteria for Adverse Events; DCO Data cut-off; N Total number of patients; SAE Serious adverse event; SAS Safety Analysis Set. (DCO: 22 March 2019).

Dysgeusia

Table 67:PAOLA-1 and the 300 mg bd pool: Patients who had at least one AE of dysgeusia reported in any category

AE category[a]	Number (%) of patients		
	PAOLA-1 SAS, overall study duration		Olaparib 300 mg bd pool (N=1585)
	Olaparib/ bevacizumab N=535	Placebo/ bevacizumab N=267	
Any AE	42 (7.9)	3 (1.1)	236 (14.9)
Any AE of CTCAE Grade 3 or higher	1 (0.2)	0	0
Any AE with outcome = death	0	0	0
Any SAE	0	0	0
AEs leading to dose reduction of olaparib or placebo	1 (0.2)	0	3 (0.2)
AEs leading to treatment interruption of olaparib or placebo	2 (0.4)	0	0
Any AE leading to discontinuation of olaparib or placebo	1 (0.2)	0	0

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

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

AE Adverse event; bd Twice daily; CTCAE Common Terminology Criteria for Adverse Events; DCO Data cut-off; N Total number of patients; SAE Serious adverse event; SAS Safety Analysis Set. (DCO: 22 March 2019).

Cough

Table 68: PAOLA-1 and the 300 mg bd pool: Patients who had at least one AE of cough (grouped term analysis) reported in any category

AE category[a]	Number (%) of patients		
	PAOLA-1 SAS, overall study duration		Olaparib 300 mg bd pool (N=1585)
	Olaparib/ bevacizumab N=535	Placebo/ bevacizumab N=267	
Any AE	25 (4.7)	11 (4.1)	224 (14.1)
Any AE of CTCAE Grade 3 or higher	0	0	2 (0.1)
Any AE with outcome = death	0	0	0
Any SAE	0	0	1 (0.1)
AEs leading to dose reduction of olaparib or placebo	0	0	0
AEs leading to treatment interruption of olaparib or placebo	2 (0.4)	0	9 (0.6)
Any AE leading to discontinuation of olaparib or placebo	0	0	1 (0.1)

Grouped term consisting of cough and productive cough

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

Includes AEs with an onset date between the date of first dose and 30 days following the date of last dose of study treatment. Hypersensitivity grouped term consisting of hypersensitivity and drug hypersensitivity.

AE Adverse event; bd Twice daily; CTCAE Common Terminology Criteria for Adverse Events; DCO Data cut-off; N Total number of patients; SAE Serious adverse event; SAS Safety Analysis Set. (DCO: 22 March 2019).

Dyspnoea

Table 69: PAOLA-1 and the 300 mg bd pool: Patients who had at least one AE of dyspnoea (grouped term analysis) reported in any category

AE category[a]	Number (%) of patients		
	PAOLA-1 SAS, overall study duration		Olaparib 300 mg bd pool (N=1585)
	Olaparib/ bevacizumab N=535	Placebo/ bevacizumab N=267	
Any AE	42 (7.9)	9 (3.4)	218 (13.8)
Any AE of CTCAE Grade 3 or higher	5 (0.9)	1 (0.4)	18 (1.1)
Any AE with outcome = death	0	1 (0.4)	0
Any SAE	2 (0.4)	1 (0.4)	8 (0.5)
AEs leading to dose reduction of olaparib or placebo	2 (0.4)	0	2 (0.1)
AEs leading to treatment interruption of olaparib or placebo	3 (0.6)	1 (0.4)	15 (0.9)
Any AE leading to discontinuation of olaparib or placebo	1 (0.2)	2 (0.7)	2 (0.1)

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

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

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

AE Adverse event; bd Twice daily; CTCAE Common Terminology Criteria for Adverse Events; DCO Data cut-off; N Total number of patients; SAE Serious adverse event; SAS Safety Analysis Set. (DCO: 22 March 2019).

Important potential risks for olaparib

MDS/AML, pneumonitis and new primary malignancies have been classified in the risk management plan as important potential risks. For the majority of studies with olaparib, including PAOLA-1, 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 is 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) consists 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 are included in the olaparib monotherapy combined therapeutic dose pool.

Olaparib monotherapy all doses pool (n=2783 patients) consists of all patients who have received at least 1 dose of olaparib as a monotherapy treatment (tablet or capsule formulation) at any dose. In addition, 66 patients from Study 41 are included (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 are included in the olaparib monotherapy all doses pool.

The entire clinical programme pool as of 15 June 2019 (n=11919 patients) includes all the studies shown in 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 PAOLA-1, there were 4 patients with events of MDS or AML in the olaparib/bevacizumab arm and 1 patient with an event of AML in the placebo/bevacizumab arm, which occurred on treatment, within the 30-day follow-up or in the post-follow-up period.

Table 70: Events of MDS/AML occurring in PAOLA-1

Event		***tBRCA* status**	**Day of last dose of study treatment in PAOLA-1**	**Reason for treatment discontinuation**	**Day of MDS/AML AE onset (from start of study treatment)**	**Number of cycles of prior platinum therapy**	**AE outcome**
Olaparib/bevacizumab arm							
MDS evolving to AML		Non-*tBRCA*	212	Anaemia	234	9 cycles carboplatin/ paclitaxel	Fatal Possibly related to olaparib*
MDS evolving to AML		Non-*tBRCA*	378	MDS	377	6 cycles carboplatin/ paclitaxel	Fatal Possibly related to olaparib*
AML		*tBRCA* (*BRCA1*)	627	Neutropenia	652	8 cycles carboplatin/ paclitaxel	Not recovered Possibly related to olaparib*
MDS		Non-*tBRCA*	196	MDS	201	6 cycles carboplatin/ paclitaxel	Recovered Possibly related to olaparib*
Placebo/bevacizumab arm							
Acute leukaemia		*tBRCA* (*BRCA1*)	340	Disease progression on Day 340	554	6 cycles carboplatin/ paclitaxel	Recovered with sequelae

CTCAE Version 4.03.

AE Adverse event; AML Acute myeloid leukaemia; CSR Clinical study report; CTCAE Common Terminology Criteria for Adverse Events; DCO Data cut-off; MDS Myelodysplastic syndrome; *tBRCA* Tumour breast cancer susceptibility gene.

(DCO: 22 March 2019)

* As assessed by the investigator.

The incidence in the olaparib/bevacizumab arm of PAOLA-1 (0.7%) was lower than that seen for olaparib in studies in ovarian cancer (SOLO1 [1.2%], SOLO2 [2.1%], Study 19 [1.5%]) and consistent with the incidence in the larger monotherapy pool population for the olaparib clinical programme (1.1%). The incidence of MDS/AML cases was similar among g*BRCA1m* and g*BRCA2m* patients (1.6% and 1.0%, respectively) in patients treated in clinical trials with Lynparza monotherapy.

Including all patients exposed to olaparib during clinical development provides data for 11919 patients (as of 15 June 2019). In this population, 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 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 outcome was reported as recovered.

There have also been reports of MDS/AML from post marketing surveillance, consistent with the characterisation of the events reported from monotherapy clinical studies, the ongoing open-label monotherapy studies, the ongoing MAP programme, combination studies with olaparib and events from placebo-controlled, blinded monotherapy studies.

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 outcome was reported as recovered.

There have also been reports of MDS/AML from post marketing surveillance, consistent with the characterisation of the events reported from monotherapy clinical studies.

New primary malignancies

A review of the SOC of "Neoplasms benign, malignant and unspecified" showed that during treatment, 9 patients (1.7%) in the olaparib/bevacizumab arm and 3 (1.1%) patients in the placebo/bevacizumab arm had events in this SOC. In the post-follow-up period, there were 5 (0.9%) patients in the olaparib/bevacizumab arm and 2 (0.2%) patients in the placebo/bevacizumab arm who had events in this SOC.

The following events were excluded for the reasons described below:

- AEs of MDS/AML were considered separately

- In the olaparib/bevacizumab arm, 1 patient with a squamous cell carcinoma was excluded as this was a non-melanoma skin cancer; 1 patient with liver metastases and 1 patient with tumour pain were excluded as these were considered disease progression AEs.

- In the placebo/bevacizumab arm, 1 patient with an AE of paraganglion neoplasm was excluded as this was a benign tumour.

Therefore, there were 6 (1.1%) patients in the olaparib/bevacizumab arm and 3 (1.1%) patients in the placebo/bevacizumab arm with new primary malignancies. The AEs of new primary malignancies in PAOLA-1 compared with other studies in the clinical programme. 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 71: Summary of AEs of new primary malignancies occurring across the olaparib programme

		Olaparib		Comparator[a]	
		Number of AEs	Incidence	Number of AEs	Incidence
PAOLA-1 N=535 olaparib/bevacizumab N=267 placebo/bevacizumab	Ovarian	6	1.1%	3	1.1%
SOLO3 N=178 olaparib N=76 chemotherapy	Ovarian	3	1.7%	0	0
SOLO1 N=260 olaparib N=130 placebo	Ovarian	5	1.9%	3	2.3%
SOLO2 N=195 olaparib N=99 placebo	Ovarian	1	1.5%	1	1.0%
Study 19 N=136 olaparib N=128 placebo	Ovarian	4	2.9%	1	0.8%
PROfound N=256 olaparib N=130 investigators choice of NHA	Prostate cancer	1	0.4%	2	1.5%
POLO N=91 olaparib N=60 placebo	Pancreatic cancer, prior platinum	0	0	0	NA
OlympiAD N=205 olaparib N=91 physician's choice	Breast cancer, prior platinum	1	0.5%	0	0
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), one patient reported both a basal cell carcinoma and squamous cell carcinoma and one 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, glioma, 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, ESRs and the MAP) provides data for 11919 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 PAOLA-1 (22 March 2019), it was reported that 6 (1.1%) patients in the olaparib/bevacizumab arm (3 AE of interstitial lung disease, 2 AEs of pneumonitis and 1 AE of bronchiolitis) and no patients in the placebo/bevacizumab arm had an AE of pneumonitis.

The pneumonitis AEs reported with olaparib in PAOLA-1 were generally mild or moderate; all of the 6 AEs were CTCAE Grade 1 or 2 and 2 of the 6 cases were non-serious. There were no AEs of CTCAE Grade 3 severity and 4 SAEs. In 4 of the 6 patients, treatment was interrupted and the pneumonitis AE resolved; no re-occurrence or worsening of pneumonitis was reported following treatment restart (negative re-challenge). Olaparib treatment was continued in 1 patient and in 1 patient, the pneumonitis AEs led to treatment discontinuation.

In the larger pool (therapeutic dose pool), the incidence of pneumonitis events was 0.9% (20 cases reported). Of the 20 pneumonitis AEs in the olaparib monotherapy combined therapeutic dose pool (n = 2351), 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.

AstraZeneca's global Patient Safety database contains all AE reports, from spontaneous sources (eg, 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 onto 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 AstraZeneca 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 (e.g., 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, as potential confounders before starting olaparib treatment.

