APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1 NAME OF THE MEDICINE

LYNPARZA® 100 mg, Film-coated Tablets

LYNPARZA® 150 mg, Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100 mg film-coated tablet contains 100 mg of olaparib

Each 150 mg film-coated tablet contains 150 mg of olaparib.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablets.

The LYNPARZA 100 mg tablet is a yellow to dark yellow, oval, bi-convex tablet debossed with 'OP100' on one side and plain on the reverse side.

The LYNPARZA 150 mg tablet is a green to green/grey, oval, bi-convex tablet debossed with 'OP150' on one side and plain on the reverse side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ovarian cancer

LYNPARZA is indicated as monotherapy for the:

- maintenance treatment of adult patients with advanced *BRCA* mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to first-line platinum-based chemotherapy.
- maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

LYNPARZA in combination with bevacizumab is indicated 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.

Breast cancer

LYNPARZA is indicated as monotherapy for the:

- treatment of adult patients with germline *BRCA*-mutated HER2-negative metastatic breast cancer who have previously been treated with chemotherapy. These patients could have received chemotherapy in the neoadjuvant, adjuvant or metastatic setting.

Adenocarcinoma of the pancreas

LYNPARZA is indicated as monotherapy for the:

- maintenance treatment of adult patients with germline *BRCA*-mutated metastatic adenocarcinoma of the pancreas whose disease has not progressed on first-line platinum-based chemotherapy.

Prostate cancer

LYNPARZA is indicated as monotherapy for the:

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

4.2 Posology and method of administration

Treatment with LYNPARZA should be initiated and supervised by a medical practitioner experienced in the use of anticancer medicines.

Detection of BRCA and other HRR gene mutations:

Gene mutation status should be determined by an experienced laboratory using a validated test method.

Patient selection

Monotherapy maintenance treatment of advanced BRCA-mutated ovarian cancer:

Patients must have confirmation of a breast cancer susceptibility gene (*BRCA)* mutation (identified by either germline or tumour testing) before LYNPARZA treatment is initiated.

Metastatic HER2-negative breast cancer:

Patients must have confirmation of a *BRCA* mutation (identified by germline testing) before LYNPARZA treatment is initiated.

Maintenance following first-line treatment of metastatic gBRCA-mutated metastatic adenocarcinoma of the pancreas:

Patients must have confirmation of a *BRCA* mutation (identified by germline testing) before LYNPARZA treatment is initiated.

HRR-gene mutated metastatic castration-resistant prostate cancer (mCRPC):

Patients must have confirmation of a homologous recombination repair (HRR) gene mutation (using either tumour DNA from a tissue sample, ctDNA obtained from a plasma sample or germline DNA obtained from a blood or another non-tumour sample) before LYNPARZA treatment is initiated. HRR genetic status should be determined by an experienced laboratory using a validated test method.

Posology

LYNPARZA is available as 100 mg and 150 mg tablets.

The recommended dose of LYNPARZA is 300 mg (two 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg.

The 100 mg tablet is available for dose reduction.

Duration of treatment

Monotherapy maintenance treatment of advanced BRCA-mutated ovarian cancer:

Patients can continue treatment for 2 years or until radiological disease progression.

Patients with a complete response (no radiological evidence of disease) at 2 years should stop treatment.

Patients with evidence of disease at 2 years, who in the opinion of the treating medical practitioner can derive further benefit from continuous treatment, can be treated beyond 2 years.

Platinum-sensitive relapsed ovarian cancer:

It is recommended that treatment be continued until progression of the underlying disease or unacceptable toxicity.

Maintenance treatment of advanced ovarian cancer in combination with bevacizumab:

Patients can continue treatment with PRODUCT NAME for 2 years or until radiological disease progression, unacceptable toxicity. Patients with a complete response (no radiological evidence of disease) at 2 years should stop treatment. Patients with evidence of disease at 2 years, who in the opinion of the treating medical practitioner can derive further benefit from continuous LYNPARZA treatment, can be treated beyond 2 years. When LYNPARZA is used in combination with bevacizumab, refer to the Prescribing Information for bevacizumab for recommended dosing information (see section 5.1).

Metastatic HER2-negative breast cancer: it is recommended that treatment be continued until progression of the underlying disease or unacceptable toxicity.

Maintenance following first-line treatment of metastatic adenocarcinoma of the pancreas: it is recommended that treatment be continued until progression of the underlying disease or unacceptable toxicity.

HRR-gene mutated metastatic castration-resistant prostate cancer: it is recommended that treatment be continued until progression of the underlying disease or unacceptable toxicity.

Missing dose

If a patient misses a dose of LYNPARZA, the patient should take their next normal dose at its scheduled time.

Dose adjustments

For adverse events

Treatment may be interrupted to manage adverse events such as nausea, vomiting, diarrhoea and anaemia and dose reduction can be considered (see section 4.8). The recommended dose reduction is to 250 mg (one 150 mg tablet and one 100 mg tablet) twice daily (equivalent to a total daily dose of 500 mg).

If a further dose reduction is required, then reduction to 200 mg (two 100 mg tablets) twice daily (equivalent to a total daily dose of 400 mg) is recommended.

For co-administration with CYP3A inhibitors

Concomitant use of strong or moderate CYP3A inhibitors is not recommended and alternative medicines should be considered. If a strong CYP3A inhibitor must be co-administered, the recommended LYNPARZA dose reduction is to 100 mg (one 100 mg tablet) taken twice daily (equivalent to a total daily dose of 200 mg).

If a moderate CYP3A inhibitor must be co-administered, the recommended LYNPARZA dose reduction is to 150 mg (one 150 mg tablet) taken twice daily (equivalent to a total daily dose of 300 mg) (see sections 4.4 and 4.5).

Special patient populations

Children or adolescents: LYNPARZA is not indicated for use in paediatric patients, as safety and efficacy of LYNPARZA in children and adolescents have not been established.

Elderly (>65 years): No adjustment in starting dose is required for elderly patients. There are limited clinical data in patients aged 75 years and over.

Renal impairment: For patients with moderate renal impairment (creatinine clearance 31 – 50 ml/min) the recommended dose of LYNPARZA is 200 mg (two 100 mg tablets) twice daily (equivalent to a total daily dose of 400 mg). LYNPARZA is not recommended for patients with severe renal impairment or end-stage renal disease (creatinine clearance ≤30 ml/min), as safety and pharmacokinetics have not been studied in these patients. LYNPARZA can be administered to patients with mild renal impairment (creatinine clearance 51 – 80 ml/min) with no dose adjustment (see section 5.2).

Hepatic impairment: LYNPARZA can be administered to patients with mild or moderate hepatic impairment (Child-Pugh classification A or B) with no dose adjustment (see section 5.2). LYNPARZA is not recommended for use in patients with severe hepatic impairment (Child-Pugh classification C), as safety and pharmacokinetics have not been studied in these patients.

Method of administration

For oral use. LYNPARZA tablets should be swallowed whole and not chewed, crushed, dissolved or divided.

LYNPARZA tablets can be taken with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients of LYNPARZA listed in section 6.1.
- Severe renal impairment CrCl < 30 ml/min (see section 4.2).
- Severe hepatic impairment (Child-Pugh class C) (see section 4.2).
- Pregnancy and lactation and for 1 month after the last dose (see section 4.6).

4.4 Special warnings and precautions for use

Haematological toxicity

Haematological toxicity has been reported in patients treated with LYNPARZA, including clinical diagnoses and/or laboratory findings of (CTCAE grade 1 or 2) anaemia, neutropenia, thrombocytopenia and lymphopenia. Patients should not start treatment with LYNPARZA until they have recovered from haematological toxicity caused by previous anti-cancer therapy (haemoglobin, platelet and neutrophil levels should be ≤CTCAE grade 1). Baseline testing, followed by monthly monitoring, of complete blood counts is recommended for the first 12 months of treatment and periodically after this time to monitor for clinically significant changes in any parameter during treatment (see section 4.8).