Main adverse drug reactions related to bevacizumab

The purpose of this section is to provide a more detailed assessment of the AEs for bevacizumab that are listed in the product label as ADRs and are considered to be AESIs. This summary focuses only on data from the PAOLA-1 SAS (overall study duration). The section does not discuss hematologic toxicity which is also known for bevacizumab but is discussed above in the subsection on ADR related to olaparib.

Hypertension

Hypertension is reported as a very common ADR for bevacizumab treatment (AEs and clinically significant/severe AEs of hypertension are reported to occur at an incidence of more than ≥1/10 patients).

AEs of hypertension were reported for a lower percentage of patients in the olaparib/bevacizumab arm (45.8%) and the placebo/bevacizumab arm (59.9%). More than half of the hypertension AEs were mild or moderate in severity and the majority of patients with hypertension AEs had events in the combination period in both treatment arms, (223 [91.0%] of 245 patients in the olaparib/bevacizumab arm and 153 [95.6%] of 160 patients in the placebo/bevacizumab arm).

The proportion of patients with CTCAE Grade 3 AEs of hypertension was lower in the olaparib/bevacizumab arm, compared with the placebo/bevacizumab arm of PAOLA-1. There were no Grade 4 AEs of hypertension. SAEs of hypertension were reported in a slightly lower proportion of patients in olaparib/bevacizumab arm (9.0% of patients) compared with the placebo/bevacizumab arm (13.1% of patients).

AE onset data for PAOLA-1 showed that the majority of first AEs of hypertension in both treatment arms of PAOLA-1 occurred in the first 360 days of study treatment. This corresponds with the median duration of bevacizumab treatment in each treatment arm (11.0 months [approximately 336 days] in the olaparib/bevacizumab arm and 10.4 months [approximately 316 days] in the placebo/bevacizumab arm; consistent with most of the AEs of hypertension being associated with bevacizumab treatment. A similar number of patients in each arm had a first AE of hypertension in the first month of treatment with rates of 17.8% and 20.2%, for olaparib/bevacizumab and placebo/bevacizumab treated patients, respectively.

Despite the incidence of AEs, CTCAE Grade ≥3 AEs and SAEs of hypertension, AEs of hypertension rarely led to dose modification of olaparib or placebo treatment in PAOLA-1 and none led to discontinuation of olaparib or placebo treatment.

Proteinuria

Proteinuria is reported as a very common ADR for bevacizumab treatment (AEs of proteinuria are reported to occur at an incidence of more than ≥1/10 patients and clinically significant/severe AEs of proteinuria are reported to occur at an incidence of between ≥1/100 and <1/10 patients). Proteinuria was reported as an AE for a lower proportion of patients in the olaparib/bevacizumab arm (5.8%), compared the placebo/bevacizumab arm (15.4%). AEs of proteinuria were predominantly Grade 1 or 2 in severity and none led to permanent discontinuation of treatment.

The majority of patients with proteinuria AEs had events in the combination period in both treatment arms, (26 [83.9%] of 31 patients in the olaparib/bevacizumab arm and 37 [90.2%] of 41 patients in the placebo/bevacizumab arm).

The time to first AE of proteinuria was similar in the two arms. All of the AEs of proteinuria in the olaparib/bevacizumab arm, and the majority in the placebo/bevacizumab arm, had a first onset in the first 450 days of study (only 2 patients in the placebo/bevacizumab arm had AEs of proteinuria in the period from Day 451 to Day 540 and no patients in either arm had AEs after Day 541. This corresponds with the median duration of bevacizumab treatment in each treatment arm (11.0 months [approximately 336 days] in the olaparib/bevacizumab arm and 10.4 months [approximately 316 days] in the placebo/bevacizumab arm consistent with most of the AEs of proteinuria being associated with bevacizumab treatment.

An analysis of urinary protein values showed that the majority of patients in both treatment arms had values that were normal or showed a trace of urinary protein at each visit.

GI perforation, abscesses and fistulae (any grade)

AEs of GI perforation, abscesses and fistulae are reported as common ADRs for bevacizumab treatment (AEs and clinically significant/severe AEs are reported to occur at an incidence of between ≥1/100 and <1/10 patients). AEs of GI perforation, abscesses and fistulae were reported for a low percentage of patients in the olaparib/bevacizumab arm (2 patients [0.4%]) and the placebo/bevacizumab arm (2 patients [0.7%]). All AEs were reported during the combination phase. All events were Grade ≥3 in severity and 1 event (intestinal perforation) was reported as fatal in a patient in the placebo/bevacizumab arm. One patient on each arm reported an SAE. AEs of GI perforation, abscesses and fistulae led to treatment interruption of olaparib in 0.4% of the olaparib/bevacizumab arm. There were no dose reductions or discontinuation of olaparib or placebo treatment.

Haemorrhagic events (including wound healing complication)

Wound healing complications are reported as common/very common ADRs for bevacizumab treatment (AEs of wound healing complications are reported to occur at an incidence of more than ≥1/10 patients and clinically significant/severe AEs of wound healing complications are reported to occur at an incidence of between ≥1/100 and <1/10 patients).

AEs of haemorrhagic events (reported terms: cerebral haemorrhage, contusion, epistaxis, gastric haemorrhage, gingival bleeding, haemorrhagic disorder, intestinal haemorrhage, melaena, petechiae, rectal haemorrhage and vaginal haemorrhage) were reported for a similar percentage of patients in the olaparib/bevacizumab arm (9.7%) and the placebo/bevacizumab arm (10.5%). These events were predominantly Grade 1 or 2 in severity and none of the AEs in the olaparib/bevacizumab arm led to permanent discontinuation of treatment. The majority of patients with haemorrhage AEs had events in the combination period in both treatment arms, (48 [92.3%] of 52 patients in the olaparib/bevacizumab arm and 24 [85.7%] of 28 patients in the placebo/bevacizumab arm).

A low number of patients had AEs of wound healing complications. In the olaparib/bevacizumab arm 3 (0.6%) patients, had AEs, all of which occurred during the combination phase; in the placebo/bevacizumab arm, 5 (1.9%) patients had 6 AEs (only 1 patient had 1 AE during the combination phase). One AE in each arm was CTCAE Grade 3 (an AE of wound dehiscence in the olaparib/bevacizumab arm and an AE of wound complication in the placebo/bevacizumab arm), all other events were mild or moderate in severity. One placebo/bevacizumab-treated patient reported an SAE (of impaired healing, CTCAE Grade 2) on Day 362 of study. There were no AEs of wound healing that led to treatment interruption in the olaparib/bevacizumab arm and 0.7% AEs of wound healing led to treatment interruption of placebo in the placebo/bevacizumab arm. There were no dose reductions or discontinuations of olaparib or placebo due to AEs of wound healing.

In addition, there were 6 patients who had AEs of wound evisceration, which were not included in the grouped term for wound healing complications. Four (0.7%) patients were in the olaparib/bevacizumab arm and 2 (0.7%) patients were in the placebo/bevacizumab arm; none of the AEs in the olaparib/bevacizumab arm and 1 of the 2 AEs in the placebo/bevacizumab arm occurred during the combination phase. Of the 4 AEs in the olaparib/bevacizumab arm, 1 patient had a CTCAE Grade 3 SAE which was considered related to olaparib and also led to treatment discontinuation; this event recovered after 6 days. Of the 3 remaining events, 2 were CTCAE Grade 2 (1 event was an SAE and 1 event led to dose interruption; both events were reported as resolved) and 1 was CTCAE Grade 1 (this event occurred in follow-up and a resolution date was not provided). In the placebo/bevacizumab arm, 1 patient had a CTCAE Grade 2 SAE which led to discontinuation and 1 patient had a CTCAE Grade 1 AE. None of the CTCAE Grade ≤2 AEs were considered related to olaparib and none of the patients with AEs of wound evisceration had other AEs that were included in the grouped term for wound healing complications.

Thromboembolic events

Thromboembolic events are reported as common/very common ADR for bevacizumab treatment (AEs of venous thromboembolic events are reported to occur at an incidence of more than ≥1/10 patients and clinically significant/severe AEs of arterial thromboembolic events are reported to occur at an incidence of between ≥1/100 and <1/10 patients). AEs of arterial thromboembolic events (reported terms of acute myocardial infarction, cerebrovascular accident, embolism, myocardial infarction, thrombosis and transient ischaemic attack) were reported for 9 (1.7%) patients in the olaparib/bevacizumab arm and 8 (3.0%) patients in the placebo/bevacizumab arm.

The majority of patients with AEs in the grouped term of arterial thromboembolic events occurred in the combination period in both treatment arms, (6 [66.7%] of 9 patients in the olaparib/bevacizumab arm and 5 [62.5%] of 8 patients in the placebo/bevacizumab arm).

In the olaparib/bevacizumab arm 0.6% of patients reported CTCAE Grade 3 events, no patients reported Grade 4 events. In the placebo/bevacizumab arm 2.6% of patients reported CTCAE Grade ≥3 events, of which 2 patient (0.7%) reported Grade 4 events and 1 patient (0.4%) reported a fatal event. All Grade 4 and 5 events were myocardial infarction. Two patients in the olaparib/bevacizumab arm had SAEs (both SAEs of embolism), compared with 6 patients in the placebo/bevacizumab arm (4 patients with myocardial infarction, 1 patient with an acute myocardial infarction and 1 patient with a cerebrovascular accident). Two of the myocardial infarction AEs in the placebo/bevacizumab arm were fatal. Two patients in the placebo/bevacizumab arm discontinued study treatment due to AEs of myocardial infarction.

AEs of venous thromboembolic events (grouped term consisting of the PTs of deep vein thrombosis, pulmonary embolism, thrombophlebitis and venous thrombosis) were reported for 17 (3.2%) of patients in the olaparib/bevacizumab arm and 4 (1.5%) of patients in the placebo/bevacizumab arm. The majority of patients with AEs in the grouped term of venous thromboembolic events occurred in the combination period in both treatment arms, (10 [58.8%] of 17 patients in olaparib/bevacizumab arm and 3 [75.0%] of 4 patients in the placebo/bevacizumab arm). At the event level, 10 (52.6%) of 19 AEs in the venous thromboembolic events grouped term in the olaparib/bevacizumab arm and 3 (75.0%) of 4 AEs in the placebo/bevacizumab arm occurred in the combination period.

On the olaparib/bevacizumab arm, 8 (1.5%) of patients reported CTCAE Grade ≥3 events, 2 patients reported CTCAE Grade 4 events (both had pulmonary embolism SAEs). In the placebo/bevacizumab arm, 1 (0.4%) patient a reported CTCAE Grade 3 AE (pulmonary embolism); no patients reported Grade 4 events. Six patients in the olaparib/bevacizumab arm had SAEs (5 patients with SAEs of pulmonary embolism and 1 patient with an SAE of venous thrombosis), compared with 1 patient in the placebo/bevacizumab arm (1 patient with an SAE of pulmonary embolism). None of the events were fatal or led to discontinuation of olaparib or placebo treatment.