If a patient develops severe haematological toxicity or blood transfusion dependence, treatment with LYNPARZA should be interrupted and appropriate haematological testing should be initiated. If the blood parameters remain clinically abnormal after 4 weeks of LYNPARZA dose interruption, bone marrow analysis and/or blood cytogenetic analysis are recommended.

Myelodysplastic Syndrome/Acute Myeloid Leukaemia (MDS/AML)

The incidence of MDS/AML in patients treated in clinical trials with LYNPARZA monotherapy, including long-term survival follow up, was <1,5 %, with higher incidence in patients with *BRCA*m platinum-sensitive relapsed ovarian cancer who had received at least two prior lines of platinum chemotherapy and were followed up for 5 years (see section 4.8). The majority of events had a fatal outcome. The duration of therapy with LYNPARZA in patients who developed MDS/AML varied from < 6 months to > 4 years. All patients had potential contributing factors for the development of MDS/AML, having received previous chemotherapy with platinum medicines. Many had also received other DNA damaging treatments. The majority of reports were

in germline *BRCA* mutation (*gBRCAm*) carriers and some of the patients had a history of more than one primary malignancy or of bone marrow dysplasia. If MDS and/or AML are confirmed while on treatment with LYNPARZA, it is recommended that LYNPARZA should be discontinued and the patient be treated appropriately.

Pneumonitis

Pneumonitis has been reported in <1,0 % patients treated with LYNPARZA monotherapy in clinical studies. Reports of pneumonitis had no consistent clinical pattern and were confounded by a number of pre-disposing factors (cancer and/or metastases in lungs, underlying pulmonary disease, smoking history, and/or previous chemotherapy and radiotherapy). When LYNPARZA was used in clinical studies in combination with other therapies there have been events with a fatal outcome. If patients present with new or worsening respiratory symptoms such as dyspnoea, cough and fever, or an abnormal chest radiologic finding is observed, LYNPARZA treatment should be interrupted and prompt investigation initiated. If pneumonitis is confirmed, LYNPARZA treatment should be discontinued and the patient treated appropriately.

Embryofoetal toxicity

Based on its mechanism of action (PARP inhibition), LYNPARZA could cause foetal harm when administered to a pregnant woman. Nonclinical studies in rats have shown that LYNPARZA causes adverse effects on embryofoetal survival and induces major foetal malformations at exposures below those expected at the recommended human dose of 300 mg twice daily.

LYNPARZA should not be taken during pregnancy. If the patient becomes pregnant while taking LYNPARZA, the patient should be apprised of the potential hazard to a foetus.

Pregnancy/contraception

LYNPARZA should not be used during pregnancy. Women of childbearing potential must use two forms of reliable contraception before starting LYNPARZA treatment, during therapy and for 6 months after receiving the last dose of LYNPARZA (see section 4.6). Two highly effective and complementary forms of contraception are recommended (see section 4.6).

Male patients and their female partners of childbearing potential should be advised that they must use effective contraception during LYNPARZA treatment and for 3 months after receiving the last dose of

LYNPARZA (see section 4.6).

Breastfeeding

Breastfeeding mothers should not breastfeed during treatment with LYNPARZA and for one month after receiving the last dose of LYNPARZA (see section 4.6).

Interactions with other medicines

Co-administration of LYNPARZA with strong or moderate CYP3A inhibitors is not recommended (see section 4.5). If a strong or moderate CYP3A inhibitor must be co-administered, the dose of LYNPARZA should be reduced (see section 4.2).

Co-administration of LYNPARZA with strong or moderate CYP3A inducers is not recommended. In the event that a patient already receiving LYNPARZA requires treatment with a strong or moderate CYP3A inducer, the prescriber should be aware that the efficacy of LYNPARZA may be substantially reduced (see section 4.5).

4.5 Interaction with other medicines and other forms of interaction

Clinical studies of LYNPARZA in combination with other anticancer medicines, including DNA damaging medicines, indicate a potentiation and prolongation of myelosuppressive toxicity. The recommended LYNPARZA monotherapy dose is not suitable for combination with myelosuppressive anticancer medicines.

Effect of other medicines on LYNPARZA

Strong and moderate CYP3A inhibitors

CYP3A4/5 are the isozymes predominantly responsible for the metabolic clearance of LYNPARZA. Co-administration of LYNPARZA with a strong CYP3A inhibitor (itraconazole) increased LYNPARZA C_{max} by 42 % and increased AUC by 170 %. Therefore, concomitant use of itraconazole as well as other strong CYP3A inhibitors such as, but not limited to, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir and telaprevir is not recommended with LYNPARZA (see section 4.4).

Physiologically-based pharmacokinetic (PBPK) modelling has shown that moderate inhibitors will alter the clearance of LYNPARZA and therefore, concomitant use of moderate CYP3A inhibitors such as, but not limited to, ciprofloxacin, erythromycin, diltiazem, fluconazole and verapamil is not recommended with

LYNPARZA (see section 4.4).

If strong or moderate CYP3A inhibitors must be co-administered, the dose of LYNPARZA should be reduced (see section 4.2). It is also not recommended to consume grapefruit juice while on LYNPARZA therapy as it is a CYP3A inhibitor.

Strong and moderate CYP3A inducers

Co-administration of LYNPARZA with a strong CYP3A inducer (rifampicin) decreased LYNPARZA C_{max} by 71 % and AUC by 87 %. It is therefore possible that CYP3A inducers could substantially diminish the clinical efficacy of LYNPARZA and as such concomitant use of strong inducers such as, but not limited to, phenytoin, rifabutin, rifampin (rifampicin), rifapentine, carbamazepine, nevirapine, phenobarbitone and St John's Wort (Hypericum perforatum) is not recommended with LYNPARZA (see section 4.4).

PBPK modelling has shown that moderate CYP3A inducers will decrease LYNPARZA AUC by approximately 60 % and therefore concomitant use of moderate CYP3A inducers such as, but not limited to bosentan, efavirenz, etravirine, modafinil and nafcillin is not recommended with LYNPARZA. If a moderate CYP3A inducer must be co-administered, the prescriber should be aware of a potential for decreased efficacy of LYNPARZA (see section 4.4).

Effect of LYNPARZA on other medicines

CYP interactions

Both induction and inhibition of CYP3A4 has been shown *in vitro*, however, PBPK simulations and clinical data suggest that the net effect of LYNPARZA *in vivo* is weak inhibition of CYP3A. Therefore, caution should be exercised when sensitive CYP3A substrates or substrates with a narrow therapeutic margin (e.g. simvastatin, cisapride, ciclosporin, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine) are combined with LYNPARZA.

Appropriate clinical monitoring is recommended for patients receiving CYP3A substrates with a narrow therapeutic margin concomitantly with LYNPARZA.

Induction of CYP1A2 and 2B6 has been shown *in vitro* with CYP2B6 being most likely to be induced to a clinically relevant extent. Therefore, LYNPARZA upon co-administration may reduce the exposure to

substrates of these metabolic enzymes.

Drug transporter interactions

LYNPARZA has also been shown to be an *in vitro* inhibitor of OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. The clinical relevance of these findings is unknown, however, it cannot be excluded that LYNPARZA may increase the exposure to substrates of OATP1B1 (e.g. bosentan, glibenclamide, repaglinide, statins and valsartan), OCT1 (e.g. metformin), OCT2 (e.g. serum creatinine), OAT3 (e.g. furosemide and methotrexate), MATE1 (e.g. metformin and cisplatin) and MATE2K (e.g. metformin). In particular, caution should be exercised if LYNPARZA is administered in combination with any statin**.**

4.6 Fertility, pregnancy and lactation

Woman of childbearing potential/contraception in Males and Females

Women of childbearing potential must use two forms of effective contraception before starting LYNPARZA treatment during therapy and for 6 months after receiving the last dose of LYNPARZA (see section 4.4). A pregnancy test should be performed on all women of childbearing potential prior to treatment, and pregnancy tests should be performed at regular intervals during treatment and at 6 months after receiving the last dose.

It is not known whether LYNPARZA or its metabolites are found in seminal fluid. Male patients must use a condom during therapy and for 3 months after receiving the last dose of LYNPARZA when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male patients must also use effective contraception if they are of childbearing potential (see section 4.4). Male patients should not donate sperm during therapy and for 3 months after receiving the last dose of LYNPARZA.

Pregnancy

LYNPARZA is contraindicated during pregnancy due to the teratogenic and genotoxic potential of LYNPARZA (see section 4.3 and 4.4). Female partners of male patients taking LYNPARZA should also avoid pregnancy. No studies have been conducted in pregnant women (see section 5.3). If a female patient or a female partner of a male patient receiving LYNPARZA becomes pregnant, she should be apprised of the potential hazard to the foetus or potential risk of loss of the pregnancy (see section 4.4).

Breastfeeding

Mothers must not breastfeed their infants while taking LYNPARZA, nor for one month after the last dose (see section 4.3 and 4.4).

Fertility

There are no clinical data on human fertility. In animal studies, no effect on conception was observed but there were adverse effects on embryofoetal survival (see section 5.3).

4.7 Effects on ability to drive and use machines

During treatment with LYNPARZA, asthenia, fatigue, and dizziness have been reported and those patients who experience these symptoms should observe caution when driving or using machines.

4.8 Undesirable effects

b. Tabulated summary of adverse reactions

The safety profile is based on pooled data from 3077 patients with solid tumours treated with LYNPARZA monotherapy and 535 patients treated with LYNPARZA in combination with bevacizumab in clinical trials at the recommended dose.

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

The following adverse reactions have been identified in completed clinical trials with patients receiving LYNPARZA monotherapy where patient exposure is known. Adverse Drug Reactions are organised by MedDRA System Organ Class (SOC) and then by MedDRA preferred term in Table 1. Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); and very rare (<1/10 000) including isolated reports.

Table 1 Adverse drug reactions reported in clinical trials with LYNPARZA monotherapy

MedDRA SOC	MedDRA Term	CIOMS descriptor/	Frequency of

		Overall Frequency (All CTCAE grades)	**CTCAE grade 3 and above**
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Myelodysplastic syndrome/Acute myeloid leukaemia[a]	Uncommon	Uncommon
Blood and lymphatic system disorders	Anaemia[a]	Very common	Very common
	Neutropenia[a]	Very common	Common
	Leukopenia[a]	Very common	Common
	Thrombocytopenia[a]	Very common	Common
	Lymphopenia[a]	Common	Uncommon
Immune system disorders	Hypersensitivity[a]	Uncommon	Rare
	Angioedema[*]	Uncommon	-
Metabolism and nutrition disorders	Decreased appetite	Very common	Uncommon
Nervous system disorders	Dizziness	Very common	Uncommon
	Headache	Very common	Uncommon
	Dysgeusia[a]	Very common	-
Respiratory, thoracic and mediastinal disorders	Cough[a]	Very common	Uncommon
	Dyspnoea[a]	Very common	Common
Gastrointestinal disorders	Vomiting	Very common	Common
	Diarrhoea	Very common	Common
	Nausea	Very common	Common
	Dyspepsia	Very common	Rare
	Stomatitis	Common	Uncommon
	Upper abdominal pain	Common	Uncommon
Skin and subcutaneous tissue disorders	Rash[a]	Common	Uncommon
	Dermatitis[a]	Uncommon	-
	Erythema nodosum	Rare	-
General disorders	Fatigue (including	Very common	Common

	asthenia)		
Investigations	Blood creatinine increased	Common	Rare
	Mean cell volume increased	Uncommon	-

[a] MDS/AML includes preferred terms (PTs) of acute myeloid leukaemia, myelodysplastic syndrome and myeloid leukaemia.

Anaemia includes PTs of anaemia, anaemia macrocytic, erythropenia, haematocrit decreased, haemoglobin decreased, normocytic anaemia and red blood cell count decreased.

Neutropenia includes PTs of febrile neutropenia, neutropenia, neutropenic infection, neutropenic sepsis and neutrophil count decreased.

Leukopenia includes PTs of leukopenia and white blood cell count decreased.

Thrombocytopenia includes PTs of platelet count decreased and thrombocytopenia.

Lymphopenia includes PTs of lymphocyte count decreased and lymphopenia.

Hypersensitivity includes PTs of drug hypersensitivity and hypersensitivity.

Cough includes PTs of cough and productive cough.

Dyspnoea includes PTs of dyspnoea and dyspnoea exertional.

Dysgeusia includes PTs of dysgeusia and taste disorder.

Stomatitis includes PTs of aphthous ulcer, mouth ulceration and stomatitis.

Rash includes PTs of erythema, exfoliative rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular and rash pruritic.

Dermatitis includes PTs of dermatitis and dermatitis allergic.

*As observed in post-marketing setting.

c. Description of selected adverse reactions

Myelodysplastic syndrome/Acute myeloid leukaemia

In clinical studies, across all indications, MDS/AML occurred uncommonly in patients on treatment and during the 30-day safety follow up, and <1,5 % at any time after starting LYNPARZA, including cases actively solicited during the long term follow up for overall survival.

In patients with *BRCA*m platinum-sensitive relapsed ovarian cancer who had received at least two prior lines of platinum chemotherapy and received study treatment until disease progression (SOLO2 study, with

LYNPARZA treatment ≥ 2 years in 45 % of patients), the incidence of MDS/AML was 8 % in patients receiving LYNPARZA and 4 % in patients receiving placebo at a follow-up of 5 years. In the LYNPARZA arm, 9 out of 16 MDS/AML cases occurred after discontinuation of LYNPARZA during the survival follow-up. The incidence of MDS/AML was observed in the context of extended overall survival in the LYNPARZA arm and late onset of MDS/AML. The risk of MDS/AML remains < 1,5 % at 5 year follow up in the first-line setting when LYNPARZA maintenance treatment is given after one line of platinum chemotherapy for a duration of 2 years.

Haematological toxicity

Anaemia was the most common CTCAE grade ≥3 adverse reaction reported in clinical studies with first onset generally reported in the first 3 months of treatment. An exposure-response relationship between LYNPARZA and decreases in haemoglobin has been demonstrated.

In clinical studies with LYNPARZA monotherapy 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 upper limit of normal was approximately 58 %. Levels appeared to return to normal after treatment discontinuation and did not appear to have any clinical consequences.

Baseline testing, followed by monthly monitoring, of complete blood counts is recommended for the first 12 months of treatment, and periodically after this time, to monitor for clinically significant changes in any parameter during treatment which may require dose interruption or reduction and/or further treatment (see sections 4.2 and 4.4).

Other laboratory findings

In clinical studies with LYNPARZA monotherapy the incidence of CTCAE grade ≥2 shifts (elevations) from baseline in blood creatinine was approximately 11 %. Data from a double-blind placebo-controlled study showed median increase up to 23 % from baseline remaining consistent over time and returning to baseline after treatment discontinuation.

90 % of patients had creatinine values of CTCAE grade 0 at baseline and 10 % were CTCAE grade 1 at baseline.