Posterior reversible encephalopathy syndrome (PRES)

AEs of PRES are reported rare AEs for bevacizumab treatment (AEs of PRES are reported to occur at an incidence of between ≥1/10,000 and <1/1,000 patients). An AE of PRES was reported for 1 patient in the placebo/bevacizumab arm, which occurred during the combination phase. This AE was CTCAE Grade 2, non-serious, and did not lead to death, discontinuation, dose reduction or modification.

Congestive heart failure (CHF)

Congestive heart failure is reported as a common ADR for bevacizumab treatment (AEs and clinically significant/severe AEs of congestive heart failure [reported term: cardiac failure chronic] are reported to occur at an incidence of between ≥1/100 and <1/10 patients). An AE of cardiac failure chronic was reported

for 1 patient in the olaparib/bevacizumab arm, which occurred outside of the combination phase. The AE was CTCAE Grade 3, non-serious, and did not lead to death, discontinuation, dose reduction or modification.

Non-GI fistula or abscess (any grade)

AEs of fistula in the SOC of musculoskeletal and connective tissue disorders are reported as common AEs for bevacizumab treatment (AEs and clinically significant/severe AEs of fistula [grouped term] are reported to occur at an incidence of between ≥1/100 and <1/10 patients). Two AEs of non-GI fistula or abscess (reported terms of abscess, fistula, nasal septum perforation and urogenital fistula) were reported in the olaparib/bevacizumab arm (urogenital fistula [1 patient, 0.2%] and fistula [1 patient, 0.2%]) and 2 AEs in the placebo/bevacizumab arm (nasal septum perforation [1 patient, 0.4%] and abscess [1 patient, 0.4%]). One AE in each arm was CTCAE Grade 3: urogenital fistula in the olaparib/bevacizumab arm (also an SAE), and the event of nasal septum perforation in the placebo/bevacizumab arm. Only the AE of abscess in the placebo/bevacizumab arm led to dose interruption.

Laboratory findings

Haematology

The proportion of olaparib/bevacizumab-treated patients with a decrease in haemoglobin of CTCAE Grade ≥3 during the study was 12.5%; the proportion of olaparib/bevacizumab-treated patients with abnormal CTCAE Grade of 3 or 4 values for other haematological parameters was generally ≤10%. Anaemia was the second most frequently reported CTCAE Grade ≥3 AE and SAE, and the most frequently reported DAE.

In the olaparib/bevacizumab treatment arm, the proportion of patients with abnormal haematology values of CTCAE Grade ≥3 was similar for each parameter for the overall study period and the combination only phase, when corrected for duration of exposure (Table 72).

Table 72: PAOLA-1: Number (%) of patients with maximum overall CTCAE grades during treatment for key haematological parameters (SAS)

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Haemoglobin (low)					
Olaparib/bevacizumab (overall study duration)	114/534 (21.3%)	246/534 (46.1%)	107/534 (20.0%)	67/534 (12.5%)	0
Olaparib/bevacizumab (combination phase only)	138/530 (26.0%)	238/530 (44.9%)	95/530 (17.9%)	59/530 (11.1%)	0
Placebo/bevacizumab	131/267 (49.1%)	120/267 (44.9%)	16/267 (6.0%)	0	0
Platelets					
Olaparib/bevacizumab (overall study duration)	354/534 (66.3%)	155/534 (29.0%)	13/534 (2.4%)	8/534 (1.5%)	4/534 (0.7%)
Olaparib/bevacizumab (combination phase only)	370/530 (69.8%)	141/530 (26.6%)	12/530 (2.3%)	6/530 (1.1%)	1/530 (0.2%)
Placebo/bevacizumab	197/267 (73.8%)	69/267 (25.8%)	1/267 (0.4%)	0	0
Leukocytes					
Olaparib/bevacizumab (overall study duration)	220/534 (41.2%)	190/534 (35.6%)	107/534 (20.0%)	14/534 (2.6%)	3/534 (0.6%)
Olaparib/bevacizumab (combination phase only)	242/530 (45.7%)	184/530 (34.7%)	93/530 (17.5%)	11/530 (2.1%)	0
Placebo/bevacizumab	152/267 (56.9%)	83/267 (31.1%)	29/267 (10.9%)	2/267 (0.7%)	1/267 (0.4%)
Neutrophils					
Olaparib/bevacizumab (overall study duration)	346/534 (64.8%)	71/534 (13.3)	83/534 (15.5%)	24/534 (4.5%)	10/534 (1.9%)
Olaparib/bevacizumab (combination phase only)	360/530 (67.9%)	72/530 (13.6%)	73/530 (13.8%)	21/530 (4.0%)	4/530 (0.8%)
Placebo/bevacizumab	191/267 (71.5%)	31/267 (11.6%)	38/267 (14.2%)	7/267 (2.6%)	0

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Lymphocytes (low)					
Olaparib/bevacizumab (overall study duration)	199/533 (37.3%)	149/533 (28.0%)	135/533 (25.3%)	47/533 (8.8%)	3/533 (0.6%)
Olaparib/bevacizumab (combination phase only)	238/529 (45.0%)	146/529 (27.6%)	111/529 (21.0%)	33/529 (6.2%)	1/529 (0.2%)
Placebo/bevacizumab	161/267 (60.3%)	69/267 (25.8%)	31/267 (11.6%)	5/267 (1.9%)	1/267 (0.4%)

CSR Clinical study report; CTCAE Common Terminology Criteria for Adverse Events; DCO Data cut-off; SAS Safety Analysis Set.

Derived from laboratory assessments using local reference ranges after start of treatment up to the last dose of study medication.

Data derived from Table 14.3.7.1.2.1.1, PAOLA-1 CSR, Module 5.3.5.1 (DCO: 22 March 2019).

Clinical chemistry

Table 73: PAOLA-1: Number (%) of patients with maximum overall CTCAE grades during treatment for key clinical chemistry parameters (SAS)

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
ALT elevated					
Olaparib/bevacizumab (overall study duration)	408/534 (76.4%)	119/534 (22.3%)	6/534 (1.1%)	1/534 (0.2%)	0
Olaparib/bevacizumab (combination phase only)	434/530 (81.9%)	92/530 (17.4%)	4/530 (0.8%)	0	0
Placebo/bevacizumab	191/267 (71.5%)	71/267 (26.6%)	3/267 (1.1%)	2/267 (0.7%)	0
AST elevated					
Olaparib/bevacizumab (overall study duration)	369/534 (69.1%)	154/534 (28.8%)	8/534 (1.5%)	3/534 (0.6%)	0
Olaparib/bevacizumab (combination phase only)	399/530 (75.3%)	125/530 (23.6%)	5/530 (0.9%)	1/530 (0.2%)	0
Placebo/bevacizumab	179/267 (67.0%)	85/267 (31.8%)	1/267 (0.4%)	2/267 (0.7%)	0
ALP elevated					
Olaparib/bevacizumab (overall study duration)	423/531 (79.7)	97/531 (18.3%)	8/531 (1.5%)	3/531 (0.6%)	0
Olaparib/bevacizumab (combination phase only)	463/527 (87.9%)	56/527 (10.6%)	5/527 (0.9%)	3/527 (0.6%)	0
Placebo/bevacizumab	208/263 (79.1)	53/263 (20.2%)	1/263 (0.4%)	1/263 (0.4%)	0
Bilirubin elevated					
Olaparib/bevacizumab (overall study duration)	481/534 (90.1%)	40/534 (7.5%)	10/534 (1.9%)	3/534 (0.6%)	0
Olaparib/bevacizumab (combination phase only)	489/529 (92.4%)	31/529 (5.9%)	7/529 (1.3%)	2/529 (0.4%)	0
Placebo/bevacizumab	253/267 (94.8%)	12/267 (4.5%)	1/267 (0.4%)	1/267 (0.4%)	0

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Creatinine increased					
Olaparib/bevacizumab (overall study duration)	210/533 (39.4%)	173/533 (32.5%)	148/533 (27.8%)	0	2/533 (0.4%)
Olaparib/bevacizumab (combination phase only)	233/529 (44.0%)	184/529 (34.8%)	110/529 (20.8%)	0	2/529 (0.4%)
Placebo/bevacizumab	168/266 (63.2%)	79/266 (29.7%)	17/266 (6.4%)	1/266 (0.4%)	1/266 (0.4%)

ALP Alkaline phosphatase; ALT Alanine aminotransferase; AST Aspartate aminotransferase; CSR Clinical study report; CTCAE Common Terminology Criteria for Adverse Events; DCO Data cut-off; SAS Safety Analysis Set.

Derived from laboratory assessments using local reference ranges after start of treatment up to the last dose of study medication.

Data derived from Table 14.3.7.1.2.1.1, PAOLA-1 CSR, Module 5.3.5.1 (DCO: 22 March 2019).

Assessment of the potential for drug-induced liver injury

Based on all available data there is no evidence to suggest that olaparib causes DILI. There were no confirmed or suspected Hy's Law cases. No olaparib/bevacizumab-treated patients in PAOLA-1 had concurrent elevations of bilirubin and ALT/AST.

In PAOLA-1, the majority of patients in the olaparib/bevacizumab arm and placebo/bevacizumab arms had a maximum on-treatment AST (522/534 [97.8%] and 262/267 [98.1%] patients, respectively) and ALT (523/534 [97.9%] and 261/267 [97.7%] patients, respectively) below 3 × ULN.

Of the few patients with AST or ALT values above 3 × ULN in PAOLA-1, 3 olaparib/bevacizumab-treated patients and 1 placebo/bevacizumab-treated patient had AST or ALT values in the range ≥10 × ULN to <20 × ULN. No patients in either treatment arm had an AST or ALT value of ≥20 × ULN.

In PAOLA-1, there were no patients who had CTCAE Grade 4 laboratory values for ALT and AST; the proportion of patients with CTCAE Grade 3 elevations was low in both treatment arms.

An assessment of ALT, AST maximal elevations during treatment by maximal total bilirubin elevations showed that no patients in the either treatment arm had concurrent elevation of bilirubin and either ALT or AST. A similar proportion of olaparib/bevacizumab-treated patients in the PAOLA-1 study had hepatic metastases (6.0% of patients) at baseline, compared with SOLO1 (5.0% patients) and PROfound (9.8% of patients); the proportion of olaparib/bevacizumab-treated patients in the PAOLA-1 study with hepatic metastases was lower than for SOLO2 (13.8% patients), SOLO3 (12.4% patients); OlympiAD (38.5% patients) and POLO (66.3%).

In the 300 mg bd pool, the majority (1469/1572 [93.4%] patients) had combined AST or ALT below 3 × ULN. In the 300 mg bd pool, 26 (1.7%) patients had an ALT increased laboratory value (worst grade) of CTCAE Grade 3 and 2 patients (0.1%) had an ALT increased laboratory value of CTCAE Grade 4; 36 (2.3%) patients had a CTCAE Grade 3 laboratory value of AST increased; no patients had an AST increased laboratory value of CTCAE Grade 4. The proportion of patients with CTCAE Grade ≥3 laboratory values of ALT or AST in the 300 mg bd pool was higher than that in the olaparib/bevacizumab arm of the PAOLA-1 study (0.2% and 0.6%, respectively)

The proportion of olaparib/bevacizumab-treated patients with CTCAE Grade 3 AEs in the PAOLA-1 study and in the 300 mg bd pool was low and similar to the proportion of patients with CTCAE Grade 3 abnormal laboratory values. In PAOLA-1, 1 (0.2%) olaparib/bevacizumab-treated patient had CTCAE Grade 3 AE report of AST increased (there were no CTCAE Grade 3 AE reports of ALT increased). In the 300 mg bd pool, 11 (0.7%) patients had a CTCAE Grade 3 AE report of AST increased and 10 (0.6%) patients had a CTCAE Grade 3 AE report of ALT increased;

An assessment of combined elevations of ALT and bilirubin was conducted for all patients in the 300 mg bd pool. Of these 1585 patients, 23 patients reported elevations of both AST or ALT >3 × ULN and total bilirubin >2 × ULN, irrespective of ALP, at any point during their study treatment. A detailed evaluation of medical history, progression of disease, temporal association for the 23 patients with elevated ALP (>2 × ULN for 21 patients and <1 × ULN for 2 patients) and other factors showed that all 23 patients had alternative explanations for elevations of ALT and bilirubin, generally suggestive of obstructive causes, or cancer disease progression, including disease progression in the liver.

The evaluation of hepatic function laboratory data, in conjunction with an assessment of reported hepatobiliary/abnormal hepatic biochemistry AEs did not identify risk of DILI in the olaparib/bevacizumab-treated patient population.

Assessment of potential for renal impairment

Mild elevations in creatinine have been observed with no apparent sequelae and with resolution on discontinuing olaparib, with no change in other renal function biochemistry tests (urea/blood urea nitrogen [BUN]). The small increases in creatinine observed with olaparib and the rapid onset of the mild changes observed, with a return to baseline after olaparib discontinuation are consistent with the finding that olaparib is known to be an inhibitor of OCT2 and MATE1.

In the olaparib/bevacizumab arm of PAOLA-1, 94.2% of olaparib/bevacizumab-treated patients had normal creatinine levels at baseline, 5.8% had CTCAE Grade 1 at baseline and no patients had CTCAE Grade ≥2 at baseline. A total of 170/533 (31.9%) patients had a single worsening change in CTCAE Grade (most changes were normal to Grade 1) and 134/533 (25.1%) patients had worsening 2 grade shifts in CTCAE Grade for creatinine; 2 patients had a shift from normal at baseline to CTCAE Grade 4 on treatment. In the placebo/bevacizumab arm of PAOLA-1, 93.2% of patients had normal creatinine at baseline and 6.8% had CTCAE Grade 1 at baseline; of these patients, 63/266 (23.7%) patients had a single change in CTCAE Grade

(all except 1 patient had changes from normal to Grade 1); 16/266 (6.0%) patients had worsening 2 grade shifts in CTCAE Grade for creatinine and 2 patients had a shift from normal at baseline to CTCAE Grade 3 or 4 on treatment.

Data from all patients in the 300 mg bd pool showed that a higher proportion of patients in the 300 mg bd pool had CTCAE grade shifts in creatinine, compared with PAOLA-1. 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%) patient had a 3 grade shift in creatinine (all were Grade 0 to Grade 3).

Safety in special populations

Intrinsic factors

Effect of gender

As all patients in the PAOLA-1 study were female, an analysis of the effects of gender has been conducted in the 300 mg bd pool.

Table 74: 300 mg bd pool: Number of patients reporting at least one adverse event by gender (SAS)

AE category	Number (%) of patients[a]	
	Olaparib 300mg bd tablet	
	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)

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

Includes AEs with an onset date between the first dose of continuous treatment and 30 days following the last dose of continuous treatment (excludes 8 patients [10 AEs] from D0816C00010 with pre-treatment AEs defined as treatment-emergent per CSR).

Effect of age

Table 75: 300 mg bd pool: number of patients reporting at least one adverse event by age group

MedDRA term	Number (%) of patients[a]			
	Age <65 years (N=1145)	Age 65 to 74 years (N=334)	Age 75 to 84 years (N=103)	Age ≥85 years (N=6)
Total AEs	1111 (97.3)	326 (97.6)	99 (96.1)	6 (100)
Total SAEs[a]	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)
Other (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)
Total 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 percentage points 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 percentage points 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 percentage points 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 did not reveal major differences.

Effect of race

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.

Table 76: 300 mg bd pool: Number (%) of patients who had at least 1 AE in any category by race (White patients, Asian patients and other non-White patients)

AE category[a]	Number (%) of patients		
		Non-White patients	
	White patients (N=1199)	Asian patients (N=331)	Other patients[b] (N=40)
Any AE	1172 (97.7)	317 (95.8)	38 (95.0)
Any AE of CTCAE Grade 3 or higher	477 (39.8)	156 (47.1)	17 (42.5)
Any AE with outcome = death	15 (1.3)	4 (1.2)	0
Any SAE (including events with outcome = death)	274 (22.9)	79 (23.9)	7 (17.5)
Any AE leading to dose reduction of study treatment	264 (22.0)	62 (18.7)	10 (25.0)
Any AE leading to interruption of study treatment	468 (39.0)	138 (41.7)	16 (40.0)
Any AE leading to discontinuation of study treatment	115 (9.6)	26 (7.9)	3 (7.5)

AEs that occurred at a higher incidence in Asian patients (≥5 percentage points 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 percentage points 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 percentage points 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 percentage points difference) compared with White patients were: asthenia, dyspepsia, fatigue, nausea, pyrexia, rash and vomiting.

AEs with a CTCAE Grade ≥3 that occurred at a higher incidence in Asian patients (≥5 percentage points 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 percentage points 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 percentage points difference) compared with White patients. Anaemia was the only AE that resulted in a dose modification that occurred at a higher incidence (≥5 percentage points 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 percentage points difference) compared with White patients. Anaemia was the only AE leading to treatment discontinuation that occurred at a higher incidence (≥5 percentage points difference) in other non-White patients compared with White patients.

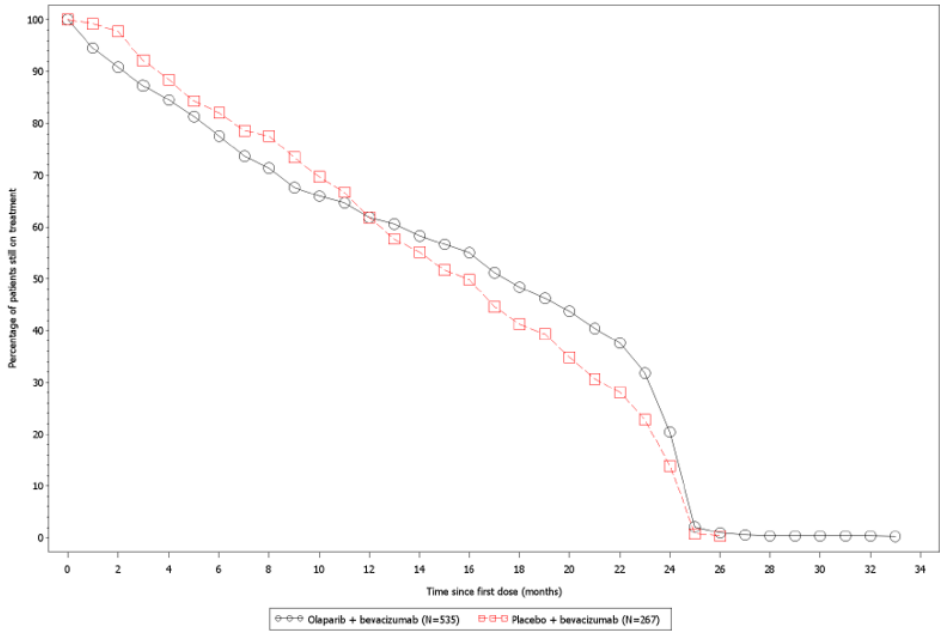
Safety related to drug-drug interactions and other interactions

No new data were submitted in the context of this procedure

Discontinuation due to adverse events

Adverse events leading to discontinuation

An assessment of the olaparib or placebo exposure over time (figure below) and the reasons for treatment discontinuation by time to treatment discontinuation (table below) showed that the higher rate of discontinuation rate from olaparib versus placebo was driven by AEs in the olaparib/bevacizumab arm in the first 3 months of treatment. Between 3 and 9 months, the overall rate of discontinuation was similar between the olaparib/bevacizumab arm and placebo/bevacizumab arm. Following completion of bevacizumab treatment at approximately 10 months, the rate of discontinuation of olaparib was reduced, in contrast to discontinuations due to progression or death occurring in a higher proportion of patients in the placebo arm.



Data derived from Figure 14.3.1.1, PAOLA-1 CSR, Module 5.3.5.1 (DCO: 22 March 2019).
CSR Clinical study report; DCO Data cut-off; SAS Safety analysis set.

Figure 29: PAOLA-1: Olaparib or placebo exposure over time (SAS)

Table 77: PAOLA-1: Reason for discontinuation over time-period (FAS)

Time period	Olaparib 300 mg bd (N=537)				Placebo bd (N=269)			
	Progression or Death[a]	AE[b]	Other	Total	Progression or Death[a]	AE[b]	Other	Total
<3 months	8 (1.5)	51 (9.5)	10 (1.9)	69 (12.8)	14 (5.2)	3 (1.1)	5 (1.9)	22 (8.2)
3-6 months	33 (6.1)	17 (3.2)	2 (0.4)	52 (9.7)	21 (7.8)	4 (1.5)	2 (0.7)	27 (10.0)
6-9 months	30 (5.6)	18 (3.4)	5 (0.9)	53 (9.9)	20 (7.4)	2 (0.7)	0	22 (8.2)
9-12 months	20 (3.7)	8 (1.5)	3 (0.6)	31 (5.8)	28 (10.4)	1 (0.4)	3 (1.1)	32 (11.9)
12-15 months	18 (3.4)	6 (1.1)	4 (0.7)	28 (5.2)	24 (8.9)	2 (0.7)	1 (0.4)	27 (10.0)
15-18 months	37 (6.9)	4 (0.7)	1 (0.2)	42 (7.8)	24 (8.9)	0	2 (0.7)	26 (9.7)
≥18 months	46 (8.6)	5 (0.9)	7 (1.3)	58 (10.8)	37 (13.8)	1 (0.4)	2 (0.7)	40 (14.9)

[g] Includes the terms 'disease progression as other reason as RECIST criteria', 'disease progression as per RECIST criteria', and 'death'

[h] Includes the terms 'toxicity of interest', 'Other unacceptable toxcity or AE'

AE Adverse event; FAS Full analysis set; RECIST Response evaluation criteria in solid tumors.

Data derived from Table 1409, Module 5.3.5.3 (DCO: 22 March 2019).