Nausea and vomiting

Nausea was generally reported very early, with first onset within the first month of LYNPARZA treatment in the majority of patients. Vomiting was reported early, with first onset within the first two months of LYNPARZA treatment in the majority of patients. Both nausea and vomiting were reported to be intermittent for the majority of patients.

d. Paediatric population

No studies have been conducted in paediatric patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms of overdose are expected to be an exacerbation of the adverse events. There is no specific treatment in the event of LYNPARZA overdose. In the event of an overdose, the medical practitioner should follow general supportive measures and should treat the patient symptomatically.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, other antineoplastic agents, ATC code: L01XK01

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 HR-deficient cancer cells, the repair of these DNA DSBs is impaired. Cancer cells can become HR deficient due to inactivation of genes with a direct or indirect role in HRR, such as *BRCA1/2*, *ATM*, *CDK12* and others. Instead, alternative and error-prone pathways are activated, such as the classical nonhomologous end joining (NHEJ) pathway, leading to increased genomic instability. After a number of rounds of replication, genomic instability can reach insupportable levels and result in cancer cell death, as cancer cells already have a high DNA damage load relative to normal cells. In the absence of deleterious mutations in key HRR genes, HRR pathway may be compromised by other mechanisms, although the causative aberrancy and penetrance are not fully elucidated. Absence of fully functional HRR pathway is one of the key determinants of platinum sensitivity in ovarian and other cancers.

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.

Clinical efficacy and Safety

Maintenance treatment of BRCA-mutated advanced ovarian cancer SOLO1 study

SOLO1 was a Phase III randomised, double-blind, placebo-controlled, multicentre trial that compared the efficacy and safety of LYNPARZA maintenance treatment (300 mg [2 x 150 mg tablets] twice daily) with placebo in patients with newly diagnosed advanced (FIGO Stage III-IV) high-grade serous or endometrioid *BRCA1/2*-mutated (*BRCA1/2m*) ovarian cancer following completion of first – line platinum –based chemotherapy. In this study 391 patients were randomised (2:1 to receive either lynparza 300 mg: 260 patients or placebo (131 patients). Patients were stratified by response to first – line platinum chemotherapy, complete response (CR) or partial response (PR).

Treatment was continued for 2 years or until radiological progression of the underlying disease, or unacceptable toxicity. For patients who remained in complete clinical response (i.e. no radiological evidence of disease), the maximum duration of treatment was 2 years; however, patients who had evidence of disease

that remained stable (i.e. no evidence of disease progression) could continue to receive LYNPARZA beyond 2 years.

Patients with *BRCA1/2* mutations were identified prospectively either from germline testing in blood via a local test (n=208) or central test (n=181) or from testing a tumour sample using a local test (n=2). The *BRCAm* status of all patients was confirmed where possible using the Myriad Integrated BRAC*Analysis*® test, the Myriad BRACAnalysis CDx® or the Foundation Medicine FoundationOne CDxTM Clinical Trial Assay.

There were 389 patients who were germline *BRCAm* and 2 who were somatic *BRCAm* in SOLO1. Demographic and baseline characteristics were generally well balanced between the olaparib and placebo treatment arms. Median age was 53 years in both arms. Ovarian cancer was the primary tumour in 85 % of the patients. The most common histological type was serous (96 %), endometrioid histology was reported in 2 % of the patients. Most patients were ECOG performance status 0 (78 %). All patients had received first-line platinum-based therapy; response to prior platinum chemotherapy was complete in 82 % and partial in 18 % of the patients. Ninety three percent (93 %) of patients were randomised within 8 weeks of their last dose of platinum-based chemotherapy.

The primary endpoint was progression-free survival (PFS), defined as time from randomisation to progression determined by investigator assessment using modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, or death. Secondary efficacy endpoints included time from randomisation to second progression or death (PFS2), overall survival (OS), time from randomisation to first subsequent anti-cancer therapy or death (TFST) and health related quality of life (HRQoL). Patients had tumour assessments at baseline and every 12 weeks for 3 years, and then every 24 weeks relative to the date of randomisation, until objective radiological disease progression.

The study demonstrated a clinically relevant and statistically significant improvement in investigator assessed PFS for olaparib compared to placebo, with a hazard ratio (HR) of 0.30 (95 % CI 0.23 – 0.41; p< 0.0001; the median was not reached for olaparib versus 13.8 months for placebo). Based on Kaplan -Meier estimates, the proportion of patients that were progression free at 12, 24 and 36 months were 88 %, 74 %, and 60 % for olaparib versus 51 %, 35 % and 27 % for placebo; the median follow-up time was 41 months for both the olaparib and placebo treatment arms. The investigator assessment of PFS was supported with a

blinded independent central radiological (BICR) review of PFS (HR 0.28; 95 % CI 0.20-0.39; p< 0.0001; median not reached for olaparib vs. 14.1 months for placebo). A clinically meaningful and statistically significant improvement in PFS2 was also observed with a HR of 0.50 (95 % CI 0.35-0.72; p=0.0002; median not reached for olaparib vs. 41.9 months for placebo) indicating that the benefit observed with olaparib continued to be evident even with the use of subsequent therapies (see Table 2).

At the time of PFS analysis, interim OS data were immature with events in 82/391 (21 %) patients (HR 0.95; 95 % CI 0.60-1.53; p=0.8903; medians not reached). A clinically meaningful and statistically significant improvement in TFST was observed for olaparib treated patients (Table 2 and Figure 1).

Table 2 Summary of key efficacy findings for newly diagnosed patients with *BRCA*-mutated advanced ovarian cancer in SOLO1

	Olaparib 300 mg bd	**Placebo**
PFS (51% maturity)		
Number of events: Total number of patients (%)	102:260 (39)	96:131 (73)
Median time (months)	NR	13.8
Progression-free at 12 months (%)[a]	88	51
Progression-free at 24 months (%)[a]	74	35
Progression-free at 36 months (%)[a]	60	27
HR (95% CI)[b]	0.30 (0.23-0.41)	
P value (2-sided)	p<0.0001	
PFS2 (31% maturity)		
Number of events: Total number of patients (%)	69:260 (27)	52:131 (40)
Median time (months)	NR	41.9
HR (95% CI)[b]	0.50 (0.35-0.72)	
P value (2-sided)	p=0.0002	
Interim OS (21% maturity)		
Number of events: Total number of patients (%)	55:260 (21)	27:131 (21)[c]
Median time (months)	NR	NR
HR (95% CI)[b]	0.95 (0.60-1.53)	

P value (2-sided)	p=0.8903	
TFST		
Number of events: Total number of patients (%)	99:260 (38)	94:131 (72)
Median time (months)	51.8	15.1
HR (95% CI)[b]	0.30 (0.22-0.40)	
P value[*] (2-sided)	p<0.0001	

[a] Kaplan-Meier estimates.

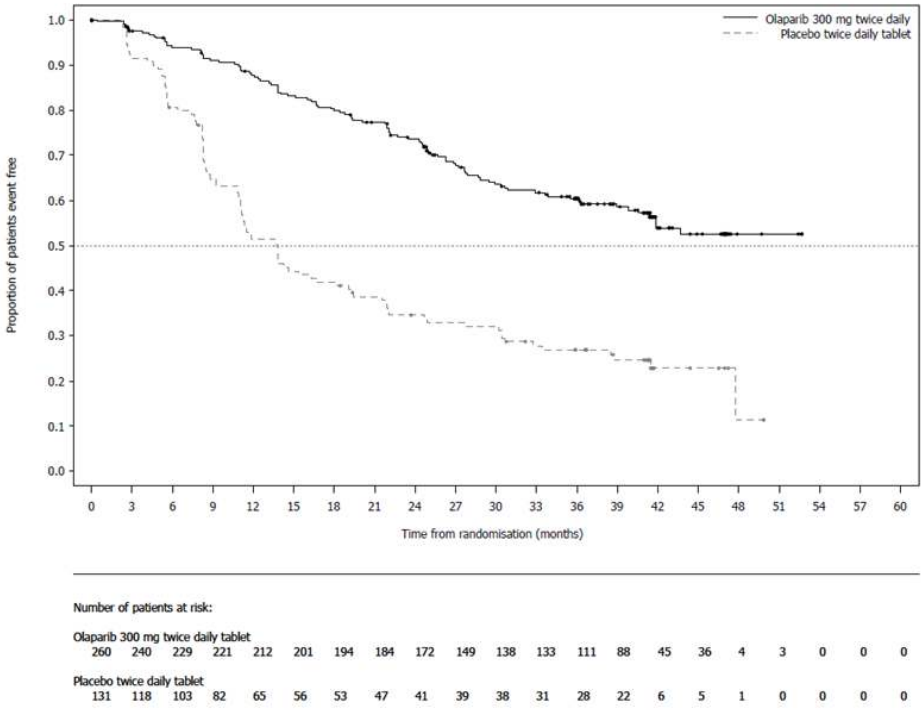
[b] A value <1 favours olaparib. The analysis was performed using a Cox proportional hazards model includingresponse to previous platinum chemotherapy (CR or PR) as a covariate.