In PAOLA-1, a higher proportion of patients had DAEs (from olaparib or placebo) in the olaparib/bevacizumab arm (20.4%), compared with the placebo/bevacizumab arm (5.6%). The majority of DAEs were reported during the combination period.

In the olaparib/bevacizumab arm, 34 (6.4%) patients discontinued treatment within the first month on study. The most common DAE in the first month on study was nausea, which resulted in olaparib discontinuation in 11 (2.1%) patients; DAEs of blood creatinine increased, fatigue and vomiting each occurred in 3 (0.6%) patients in the olaparib/bevacizumab arm. The only AEs leading to discontinuation of olaparib that were reported in >3 olaparib/bevacizumab-treated patients were: anaemia, fatigue, nausea and vomiting.

Table 78: PAOLA-1: AEs leading to olaparib or placebo discontinuation occurring in ≥ 2 patients in either treatment group (SAS).

MedDRA SOC preferred term[b]	Number (%) of patients[a]			
	Overall study duration		Combination treatment phase only	
	Olaparib/ bevacizumab N=535	Placebo/ bevacizumab N=267	Olaparib/ bevacizumab N=534	Placebo/ bevacizumab N=267
Patients with any AE leading to discontinuation	**109 (20.4)**	**15 (5.6)**	**86 (16.1)**	**10 (3.7)**
Gastrointestinal disorders	**33 (6.2)**	**4 (1.5)**	**30 (5.6)**	**2 (0.7)**
Nausea	18 (3.4)	1 (0.4)	16 (3.0)	1 (0.4)
Vomiting	5 (0.9)	0	5 (0.9)	0
Abdominal pain	3 (0.6)	0	3 (0.6)	0
Diarrhoea	3 (0.6)	0	3 (0.6)	0
Blood and lymphatic system disorders	**23 (4.3)**	**0**	**17 (3.2)**	**0**
Anaemia	19 (3.6)	0	15 (2.8)	0
Neutropenia	2 (0.4)	0	1 (0.2)	0
General disorders and administration site conditions	**13 (2.4)**	**0**	**9 (1.7)**	**0**
Fatigue	8 (1.5)	0	6 (1.1)	0
Mucosal inflammation	2 (0.4)	0	1 (0.2)	0
Investigations	**8 (1.5)**	**0**	**8 (1.5)**	**0**
Blood creatinine increased	3 (0.6)	0	3 (0.6)	0
Gamma-glutamyltransferase increased	2 (0.4)	0	2 (0.4)	0
Infections and infestations	**5 (0.9)**	**2 (0.7)**	**3 (0.6)**	**1 (0.4)**
Cytomegalovirus infection	2 (0.4)	0	1 (0.2)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**5 (0.9)**	**1 (0.4)**	**0**	**1 (0.4)**
Myelodysplastic syndrome	2 (0.4)	0	0	0
Musculoskeletal and connective tissue disorders	**4 (0.7)**	**2 (0.7)**	**4 (0.7)**	**2 (0.7)**
Arthralgia	3 (0.6)	1 (0.4)	3 (0.6)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	**3 (0.6)**	**2 (0.7)**	**2 (0.4)**	**2 (0.7)**
Dyspnoea	1 (0.2)	2 (0.7)	0	2 (0.7)
Pneumonitis	2 (0.4)	0	2 (0.4)	0
Renal and urinary disorders	**3 (0.6)**	**0**	**2 (0.4)**	**0**
Acute kidney injury	2 (0.4)	0	2 (0.4)	0
Cardiac disorders	**2 (0.4)**	**2 (0.7)**	**2 (0.4)**	**1 (0.4)**
Myocardial infarction	0	2 (0.7)	0	1 (0.4)

Table 79:Most common AEs leading to discontinuation (reported by ≥1% patients in PAOLA-1 and/or reported by ≥2% patients in the 300 mg bd pool)

Preferred term	Number (%) of patients		
	PAOLA-1 SAS, overall study duration		Olaparib 300 mg bd pool (N=1585)
	Olaparib/ bevacizumab N=535	Placebo/ bevacizumab N=267	
Patients with any AE leading to discontinuation	**109 (20.4)**	**15 (5.6)**	**148 (9.3)**
Anaemia	19 (3.6)	0	40 (2.5)
Nausea	18 (3.4)	1 (0.4)	12 (0.8)
Fatigue	8 (1.5)	0	11 (0.7)

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

Table 80:Olaparib 300 mg bd pool: Non-progression reasons for discontinuation across the Phase III studies included in the pool

Study number/name	Tumour type	% of patients with DAEs	% of patients discontinuing due to patient decision/withdrawn consent	% of patients discontinuing for other reasons[a]
D0817C00003/PAOLA-1	Ovarian (newly diagnosed)	20.4	0.7	3.6
D0818C00001/SOLO1	Ovarian (newly diagnosed)	11.5	8.5	4.2
D0816C00002/SOLO2	Ovarian (relapsed/refractory)	11.3	2.6	5.1
D0816C00010/SOLO3	Ovarian (relapsed/refractory)	7.3	2.8	2.2
D0819C00003/OlympiAD	Breast (metastatic)	4.9	3.4	2.4
D081FC00001/POLO	Pancreatic	5.4	1.1	1.1
D081DC00007/PROfound	Prostate (hormone-resistant)	11.7	6.8	8.0

[a] Note; other reasons exclude disease progression or symptomatic deterioration.
Note, PAOLA-1 and SOLO1 both had a pre-specified maximum treatment period for olaparib of 2 years; patients who discontinued treatment as they had reached this maximum period are not included in the reasons for discontinuation shown in this table.

AEs leading to treatment interruption

Table 81: PAOLA-1: AEs leading to treatment interruption occurring in ≥2% patients in either treatment group (SAS)

MedDRA Preferred term[b]	Number (%) of patients[a]	
	Overall study duration	
	Olaparib/ bevacizumab N=535	Placebo/ bevacizumab N=267
Patients with any AE leading to dose interruption	**291 (54.4)**	**65 (24.3)**
Anaemia	110 (20.6)	1 (0.4)
Nausea	39 (7.3)	4 (1.5)
Vomiting	18 (3.4)	3 (1.1)
Fatigue	17 (3.2)	2 (0.7)
Neutropenia	14 (2.6)	2 (0.7)
Diarrhoea	12 (2.2)	4 (1.5)
Thrombocytopenia	12 (2.2)	1 (0.4)
Abdominal pain	11 (2.1)	2 (0.7)

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

Table 82: PAOLA-1: AEs leading to treatment interruption occurring in ≥2% patients in the olaparib/bevacizumab arm of PAOLA-1 (SAS) or the 300 mg bd pool.

MedDRA Preferred term[b]	Number (%) of patients[a]		
	Overall study duration		Olaparib 300 mg bd pool (N=1585)
	Olaparib/ bevacizumab N=535	Placebo/ bevacizumab N=267	
Patients with any AE leading to dose interruption	**291 (54.4)**	**65 (24.3)**	**630 (39.7)**
Anaemia	110 (20.6)	1 (0.4)	280 (17.7)
Nausea	39 (7.3)	4 (1.5)	74 (4.7)
Vomiting	18 (3.4)	3 (1.1)	86 (5.4)
Fatigue	17 (3.2)	2 (0.7)	36 (2.3)
Neutropenia	14 (2.6)	2 (0.7)	82 (5.2)
Diarrhoea	12 (2.2)	4 (1.5)	39 (2.5)
Thrombocytopenia	12 (2.2)	1 (0.4)	41 (2.6)
Abdominal pain	11 (2.1)	2 (0.7)	21 (1.3)
Neutrophil count decreased	5 (0.9)	2 (0.7)	36 (2.3)
Leukopenia	1 (0.2)	1 (0.4)	39 (2.5)

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

AEs leading to dose reduction

In PAOLA-1, a higher proportion of patients had AE leading to dose reduction (from olaparib or placebo) in the olaparib/bevacizumab arm (41.1%), compared with the placebo/bevacizumab arm (7.5%). The most common (≥5% patients) AEs leading to dose reduction of olaparib or placebo were: anaemia and nausea. The majority of AEs leading to dose reduction occurred during the combination phase. About one third of dose reductions occurred in the initial treatment period of up to 3 months.

Table 83: PAOLA-1: Dose reductions of olaparib by time period (safety analysis set) (DCO 22 March 2019)

Olaparib total daily dose (mg)	Number (%) of patients by time period				
	Up to 3 months	>3 to ≤6 months	>6 to ≤9 months	>9 to ≤12 months	>12 months
	(N=535)	(N=460)	(N=402)	(N=356)	(N=324)
First dose reduction	183 (34.2)	40 (8.7)	4 (1.0)	2 (0.6)	1 (0.3)
Second dose reduction	72 (13.5)	56 (12.2)	11 (2.7)	10 (2.8)	11 (3.4)

Patients can be included more than once in each relevant time period.

Table 84: PAOLA-1: AEs leading to dose reduction occurring in ≥2 patients in either treatment group (SAS)

MedDRA Preferred term[b]	Number (%) of patients[a]	
	Overall study duration	
	Olaparib/ bevacizumab N=535	Placebo/ bevacizumab N=267
Patients with any AE leading to dose reduction	220 (41.1)	20 (7.5)
Anaemia	99 (18.5)	0
Nausea	40 (7.5)	2 (0.7)
Fatigue	21 (3.9)	2 (0.7)
Diarrhoea	8 (1.5)	4 (1.5)
Thrombocytopenia	8 (1.5)	0
Neutrophil count decreased	4 (0.7)	0
Platelet count decreased	4 (0.7)	0
Stomatitis	4 (0.7)	0
Vomiting	4 (0.7)	0
Abdominal pain	3 (0.6)	1 (0.4)
Headache	3 (0.6)	1 (0.4)
Myalgia	3 (0.6)	1 (0.4)
Neutropenia	3 (0.6)	1 (0.4)
Arthralgia	2 (0.4)	1 (0.4)
Aphthous ulcer	2 (0.4)	0
Dyspnoea	2 (0.4)	0
Oedema peripheral	2 (0.4)	0

Post marketing experience

The safety signal detection activities include review of reported AEs from post-marketed sources, and a review of the published literature relevant to Olaparib. The reports received do not change the benefit-risk profile of Olaparib (PBRER DCO 15 June 2019).

2.5.1. Discussion on clinical safety

Patient exposure

The clinical safety analysis is mainly based on data from the Phase III PAOLA-1 study in 806 randomised patients with newly-diagnosed advanced (FIGO Stage IIIB-IV) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who were in response following first line treatment, with platinum-taxane chemotherapy and bevacizumab. Combination therapy of olaparib and bevacizumab was compared to bevacizumab and placebo, followed by monotherapy of olaparib or placebo (535 patients versus 267 patients respectively) (DCO: 22 March 2019). Supportive data with a large pool of 1585 patients which received the same dose of olaparib as monotherapy in other indications were also provided and allow to better characterize the safety profile of the combination therapy.

The methodology used is acceptable and available data are considered sufficient to ensure an effective analysis of the safety profile of olaparib in association with bevacizumab in the scope of the requested indication.

Median duration of treatment was slightly higher in olaparib/bevacizumab arm compared to placebo/bevacizumab group (17.3 months vs 15.6 months) with similar duration of the combination period (10.6 months) which means that combination with olaparib does not impact bevacizumab

treatment duration as maintenance therapy. Most patients randomized in olaparib/bevacizumab arm received olaparib for a period of >12 months.

The percentage of patients remaining on treatment at 1 year was similar in the olaparib/bevacizumab and placebo/bevacizumab arms (61.9% and 61.8%, respectively); the percentage of patients remaining on treatment at 2 years was greater in the olaparib/bevacizumab arm (20.4%) than in the placebo/bevacizumab arm (13.9%). Note that in PAOLA-1 patients could continue treatment for 2 years or until disease progression. Patients who in the opinion of the treating physician could derive further benefit from continuous treatment, could be treated beyond 2 years.

However, long-term data of the combination therapy are limited since median duration of treatment was 10.6 months with range from 0.3 to 20.2 months and the MAH is recommended to submit the long-term safety data analysis of the clinical study PAOLA-1 at the time of the final OS analysis (REC).

Disease progression was the main reason for study discontinuation with a lower rate in the combination treatment group compared bevacizumab alone (34.0% vs 58.1%).

In PAOLA-1 study, patient's demographics were consistent across treatment groups and reflect the population of the proposed indication. All patients were women with mean age of 60 years old and primary tumour location was mostly ovary.

Safety monitoring and protocol amendment

No dose-finding study has been conducted for the combination of olaparib with bevacizumab to determine an optimal combination dose in maintenance setting. An interim safety analysis have been conducted on 26 April 2016 to evaluate the tolerability profile in the 42 first randomised and followed for two 3-week cycles patients that received continuous twice daily oral olaparib (300 mg twice) or placebo in patient treated in maintenance with intravenous bevacizumab at a fixed dose (15 mg/kg) administered every 21 days. The data of the interim analysis has been reviewed by the IDMC which has recommended to continue the enrolment as planned to the sponsor ARCAGY Research. IDMC was reviewing the emerging safety data during the whole duration of the trial.

To ensure robust safety monitoring, additional safety measures have been incorporated into this phase III protocol. Patients with history of MDS/AML and having experienced prolonged haematotoxicity (> 2 weeks) to first-line chemotherapy were excluded. While on treatment, regular blood tests were required to detect early haematological abnormality and the frequency of tests was increased under the protocol version 5 between 6 and 12 months of treatment to every 3 weeks instead of every 6 weeks. In case of prolonged cytopenia, patients were to be referred to an haematologist and bone marrow analysis was to be considered, with discontinuation of treatment in case of confirmed MDS or AML.

Moreover, in the protocol version 4.0 (06 January 2017), the following exploratory objective was added: "Explore the time to next severe toxicity (grade 4 neutropenia lasting > 7 days, grade ≥ 3 febrile neutropenia, grade 4 thrombocytopenia with bleeding or platelet transfusion, grade ≥ 3 non-haematological toxicity) in both arms". The objective was to explore the ability of olaparib, compared to placebo, to postpone the occurrence of a severe toxicity during the whole course of the study including study treatment and next subsequent treatments. The analysis of this exploratory endpoint has not been performed to date. This exploratory objective was planned not earlier than when final PFS2 results would be available (in order to have as much information as possible available on subsequent treatments) and will be reported separately in the CSR (REC).

Safety analyses were performed on the overall study duration (SAS) and on the population of patients in the two study arms from initiation of olaparib or placebo until the last dose of olaparib or placebo and bevacizumab given concurrently plus 21 day (Combination Phase only). Four patients were excluded from the SAS (2 patients each arm) as they did not start olaparib or placebo. One patient

olaparib/bevacizumab was excluded from the combination phase because patient discontinued bevacizumab prior to the first dose of olaparib.

Adverse events (AE)

Overall, the safety profile of olaparib in combination with bevacizumab is considered to be consistent with the known safety profiles of the combined olaparib and bevacizumab monotherapies.

The incidence and severity of the ADR identified with olaparib monotherapy treatment (300 mg bd pool data) and identified with olaparib/bevacizumab in PAOLA-1 were compared. Several ADRs had similar incidences with monotherapy and combination treatment. However, some ADRs had different incidences with monotherapy or combination treatment. The frequency was lower with combination treatment (common) than observed with monotherapy (very common) for the following ADR: thrombocytopenia, decreased appetite, dizziness, dysgeusia, cough, and dyspnoea (all grade). The frequency was higher with combination treatment (very common) than observed with monotherapy (common) for lymphopenia (all grade).

Although some differences of incidence have been noted the larger patient exposure (n=2351) from the olaparib therapeutic dose pool provides the most robust estimates of the ADR frequencies for olaparib, a separated ADR table for the combination is not warranted. The statement in section 4.8 of the SmPC "When Lynparza is used in combination with bevacizumab the safety profile is generally consistent with that of the individual therapies" is considered sufficient. For overlapping toxicities, no notable increase in severity of events has been observed.

The majority of AEs were reported during the combination treatment phase and mostly within the first 3 months of treatment.

Most commonly AEs reported were consistent with the safety of olaparib with AEs pertaining to the SOC Hematologic disorders (anaemia, 40.9%; neutropenia, 18.1%; lymphopenia, 23.6%; leukopenia, 17.8%), SOC Gastro-intestinal disorders (nausea, 53.3%; vomiting, 21.9%) and SOC General disorders (fatigue, 52.9%) as well as known AEs of bevacizumab with hypertension (45.8%) and proteinuria (5.8%). Other known AE of olaparib were reported with a lower frequency such as cough (4.7%), dyspnoea (7.9%), dizziness (2.6%) and headache (13.6%) as well as known AE of bevacizumab such as haemorrhagic events (9.7%) and thromboembolic events (1.7%).

AE were mainly manageable by treatment interruption or dose reduction and supportive treatment. There was no evidence of overlapping toxicities, although such effects are not excluded as the mechanism of action of PARP inhibitors, including olaparib, is not fully elucidated.

Most deaths reported in PAOLA-1 study were related to the disease under investigation. Four fatal cases might be related to the combination treatment including one case of aplastic anaemia and pneumonia. Appropriate warnings are mentioned in the SmPC to closely monitor haematotoxicity during olaparib treatment.

Five deaths associated with treatment emergent AEs were also reported >30 days after last treatment dose: 3 olaparib/bevacizumab-treated patients (2 from acute myeloid leukaemia - AML and 1 from acute lymphoblastic leukaemia type B - ALL, all events possibly related to olaparib) and 2 placebo/bevacizumab-treated patient. The number of patients who died post follow-up was numerically higher with the combination: 7 olaparib/bevacizumab-treated patients (various causes) and 2 placebo/bevacizumab-treated patients.

Compared to placebo/bevacizumab group, the proportion of AEs reported was slightly higher in olaparib/bevacizumab group (99.3% vs 95.9%) with similar proportion of SAEs (31.2% vs 31.1%) and slightly higher proportion of AEs of CTCAE Grade≥3 (57.6% vs 50.9%). The rate of treatment discontinuation of olaparib/placebo was higher in olaparib/bevacizumab group compared to

placebo/bevacizumab group (20.4% vs 5.6%) as well as treatment interruption (54.4% vs 24.3%) and dose reduction of olaparib (41.1% vs 7.5%). Adverse events led to dose interruption and/or reduction of olaparib in 57.4% of patients when used in combination with bevacizumab. The adverse reactions that most commonly led to dose interruption and/or reduction were anaemia (20.6%) and nausea (7.5%). The adverse reactions that most commonly led to permanent discontinuation were anaemia (3.6%), nausea (3.4%) and fatigue/asthenia (1.5%). Data on bevacizumab dose interruption and discontinuation due to AE were not collected in PAOLA-1. Dose reductions of bevacizumab were not permitted.

Discontinuations due to AE were mainly reported during the first 3 months of treatment in the olaparib/bevacizumab combination arm.

Frequencies of AEs leading to dose interruption were similar between SOLO1 (maintenance treatment of newly diagnosed advanced BRCA-mutated high-grade ovarian cancer after first line chemotherapy with olaparib monotherapy) and PAOLA-1. However, the incidence of any AE leading to dose reduction was higher in PAOLA-1 compared to SOLO-1 (41.1% vs. 28.5%, respectively). Likewise, the incidence of any AE leading to discontinuation was higher in PAOLA-1 compared to SOLO-1 (20.4% vs. 11.5%, respectively).

The differences between the two arms in PAOLA-1 were mainly driven by hematologic and gastrointestinal disorders, known ADRs of olaparib, with higher rate of anaemia (40.9% vs 10.1%) nausea (53.3% vs 21.7%) and fatigue (52.9% vs 32.2%) in olaparib/bevacizumab arm.

For non-tBRCAm/unknown patients (approximatively 70% of the patients) and tBRCAm (approximatively 30% of the patients), common adverse events, incidence of AE Grade ≥ 3, discontinuation of olaparib or placebo due to AE and AE with an outcome of death were consistent with the SAS (data not shown).

Compared to olaparib pool, the proportion of AEs reported was slightly higher in olaparib/bevacizumab group (99.3% vs 97.3%) despite shorter median treatment duration in the pool. Higher rates of SAEs and AEs of CTCAE Grade≥3 were also reported (31.2% vs 23% and 57.6% vs 41.6%) which were driven by hypertension, a known AE of bevacizumab. However, rates of discontinuation due to AEs, dose interruption and reduction of olaparib were more reported in olaparib/bevacizumab group than in the olaparib pool (20.4% vs 9.3%; 54.4% vs 39.7%; 41.1% vs 21.4%), mainly due to nausea, anaemia and fatigue. The rate of discontinuation due to AEs was higher than observed in the SOLO1 study (maintenance treatment of newly diagnosed advanced BRCA-mutated high-grade ovarian cancer after first line chemotherapy with olaparib monotherapy), in which it was 11.5% with olaparib monotherapy (and 2.3% in placebo arm). These differences could be explained by the combination therapy rather than a lower median treatment duration in olaparib pool. Hematologic toxicity which is known for both substances, does not appear to increase in terms of incidence and severity with the combination therapy such as anaemia and neutropenia, except for lymphopenia and leukopenia which were more reported in olaparib/bevacizumab arm compared to olaparib pool (23.6% vs 5.2%; 16.3% vs 13.9%).

Incidence of some AE was lower with the combination therapy such as thrombocytopenia, decreased appetite, dizziness, dysgeusia, cough, and dyspnoea (all grade).

Analysis of bevacizumab-related ADRs, including hypertension, proteinuria, haemorrhagic and thromboembolic events, has been provided. Known AEs of bevacizumab were reported with similar rates between olaparib/bevacizumab and placebo/bevacizumab arms, except for hypertension and proteinuria for which lower rates were reported in olaparib/bevacizumab group compared to placebo/bevacizumab group.