[c] Of the 94 patients on the placebo arm who received subsequent therapy, 49 (52%) received a PARP inhibitor.

[·] Not controlled for multiplicity.

[bd] Twice daily; NR not reached; CI Confidence interval

Figure 1 SOLO1: Kaplan-Meier plot of PFS for newly diagnosed patients with *BRCAm* advanced ovarian cancer (51 % maturity -investigator assessment)



There was no decrease in HRQoL from baseline for olaparib-treated patients over the 24-month treatment

period and no clinically relevant differences in HRQoL compared with placebo-treated patients as assessed by the change from baseline in the Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O).

Platinum-sensitive relapsed (PSR) ovarian cancer

The efficacy of LYNPARZA in the maintenance treatment setting in platinum-sensitive relapsed (PSR) ovarian, fallopian tube or primary peritoneal cancer is supported by 2 randomised, double-blind, placebo-controlled trials in patients with PSR and *BRCA*-mutated disease (SOLO2) and in patients with PSR disease (Study 19). In both studies, PSR patients who were in response following completion of platinum-based chemotherapy and whose disease had recurred >6 months after completion of penultimate platinum-based chemotherapy were enrolled. Patients could not have received prior olaparib or other PARP inhibitor treatment. Patients could have received prior bevacizumab, except in the regimen immediately prior to randomisation. Patients with *BRCA* mutations were identified either from germline testing in blood via a local test or the Myriad CLIA Integrated BRAC*Analysis*® test or from testing a tumour sample using a local test or a test performed by Foundation Medicine.

In addition, the efficacy of LYNPARZA in the maintenance treatment setting in non-g*BRCA*m PSR ovarian, fallopian tube or primary peritoneal cancer was also assessed in a single-arm, multicentre study (OPINION).

SOLO2 Study in Platinum – Sensitive Relapsed (PSR) patients with a BRCA mutated Ovarian Cancer

The study compared the efficacy of LYNPARZA maintenance treatment (300 mg [2 x 150 mg tablets] twice daily) taken to progression with placebo treatment in 295 patients with high-grade serous or endometrioid PSR ovarian cancer (2:1 randomisation: 196 olaparib and 99 placebo) who were in response (CR or PR) following completion of platinum-containing chemotherapy. All patients had evidence of germline *BRCA* mutation (*gBRCAm*) at baseline.

The primary endpoint was PFS determined by investigator assessment using RECIST 1.1. Secondary efficacy endpoints included PFS2; OS, TDT, TFST, TSST; and HRQoL. The study met its primary objective demonstrating a clinically meaningful and statistically significant improvement in investigator assessed PFS for olaparib compared with placebo with a HR of 0.30 (95 % CI 0.22-0.41; p<0.0001; median 19.1 months for

olaparib vs. 5.5 months for placebo). The investigator assessment of PFS was supported with a blinded independent central radiological review of PFS (HR 0.25; 95 % CI 0.18-0.35; p<0.0001; median 30.2 months for olaparib vs. 5.5 months for placebo). At 2 years, 43 % olaparib-treated patients remained progression-free compared with only 15 % placebo-treated patients. A clinically meaningful and statistically significant improvement in PFS2 was also observed with a HR of 0.50 (95 % CI 0.34-0.72; p=0.0002; median not reached for olaparib vs. 18.4 months for placebo) indicating that the benefit observed with olaparib continued to be evident even with the use of subsequent therapies. At the final analysis of OS (61 % maturity) the HR was 0,74 (95 % CI 0,54-1,00; p=0,0537; median 51,7 months for olaparib vs 38,8 months for placebo) which did not reach statistical significance.

Clinically meaningful and statistically significant improvements in TDT, TFST and TSST were also observed for olaparib-treated patients (Table 3).

A summary of key efficacy findings for patients with *gBRCAm* PSR ovarian cancer in SOLO2 is presented in Table 3, Figure 2 and Figure 3.

Table 3 Summary of key efficacy findings for patients with *gBRCAm* PSR ovarian cancer in SOLO2

	Olaparib 300 mg tablet bd	**Placebo**
PFS (63% maturity)		
Number of events: Total number of patients (%)	107:196 (55)	80:99 (81)
Median time (months)	19.1	5.5
HR (95% CI) [a]	0.30 (0.22-0.41)	
P value (2-sided)	p<0.0001	
PFS2 (40% maturity)		
Number of events: Total number of patients (%)	70:196 (36)	49:99 (50)
Median time (months)	NR	18.4
HR (95% CI) [a]	0.50 (0.34-0.72)	
P value (2-sided)	p=0.0002	
OS (61 % maturity)		

Number of events: Total number of patients (%)	116:196 (59)	65:99 (66)[b]
Median time (95 % CI), months	51,7(41,5; 59,1)	38,8 (31,4;48,6)
HR (95 % CI) [a]	0,74 (0,54 -1,00)	
P value (2-sided)	p=0,0537	
TFST		
Number of events: Total number of patients (%)	92:196 (47)	79:99 (80)
Median time (months)	27.9	7.1
HR (95% CI) [a]	0.28 (0.21-0.38)	
P value* (2-sided)	p<0.0001	
TDT		
Number of events: Total number of patients (%)	112:196 (57)	86:99 (87)
Median time (months)	19.4	5.6
HR (95% CI) [a]	0.31 (0.23-0.42)	
P value* (2-sided)	p<0.0001	
TSST		
Number of events: Total number of patients (%)	68:196 (35)	60:99 (61)
Median time (months)	NR	18.2
HR (95% CI) [a]	0.37 (0.26-0.53)	
P value* (2-sided)	p<0.0001	

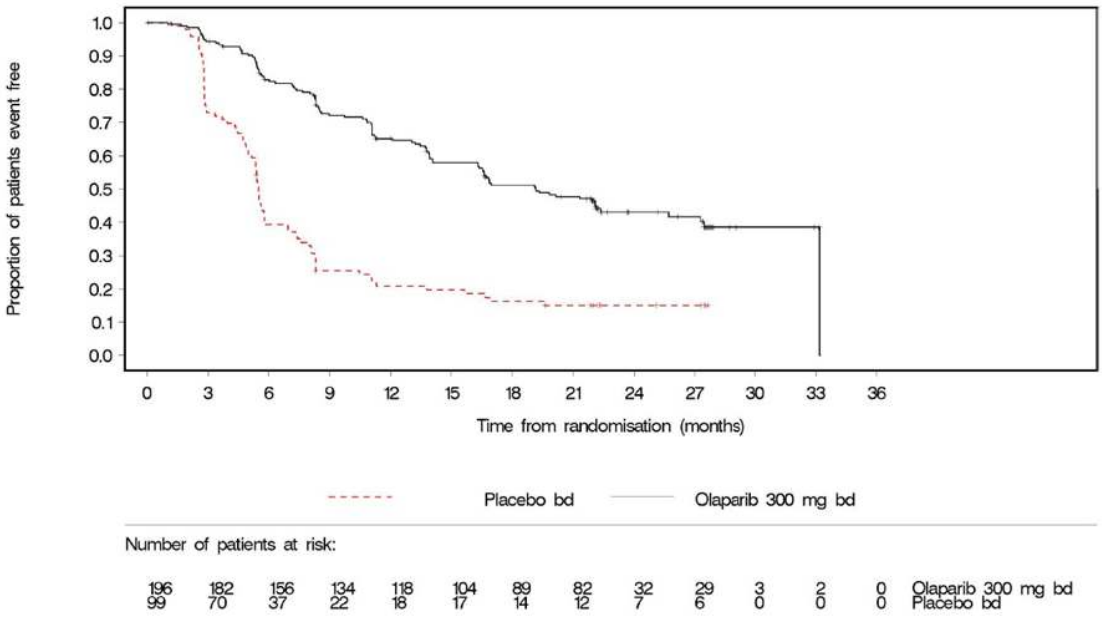
*Not controlled for multiplicity

[a] A value <1 favours olaparib. The analysis was performed using a Cox proportional hazard model including response to previous platinum chemotherapy (CR or PR), and time to disease progression (>6-12 months and >12 months) in the penultimate platinum-based chemotherapy as covariates.

[b] Approximately a third of placebo-treated patients (28/99; 28.3 %) received a subsequent PARP inhibitor.

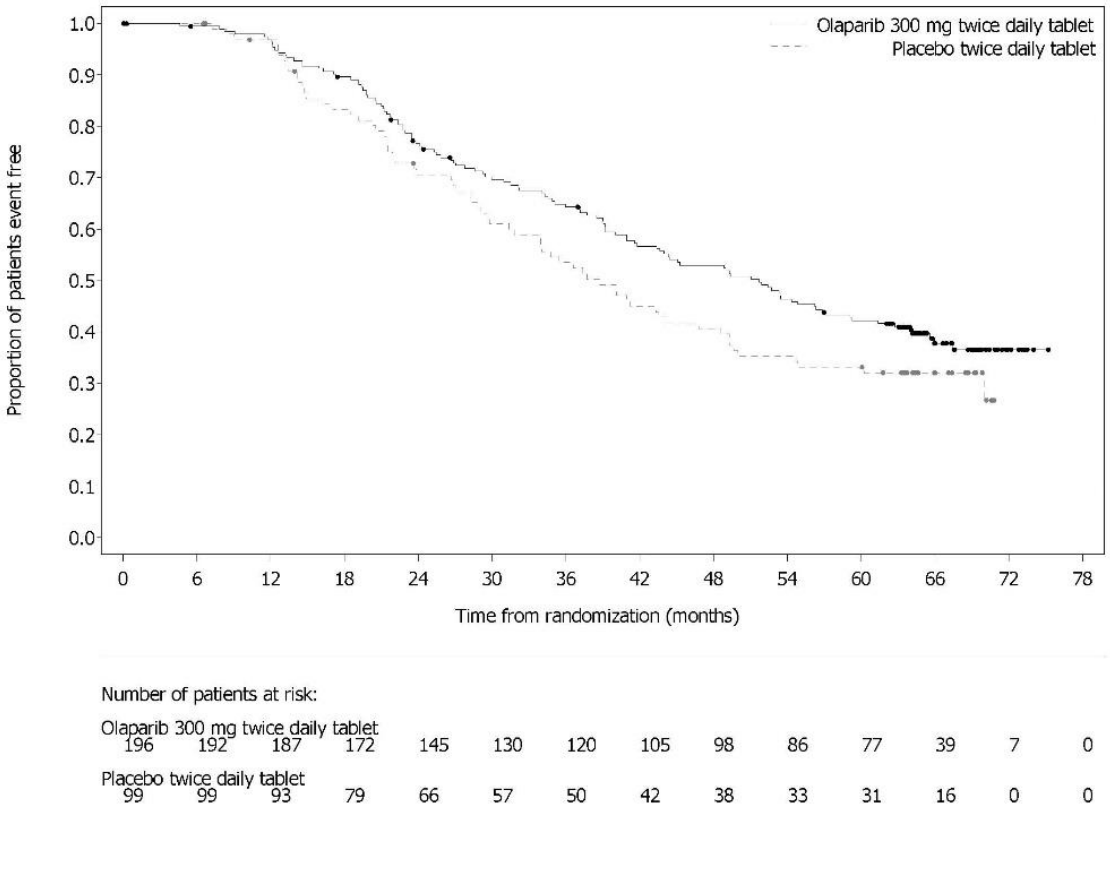
[bd] Twice daily; NR Not reached; OS Overall survival; PFS Progression-free survival; CI Confidence interval; TDT Time from randomisation to discontinuation of treatment or death; TFST Time from randomisation to start of first subsequent therapy or death; PFS2 Time from randomisation to second progression; TSST Time from randomisation to start of second subsequent therapy or death.

Figure 2 SOLO2: Kaplan-Meier plot of PFS in patients with *gBRCAm* PSR ovarian cancer (63 % maturity-investigator assessment)



bd Twice daily; PFS Progression-free survival

Figure 3: SOLO2: Kaplan-Meier plot of OS in patients with *gBRCAm* PSR ovarian cancer (61 % maturity)



There was no difference between olaparib and placebo treatment groups in HRQoL as assessed by the change from baseline in the Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O) over 12 months (estimated difference - 0.03; 95 % CI: -2.191, 2.2126; p= 0.9765).

Study 19 in PSR patients

The study compared the efficacy of LYNPARZA capsule maintenance treatment (400 mg [8 x 50 mg capsules] twice daily) taken to progression with placebo treatment in 265 (136 olaparib and 129 placebo) PSR patients who were in response (CR or PR) following completion of platinum-containing chemotherapy. The primary endpoint was PFS based on investigator assessment using RECIST 1.0.
Secondary efficacy endpoints included OS, disease control rate (DCR), HRQoL, and disease related symptoms. Exploratory analyses TFST and TSST were also performed.

The study met its primary objective demonstrating a statistically significant and clinically relevant improvement in PFS for olaparib compared with placebo with a HR of 0.35 (95 % CI 0.25-0.49; p<0.00001; median 8.4 months for olaparib vs. 4.8 months for placebo). At the final analysis (data cut off [DCO] 9 May 2016) for OS at 79 % maturity, the HR comparing olaparib with placebo was 0.73 (95 % CI 0.55-0.95;

p=0.02138 [did not meet pre-specified significance level of <0.0095]; median 29.8 months for olaparib vs. 27.8 months for placebo). TFST and TSST were also longer for olaparib-treated patients (Table 4).

Preplanned subgroup analysis identified patients with BRCAm ovarian cancer (n=136, 51.3 %) as the subgroup that derived the greatest clinical benefit from olaparib maintenance monotherapy. There were no multiplicity strategies in place for the sub-group analyses. In BRCAm patients the HR for PFS improvement was 0.18 (95 % CI 0.10-0.31; p<0.00001; median 11.2 months for olaparib vs. 4.3 months for placebo). For the secondary endpoint of OS, the HR for olaparib vs. placebo was 0.62 (95 % CI 0.42-0.93; p=0.02140; median 34.9 months for olaparib vs. 30.2 months for placebo). In the olaparib-treated group, 28.4 % of patients remained on treatment for ≥2 years and 14.9 % for ≥5 years. In the placebo-treated group, 8.1 % of patients remained on treatment for ≥2 years and 1.6 % for ≥5 years. TFST and TSST were also longer for olaparib-treated patients (Table 4).

A summary of key efficacy findings for all patients and patients with BRCAm PSR ovarian cancer in Study 19 is presented in Table 4.