The two arms of the PAOLA-1 study were homogeneous in terms of risk factors of hypertension and baseline characteristics (age, weight/body and mass index) except for tobacco use which was not presented. Relevant medical history reported as current at baseline were well balanced between the two arms as well.

Hence, the lower proportion of hypertension in the olaparib/bevacizumab arm compared to placebo/bevacizumab arm cannot be explained on the basis of baseline characteristics or medical history. Overall, these findings are quite similar to incidences reported for bevacizumab monotherapy in clinical studies. The incidence of hypertension in PAOLA-1 was 45% for all grades and 18.7% for grade ≥3 on and it was up to 42% for all grades and 17,9% for grade ≥3 in clinical studies for bevacizumab according to its SmPC.

Relevant medical history reported as current at baseline associated with AEs proteinuria and baseline characteristics were well balanced between both groups in PAOLA-1 study and thus cannot explain the reported incidence differences in proteinuria. However, the incidence of proteinuria in olaparib/bevacizumab arm were in the range of incidence reported in clinical studies of bevacizumab according to its SmPC (0.7 to 38 %).

Regarding potential important risks, 4 cases of MDS/AML (0.7%) were reported in olaparib/bevacizumab group including two fatal events. All patients had risk factors such as several previous cycles of platinum agents or BRCA mutation and similar rates were reported in SOLO studies (between 1.2% and 2.1%) which involved similar patient population. In addition, 6 cases of new primary malignancies were reported (1.1%) including 4 in patients with documented mutations in BRCA1/2 genes. However, despite similar and consistent rates reported for both safety concerns compared to olaparib entire program (0.6% and 0.8% respectively), low rates reported make the interpretation of differences observed difficult between groups. Due to mechanism of action of PARP inhibitors which lead to genome instability, causal role of olaparib cannot be excluded for these two risks and a close monitoring will be maintained in post-marketing setting.

MDS/AML remain as important potential risks in the RMP. Appropriate warnings are mentioned in the product information to monitor blood count and to discontinue treatment in case of MDS/AML occurrence. In addition, a targeted questionnaire has been implemented to better document cases reported.

Six cases of pneumonitis (1.1%) were reported in olaparib/bevacizumab group. Despite similar and consistent rates observed compared to olaparib 300mg bd pool (0.9%), interpretation of differences is challenging. A close monitoring will be maintained in post-marketing setting. All 6 patients who reported pneumonitis received previously platinum chemotherapy treatment which is a risk factor. Moreover, the mechanisms of drug-induced interstitial lung disease/pneumonitis is still not well understood. All AEs of pneumonitis were mild or moderate in severity, two cases were non-serious and all of them had a favourable outcome. The management of pneumonitis required dose modifications and corrective treatment and two patients had permanent treatment discontinuation. Overall, the causality of olaparib for pneumonitis remains uncertain. Pneumonitis is an important potential risks (RMP) and adequate information is included in the SmPC in this regard. The MAH will continue to closely monitor pneumonitis cases in post-marketing setting.

In PAOLA-1, a higher proportion of patients in the olaparib/bevacizumab arm had ≥2 grade changes in haematological laboratory parameters, compared with patients in the placebo/bevacizumab arm. Anaemia was the most frequently reported CTCAE Grade ≥3 AE. The only significant changes in clinical chemistry parameters occurred for blood creatinine and proteinuria. Creatinine increases are a recognised ADR for olaparib. Proteinuria is a recognised ADR for bevacizumab.

Assessment of potential for hepatic and renal impairment was consistent with data reported from olaparib monotherapy clinical studies.

Overall, the laboratory findings were consistent with available data from the olaparib pool.

Safety data in special populations did not identify any differential effects by gender despite low number of men included and slight differences observed, which might rather be related to underlying diseases. 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.

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. With regards to safety in Japanese participants, although the proportions of patients with any treatment emergent adverse events were similar between the Japan cohort and the overall safety analysis set, the incidence of treatment-emergent grade 3 and above adverse was higher in the Japan cohort than in the Safety Analysis in the olaparib/bevacizumab arm 73% and 58%, respectively. There is a higher incidence of haematology-related adverse events in Japanese cohort compared with the overall safety analysis set. The higher haematology toxicity in Asian population compared with White populations was also observed in previous studies (SOLO1). It is unknown why Japanese participants have an increased haematological toxicity. The MAH provided one exposure-safety analysis in Asian/Japanese population based on pooled data from capsule and tablet monotherapy studies (Olaparib-MS-07) and another based on pooled data from tablet monotherapy studies (Olaparib-MS-08) (data not shown). The population pooled in these data set includes patients with various cancers (ovarian, breast, prostate or other advanced malignancies) possibly in different line of therapy. However, it remains unknown whether the differences in AEs between Japanese patients and the overall population in PAOLA-1 study were due to bevacizumab potentiation, disease setting or other factors.

2.5.2. Conclusions on clinical safety

Overall the safety profile of olaparib in combination with bevacizumab as maintenance treatment is considered acceptable for the intended population and is generally consistent with the safety profile of the individual therapies.

The results from study PAOLA-1 showed that there were no high differences in risk of the combination therapy compared to placebo/bevacizumab group and compared to olaparib pooled safety data, except for lymphopenia and leukopenia. However, slightly more AE ≥ Grade 3 and more AE leading to dose adjustment of olaparib were reported with the combination compared to monotherapy.

Nevertheless, patients experiencing ADRs need to be carefully followed by physicians as indicated in the SmPC. Furthermore, more information is needed to assess the causal relationship between olaparib and the potential risks as identified in the RMP.

Overall, no new safety signals were identified from the analyses of safety data from both treatment arms of PAOLA-1. AEs that occurred more frequently on the olaparib/bevacizumab arm than in the placebo/bevacizumab arm were consistent with the known safety profile of olaparib.

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 to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 20.3 is acceptable.

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

Safety concerns

The PRAC agrees that the safety concerns listed by the MAH are appropriate.

Table 85: Safety concerns

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

Pharmacovigilance plan

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

The PRAC, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

Risk minimisation measures

The PRAC having considered the data submitted, is of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

Table 86: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
MDS/AML	Routine risk communication in: SmPC Section 4.4 PL Section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: **SmPC Section 4.4** **PL Section 2** **PL Section 4**	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up targeted safety questionnaire Cumulative review (provided concurrent with each annual PBRER)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
New primary malignancy	None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up targeted safety questionnaire
Pneumonitis	Routine risk communication in: SmPC Section 4.4 PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: **SmPC Section 4.4:** **PL Section 2**	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up targeted safety questionnaire
Medication errors associated with dual availability of capsules and tablets	Routine risk communication in: SmPC Section 4.2 PL Section 3 Routine risk minimisation activities recommending specific clinical measures to address the risk: **SmPC Section 4.2:** **PL Section 3** **Additional risk minimisation measures:** Distribution of a DHPC to prescribers and pharmacists providing clear information on the 2 formulations.	Routine
Effects on embryofoetal survival and abnormal development	Routine risk communication in: SmPC Sections 4.4, 4.6 PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: **SmPC Section 4.4, 4.6** **PL Section 2:**	Routine
Long term exposure to/potential toxicity to olaparib	None	Routine

Overall conclusion on the RMP

The changes to the RMP and the changes to the conditions and obligations of the MA are acceptable.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, and 5.1of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) which were reviewed by QRD and accepted by the CHMP.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: Overall, the wording in the PL is similar to that already tested previously during the MA applications. Therefore, it is justified to consider the Package Leaflet User Testing report provided during review of the MA application procedure as relevant for this application, and that no updated document is needed for this submission.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The proposed indication is for Lynparza (tablet) in combination with bevacizumab for the maintenance treatment of adult patients with 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 in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a BRCA1/2 mutation and/or genomic instability.

3.1.2. Available therapies and unmet medical need

Cytoreductive surgery and platinum-based chemotherapy are considered treatments of choice for patients with newly diagnosed advanced ovarian cancer (NCCN Ovarian 2020, Karam et al 2017, Ledermann et al 2013). For patients for whom upfront surgery is unlikely to achieve a complete resection, treatment consists of neoadjuvant chemotherapy followed by interval debulking surgery and adjuvant chemotherapy (NCCN Ovarian 2020). Even though most newly diagnosed advanced ovarian cancer patients achieve complete response at the end of first line treatment, approximately 70% relapse within the first three years of diagnosis (Ledermann et al 2013). Once ovarian cancer relapses, the disease becomes largely incurable. There is a need for treatments that can delay relapse, offering the possibility to improve the long-term outcome for these patients.

Targeted treatments approved in the first line maintenance setting include olaparib for *BRCAm* patients (SOLO-1 study) and bevacizumab for frontline and maintenance therapy which can be given regardless of *BRCAm* status (study GOG-218).

3.1.3. Main clinical studies

PAOLA-1 was a phase III, randomised, double-blind, placebo-controlled trial of olaparib vs placebo added to bevacizumab for the maintenance treatment of newly diagnosed advanced ovarian cancer patients who were in response following first line platinum-based chemotherapy and bevacizumab. Patients were randomised in a 2:1 ratio to receive either olaparib 300 mg bd plus bevacizumab 15 mg/kg Q3W (N=537) or matching placebo bd plus bevacizumab 15 mg/kg Q3W (N=269). Patients were enrolled regardless of the BRCAm status, but were stratified by tBRCAm status, based on the prospectively conducted tumour tissue testing. The primary analysis was based on investigator assessment of disease progression by RECIST; a sensitivity analysis was also performed using the BICR assessment. Key secondary objectives

included PFS2, OS (adjusted for multiplicity) TFST, TSST, time to earliest progression by RECIST or CA-125 or death, TDT and HRQoL.

3.2. Favourable effects

At DCO (22 March 2019), the main analysis of investigator-assessed PFS showed a statistically significant improvement in PFS in the ITT population. Median PFS was 22.1 months in the olaparib/bevacizumab arm vs 16.6 months in the placebo/bevacizumab arm, with HR=0.59 (95%CI 0.49, 0.72), p<0.0001.

Analysis of PFS by BICR and all other sensitivity analyses were consistent with the investigator assessment of PFS. Consistent results were also shown in the subgroup analyses by stratification factors (first line treatment outcome and local tBRCAm status) and clinical characteristics.

The interim PFS 2 data with 36.5% and 44.2% of events in olaparib/bevacizumab and placebo/bevacizumab arms respectively, showed a HR of 0.86 [0.69, 1.09], p=0.2097.

The interim OS data were 25.9% mature and showed a HR of 1.01 [0.76 to 1.36] with a similar proportion of deaths occurring in each arm. At the DCO of 30 September 2019, the updated OS analysis showed a HR of 0.94; (95% CI 0.73 to 1.21) in the ITT population.

In the subgroup of patients with deleterious tBRCA1/2m (based on local test results at randomisation), the PFS HR was 0.34 (0.23, 0.51). The median PFS was 37.2 months in olaparib/bevacizumab arm versus 22 months in placebo/bevacizumab arms. The OS HR point estimate was reported as 0.66 (95% CI 0.37 to 1.21) at DCO 30 September 2019. The subgroup analysis by tBRCA status by Myriad based on retrospective analysis of tumour sample was consistent with this analysis, with the OS HR point estimate of 0.61 (95% CI 0.34 to 1.09) at the same DCO.

In the subgroup of patients whose tumours were classified as Myriad HRD positive based on combined measurement of HR deficiency-associated biomarkers (either tBRCAm or HR deficiency-associated genomic instability) in retrospectively analysed tumour samples, the PFS HR was 0.33 (95% CI 0.25, 0.45). The median PFS was 37.2 months in olaparib/bevacizumab arm versus 17.7 months in placebo/bevacizumab arms. The OS HR point estimate was reported as 0.71 (95% CI 0.47 to 1.10) at DCO 30 September 2019.

Additional analyses in subgroups of patients identified by genomic instability biomarker were consistent with results of combined biomarker measurements.

3.3. Uncertainties and limitations about favourable effects

Due to the absence of olaparib monotherapy arm, it remains currently unknown what is the contribution of components of such VEGFi-PARPi combination therapy in maintenance phase and whether they have additive, synergistic or potentially a detrimental effect in different biomarker-defined subpopulations of patients, according to known mechanisms of action. Bevacizumab is indicated in the first-line maintenance setting only after prior concomitant treatment with platinum-based chemotherapy, whereas olaparib is indicated in first-line maintenance after platinum-based chemotherapy in the subgroup of BRCA1/2-mutated (germline and/or somatic) patients. The contribution of olaparib could only be assessed as add-on therapy to bevacizumab used in both arms concurrently with chemotherapy and in maintenance setting for the total duration of treatment up to 15 months.

In the subgroup of patients without prospectively detected tBRCAm by local test (non-tBRCAm subgroup), PFS HR estimate was of 0.7 (95% CI 0.57, 0.86) while OS HR estimate was 1.02 (95% CI 0.77, 1.36). Consistently, in the Myriad non-tBRCAm subgroup HR was 1.04 (95% CI 0.77 to 1.4) at DCO 30 September 2019.

As observed in the subgroup analyses by tBRCA mutation status, an inconsistency in treatment effect was also observed in pre-specified subgroup analyses by Myriad HRD status combining measurements of tBRCAm and HRD score (GIS, genomic instability score), as well as in subgroups defined using GIS only. Notably, in subgroups defined as negative for biomarkers of HR deficiency, OS HR estimates at relatively low maturity were exceeding 1, although with large 95% CI.

PFS 2 and OS data are still immature and are confounded by exposure to PARP inhibitors outside of the study. The MAH is recommended to provide updated PFS 2 and OS data including additional analyses adjusting for impact of subsequent PARP inhibitor treatment.

3.4. Unfavourable effects

Overall, the safety profile of the combination therapy appears to be the juxtaposition of both safety profiles of olaparib and bevacizumab with slight differences in terms of frequency and severity compared to individual treatments and no emergence of new AE.

The majority of AEs were reported during the first 3 months of treatment and included among the most reported events known AE of olaparib (anaemia, lymphopenia, leukopenia, neutropenia, nausea and vomiting) as well as known AE of bevacizumab (hypertension, proteinuria and hemorrhagic events).

AE related to olaparib were mainly manageable by treatment interruption (54.4%) or dose modification (41.1%) and supportive treatment. These proportions were higher in combination than for olaparib in monotherapy (39.7% and 21.4% respectively).

Discontinuation of treatment due to AEs was reported in 20.4% and 5.6% of patients treated with olaparib/bevacizumab and placebo/bevacizumab, respectively.

Compared to olaparib monotherapy, two AE, lymphopenia and leukopenia, were more reported in combination with bevacizumab.

3.5. Uncertainties and limitations about unfavourable effects

Long-term safety data of the combination therapy are limited with only 10-months data. Long-term exposure to/potential toxicity to olaparib is included in the list of safety concerns under missing information in the risk management plan.

Uncertainties remain for olaparib on potential risks of AML/MDS, new primary malignancies and pneumonitis. The causality of olaparib in occurrence of rare cases of AML/MDS, new primary malignancies and pneumonitis could not be firmly established in the context of previous courses of chemotherapy. These safety issues will continue to be closely monitored in the post-marketing setting.

3.6. Effects Table

Table 39. Effects Table for olaparib in combination with bevacizumab for the maintenance treatment of adult patients with advanced high-grade epithelial ovarian cancer who are in response following completion of first-line platinum-based chemotherapy with bevacizumab (data cut-off: 22 March 2019)

Effect	Short description	Unit	Treatment (olaparib/ bevacizumab)	Control (placebo/ bevacizumab)	Uncertainties / Strength of evidence	References
Favourable Effects- DCO 22 March 2019 unless otherwise indicated						
tBRCAm at randomisation						
Number of patients			N=161	N=80		PAOLA-1 study
PFS by investigator in tBRCAm at randomisation	Time from randomisation to progression or death	months	**37.2**	**22.0**	Subgroup analysis **HR 0.34 (0.23, 0.51)** Consistent results in Myriad tBRCAm subgroup	
Interim OS in tBRCAm at randomisation	Time from randomisation until death	months	NR	NR	Subgroup analysis HR 0.66 (95% CI 0.37 to 1.21) at DCO 30 sept 2019, updated interim analysis	
HRD positive*						
Number of patients			N=255	N=132		PAOLA-1 study
PFS by investigator in HRD positive*	Time from randomisation to progression or death	months	**37.2**	**17.7**	Subgroup analysis **HR 0.33 (0.25, 0.45)** Consistent results in subgroup identified by genomic instability only	
Interim OS in HRD positive*	Time from randomisation until death	months	NR	NR	Subgroup analysis HR 0.71 (95% CI 0.47 to 1.10) at DCO 30 sept 2019, updated interim analysis, consistent results in subgroup identified by genomic instability only	
Interim PFS2, by investigator in HRD positive*	Time from randomisation to the earliest of the progression subsequent to PFS or death.	months	NR	34.6	Subgroup analysis HR 0.60 (95%CI 0.41, 0.88)	
Unfavourable Effects						
CTCAE Grade ≥3 AEs		%	57.6	50.9	41.6% in olaparib 300mg bd pool	PAOLA-1 study (overall study duration)
AE with death outcome		%	0.2	1.5	1.2% in olaparib 300mg bd pool	
Serious AEs		%	31.2	31.1	23.0% in olaparib 300mg bd pool	
AEs leading to discontinuation of study treatment		%	20.4	5.6	9.3% in olaparib 300mg bd pool	

Abbreviations: NR: Not reached

*HRD positive status was defined in this study by using a combined measurement of two biomarkers associated with HR deficiency: tBRCAm and HR deficiency-associated genomic instability.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

An improvement of 5.5 months in median PFS, with a HR of 0.59 in the ITT population is considered clinically relevant, keeping however in mind that only patients responding to initial chemotherapy in combination with bevacizumab have been randomised to receive maintenance treatment.

Differential effects in the subgroups defined by biomarkers of HR deficiency (tBRCAm, HR deficiency-associated genomic instability or combination thereof) and insufficient follow-up for key secondary endpoints (PFS2 and OS) do not allow to exclude for the time being potential detrimental effects in smaller or larger subgroups defined as biomarker-negative.

Absence of effect on PFS is reported in patients whose tumours are not associated with HR deficiency by either biomarker (defined as HRD negative by combining results for both biomarkers used) while a large magnitude of effect is observed in the subgroups defined as biomarker-positive (tBRCAm and/or genomic instability). Furthermore, with the updated OS data, it cannot be excluded that treatment with the combination may be associated with poorer OS in patients whose tumours are not associated with HR deficiency. These findings are considered plausible and of relevance based on strong biological plausibility for differential outcomes in the context of newly diagnosed ovarian cancer with subpopulations of patients with potentially differential degree of HR deficiency and consequently different magnitude of benefit following treatment with PARPi. Besides biological rationale, previously reported data with olaparib in relapsed setting support this trend of lower magnitude of benefit or absence of such depending on the definition of subgroups by biomarkers of HRD.

It is noted that an HRD test is not available to date in Europe and different cut-offs are used across different PARPi studies to determine positivity for a genomic instability score. However, a greater treatment effect was consistently observed across several trials using Myriad HRD test at predefined cut-off (42). Post-hoc analyses using only the genomic instability score (GIS) at this cut-off showed comparable results to the one in the HRD subgroups. There is also a biological rational supporting genomic instability as a biomarker predicting magnitude of PARPi activity.

In conclusion, the therapeutic efficacy of combining olaparib and bevacizumab in the first line maintenance setting in patients with ovarian cancer without defined positivity for biomarkers associated with homologous recombination deficiency is not considered demonstrated.

Overall, combination therapy of olaparib and bevacizumab was well-tolerated with a manageable safety profile which is sufficiently characterised. While hematologic, digestive and vascular ADRs occurred at a high frequency, they are generally of low grade and easily manageable. More dose adjustments (discontinuation, interruption or dose reductions) were reported which is not unexpected for a combination of 2 active therapies with known safety profiles (e.g. haematological and GI toxicity for olaparib and hypertension for bevacizumab). These higher rates should be viewed in the context of maintenance treatment which might need for dose optimisation. Discontinuation of treatment due to AEs was reported in higher proportion of patients treated with olaparib/bevacizumab than with placebo/bevacizumab. In addition, data for long-term safety remain limited. Long term safety will continue to be monitored as reflected in the RMP.

3.7.2. Balance of benefits and risks

The magnitude of the observed effect in the ITT population should be considered in the context of the maintenance setting treatment, current uncertainties on the long-term outcomes and in regard to contribution of components in different subpopulations defined by biomarkers of HR deficiency.

Benefit-risk is considered favourable in the subgroup of patients identified as harbouring tumour BRCA1/2m. In patients without defined positivity for this biomarker (BRCAwt and/or unknown), but with higher degree HR deficiency-associated genomic instability identified based on a validated test, the overall efficacy and safety data support that benefits outweigh risks in line with biological plausibility and results of subgroup analyses. In HRD-negative subgroup of patients, defined as biomarker-negative for both biomarkers used, an additional PFS benefit with olaparib beyond that seen with bevacizumab has not been established. Therefore, the indication is restricted to exclude patients that would not benefit from treatment or with magnitude of benefit that would not outweigh risks.

Safety results of PAOLA-1 study seem to be in line with both safety profile of olaparib and bevacizumab with slight differences in terms of frequency and severity. Measures to minimize the risk are well addressed in the RMP submitted by the MAH.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Lynparza in combination with bevacizumab is considered positive for the maintenance treatment of adult patients with 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 in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a BRCA1/2 mutation and/or genomic instability.

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, II and IIIB

Extension of indication to include the use of Lynparza tablets in combination with bevacizumab for the maintenance treatment of adult patients with 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 in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a BRCA1/2 mutation and/or genomic instability. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 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. Furthermore, the PI is brought in line with the latest QRD template version 10.1. The RMP version 20.3 is approved.

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

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II and IIIB and to the Risk Management Plan are recommended.

Similarity with authorised orphan medicinal products

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