Table 4 Summary of key efficacy findings for all patients and patients with BRCAm PSR ovarian cancer in Study 19

	All patients		***BRCA*-mutated**	
	Olaparib 400 mg capsule bd	**Placebo**	**Olaparib 400 mg capsule bd**	**Placebo**
PFS – DCO 30 June 2010				
Number of events: Total number of patients (%)	60:136 (44)	94:129 (73)	26:74 (35)	46:62 (74)
Median time (months)	8.4	4.8	11.2	4.3
HR (95 % CI)[a]	0.35 (0.25-0.49)		0.18 (0.10–0.31)	
P value[*] (2-sided)	p<0.00001		p<0.00001	
OS - DCO 09 May 2016				
Number of events: Total number of patients (%)	98:136 (72)	112:129 (87)	49:74 (66)	50:62 (81)[b]
Median time (months)	29.8	27.8	34.9	30.2

	All patients		***BRCA*-mutated**	
	Olaparib 400 mg capsule bd	**Placebo**	**Olaparib 400 mg capsule bd**	**Placebo**
HR (95 % CI)[a]	0.73 (0.55–0.95)		0.62 (0.42–0.93)	
P value* (2-sided)	p=0.02138		p=0.02140	
TFST – DCO 09 May 2016				
Number of events: Total number of patients (%)	106:136 (78)	124:128 (97)	55:74 (74)	59:62 (95)
Median time (months)	13.3	6.7	15.6	6.2
HR (95 % CI)[a]	0.39 (0.30-0.52)		0.33 (0.22–0.49)	
P value* (2-sided)	p<0.00001		p<0.00001	
TSST – DCO 09 May 2016				
Number of events: Total number of patients (%)	104:136 (77)	119:128 (93)	53:74 (72)	56:62 (90)
Median time (months)	19.1	14.8	21.4	15.3
HR (95 % CI)[a]	0.53 (0.40-0.69)		0.43 (0.29-0.64)	
P value* (2-sided)	p<0.00001		p=0.00003	

* There were no multiplicity strategies in place for the sub-group analyses or for the all patients TFST and TSST

[a] HR= Hazard Ratio. A value <1 favours olaparib. The analysis was performed using a Cox proportional hazards model with factors for treatment, ethnic descent, platinum sensitivity and response to final platinum therapy as covariates.

[b] Approximately a quarter of placebo-treated patients in the *BRCA*-mutated subgroup (14/62; 22.6 %) received a subsequent PARP inhibitor.

[bd] bd Twice daily; OS Overall survival; PFS Progression-free survival; DCO Data cut off; CI Confidence interval; TFST Time from randomisation to start of first subsequent therapy or death; TSST Time from randomisation to start of second subsequent therapy or death.

Within the overall population, the DCR at 24 weeks was 53 % and 25 % for patients in the olaparib and placebo groups, respectively and in the BRCAm population was 57 % and 24 % for patients in the olaparib and placebo groups, respectively.

No statistically significant differences were observed between treatment groups in patient reported symptoms or HRQoL.

OPINION study in non-gBRCAm PSR ovarian cancer patients

OPINION was a single arm, multicentre study that investigated olaparib (300 mg [2 x 150 mg tablets] twice daily) as a maintenance treatment in patients with PSR high grade serous or endometrioid ovarian cancer following 2 or more lines of platinum based chemotherapy and who did not have a known deleterious or suspected deleterious g*BRCA* mutation. Patients whose disease was in response (CR or PR) following completion of platinum based chemotherapy were enrolled. A total of 279 patients were enrolled and received olaparib treatment until disease progression or unacceptable toxicity.

The primary endpoint was investigator-assessed PFS (time from the date of the first olaparib dose to the date of objective radiological disease progression according to modified RECIST v1.1or death by any cause in the absence of progression). Secondary endpoints included OS.

Olaparib when used as maintenance therapy, demonstrated clinical activity in patients with non-g*BRCA*m PSR ovarian cancer with a median investigator-assessed PFS of 9.2 months in the total study population. This was consistent with a sensitivity analysis in which a median investigator-assessed PFS of 9.1 months was observed in the study participants confirmed not to have a deleterious gBRCAm. At the time of primary PFS analysis, the OS data were 30 % mature.

A summary of the key efficacy findings in patients with non-g*BRCA*m PSR ovarian cancer in OPINION is presented in Table 5.

Table 5 Summary of key efficacy findings for non-g*BRCA*m patients with PSR ovarian cancer in OPINION

	Olaparib 300 mg bd
PFS (75 % maturity) (DCO 2 October 2020)	
Number of events: total number of patients (%)	210: 279 (75.3)
Median PFS (95 % CI), months[a]	9.2 (7.6, 10.9)

[a] Calculated using the Kaplan-Meier technique.

Confidence intervals for median PFS was derived based on Brookmeyer Crowley method.

[bd] Twice daily; PFS Progression-free survival; DCO Data cut off; CI Confidence interval.

First-line maintenance treatment of advanced ovarian cancer

PAOLA-1 was a Phase III randomised, double-blind, placebo-controlled, multicentre trial that compared the efficacy of LYNPARZA (300 mg [2 x 150 mg tablets] twice daily) in combination with bevacizumab (15 mg/kg of body weight given once every 3 weeks as an intravenous infusion) compared with placebo plus bevacizumab for the maintenance treatment of newly-diagnosed advanced (FIGO Stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer, following first-line platinum-based chemotherapy and bevacizumab. Treatment with bevacizumab was for a total of up to 15 months/22 cycles, including the period given with chemotherapy and given as maintenance.

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 were stratified by first-line treatment outcome (timing and outcome of cytoreductive surgery and response to platinum-based chemotherapy) and t*BRCAm* status, determined by prospective local testing. 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 for up to 2 years in the absence of unacceptable toxicity or until progression of the underlying disease was diagnosed. Patients who in the opinion of the treating physician could derive further benefit from continuous treatment could be treated beyond 2 years. Treatment with bevacizumab was for a total of up to 15 months, including the period given with chemotherapy and given as maintenance.

Demographic and baseline characteristics were well balanced between both arms. The median age of patients in both arms was 61 years overall (range 26 to 87). Most patients in both arms were ECOG performance status 0 (70 %). Ovarian cancer was the primary tumour in 86 % of the patients in both arms. The most common histological type was serous (96 %) and endometrioid histology was reported in 2 % of the patients. Most patients were diagnosed in FIGO stage IIIC (63 %). All patients had received first-line platinum-based therapy and bevacizumab. Patients were not restricted by the surgical outcome with 65 %

having complete cytoreduction at initial or interval debulking surgery and 35 % having residual macroscopic disease.

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.

Table 6 Patient demographic and baseline characteristics in PAOLA-1

	Olaparib/bevacizumab (n=537)	**Placebo/bevacizumab (n=269)**
Tumour characteristics		
Primary tumour location, n (%)		
Ovary	456 (85)	238 (88)
Fallopian tubes	39 (7)	11 (4)
Primary peritoneal	42 (8)	20 (7)
FIGO Staging, n (%)		
III	378 (70)	186 (69)
IV	159 (30)	83 (31)
Histology type, n (n%)		
Serous	519 (97)	253 (94)
Endometrioid	12 (2)	8 (3)
Clear cell	2 (0.4)	0
Undifferentiated	1 (0.2)	6 (2)
Other	3 (0,6)	2 (0,7)
First line treatment outcome at screening (obtained from the randomisation schedule)		
NED with complete macroscopic resection at initial debulking surgery	170 (32)	86 (32)
NED/CR with complete macroscopic resection at interval debulking surgery	166 (31)	84 (31)

	Olaparib/bevacizumab (n=537)	**Placebo/bevacizumab (n=269)**
NED/CR at screening, in patient who had either incomplete resection (at initial or interval debulking surgery) or no debulking surgery	82 (15)	40 (15)
Partial response	119 (22)	59 (22)
Screening laboratory t*BRCA* status (obtained from the randomisation schedule)		
Deleterious mutation	161 (30)	80 (30)
Absence of deleterious mutation[a]	376 (70)	189 (70)

[a] Includes test cancelled/failed patients.

CR Complete response; NED No evidence of disease

The primary endpoint was progression-free survival (PFS), defined as time from randomisation to progression determined by investigator assessment using modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, or death. Secondary efficacy endpoints included time from randomisation to second progression or death (PFS2), overall survival (OS), time from randomisation to first subsequent anti-cancer therapy or death (TFST) and health related quality of life (HRQoL). 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.

The study demonstrated a clinically meaningful and statistically significant improvement in investigator assessed PFS for olaparib/bevacizumab compared to placebo/bevacizumab. The investigator assessment of PFS was supported with a BICR of PFS (HR 0,63; 95 % CI 0,51-0,77, p<0,0001 with a median of 26,1 months for olaparib/bevacizumab vs 18,3 months for placebo/bevacizumab).

Final analysis of PFS2 was statistically significant. Although not controlled for multiplicity, there was a clinically meaningful delay in TFST observed for olaparib-treated patients. At the time of final PFS2 analysis, interim OS data were immature (38 %).

Table 7 Summary of key efficacy findings for newly-diagnosed patients with advanced ovarian

cancer in PAOLA-1

	Olaparib/ bevacizumab	Placebo/ bevacizumab
PFS (59 % maturity)		
Number of events: Total number of patients (%)	280:537 (52)	194:269 (72)
Median time (months)	22,1	16,6
Progression-free at 12 months (%)[a]	78	66
Progression-free at 24 months (%)[a]	46	28
HR (95 % CI)[b]	0,59 (0,49-0,72)	
P value (2-sided)	p<0,0001	
PFS2 (53 % maturity)		
Number of events: Total number of patients (%)	260:537 (48)	164:269 (61)
Median time (months)	36,5	32,6
HR (95 % CI)[b]	0,78 (0,64-0,95)	
P value (2-sided)	p=0,0125	
Interim OS (38 % maturity)		
Number of events: Total number of patients (%)	195:537 (36)	108:269 (40)[b]
Median time (months)	NR	45,8
HR (95 % CI)[b]	0,93 (0,74-1,18)	
TFST		
Number of events: Total number of patients (%)	338:537 (63)	209:269 (78)
Median time (months)	24,8	18,5
HR (95 % CI)[b]	0,63 (0,53-0,75)	
P value[*] (2-sided)	p<0,0001	

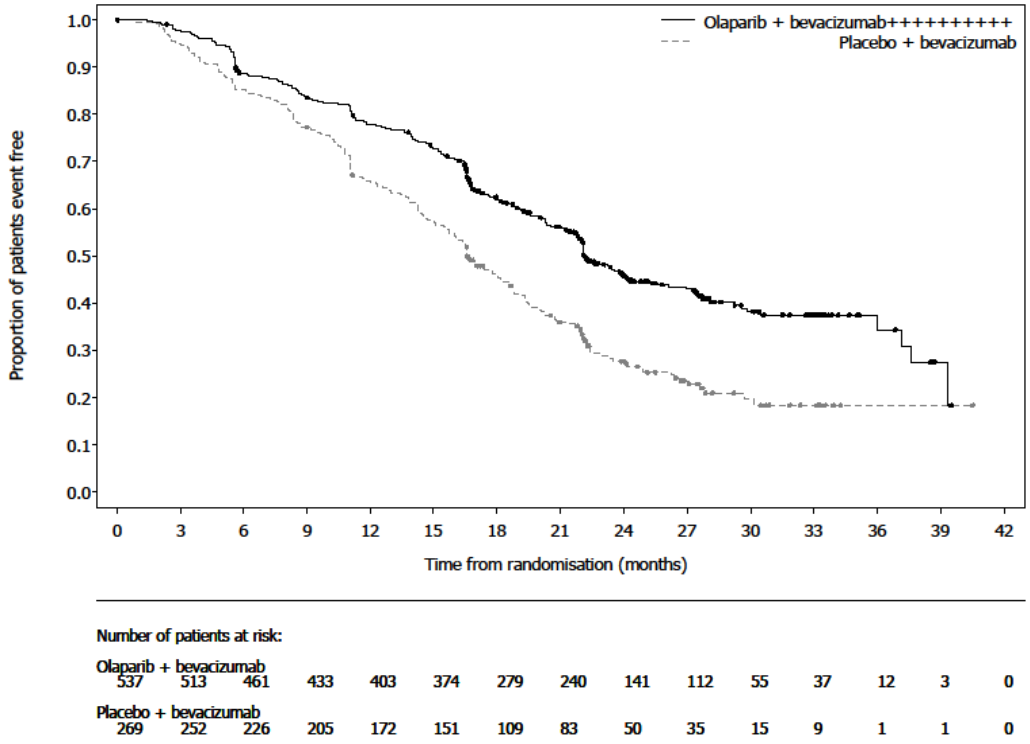
[a] Kaplan-Meier estimates.

[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.

[*] Not controlled for multiplicity.

CI Confidence interval; HR Hazard ratio; NC not calculable

Figure 4 PAOLA-1: Kaplan-Meier plot of PFS for newly-diagnosed patients with advanced ovarian cancer (59 % maturity - investigator assessment)



Overall, HRQoL remained stable across the 24-month treatment period in patients receiving olaparib or placebo in combination with bevacizumab. There was no clinically meaningful difference in mean change from baseline of the EORTC QLQ-C30 global health status/QoL score for olaparib/bevacizumab-treated patients compared with placebo/bevacizumab-treated patients (estimated difference 0,59; 95 % CI -1,40 – 2,57, p=0,5626).

Germline *BRCA*-mutated HER2-negative metastatic breast cancer

OlympiAD in HER2-negative metastatic breast cancer patients with a gBRCA mutation

The study was a Phase III randomised, open-label, controlled trial that compared the efficacy of olaparib (300 mg [2 x 150 mg tablets] twice daily) taken to progression with a comparator arm of medical practitioner's choice of chemotherapy (capecitabine, eribulin or vinorelbine). In the study 302 patients with *gBRCAm* HER2- negative metastatic breast cancer who had previously received up to two lines of chemotherapy for the treatment of metastatic disease were randomised (2:1 randomisation: 205 olaparib and 97 comparator). Patients were stratified based on: receipt of prior chemotherapy regimens for metastatic breast cancer, oestrogen receptor (ER) and / or progesterone receptor (PgR) positive vs ER and PgR

negative, prior platinum for breast cancer. The primary endpoint was PFS assessed by BICR using RECIST 1.1. Secondary endpoints included PFS2, OS, objective response rate (ORR) and HRQoL.
All patients had received prior treatment with anthracycline (unless contraindicated) and a taxane in either the neoadjuvant, adjuvant or metastatic setting. Prior therapy with platinum for metastatic breast cancer was allowed provided there had been no evidence of disease progression during platinum treatment. Prior therapy with platinum in the (neo)adjuvant setting was allowed provided the last dose was received at least 12 months prior to randomisation. Patients could not have received prior olaparib or other PARP inhibitor treatment.

Patients with ER and/or PgR positive disease must have received and progressed on at least one endocrine therapy (adjuvant or metastatic) or had disease that the treating medical practitioner believed to be inappropriate for endocrine therapy. Patients had tumour assessments at baseline and every 6 weeks for the first 24 weeks, and then every 12 weeks relative to date of randomisation, until objective radiological disease progression.

The study met its primary objective demonstrating a statistically significant and clinically meaningful improvement in PFS for olaparib-treated patients compared with those in the comparator arm with a HR of 0.58 (9 5% CI 0.43-0.80; p=0.0009; median 7.0 months for olaparib vs. 4.2 months for comparator) (Table 8).

A clinically meaningful and statistically significant improvement in PFS2 was also bserved with a HR of 0.57 (95 % CI 0.40-0.83; p=0.0033; median 13.2 months for olaparib vs 9.3 months for comparator) indicating that the benefit observed with olaparib continued to be evident even with the use of subsequent therapies. In the measurable disease patient population (77 %), ORR in olaparib-treated patients was 60 % (95 % CI 52.0-67.4) and in patients who received comparator was 29 % (95 % CI 18.3-41.3). The median time to onset of response was 47 days for olaparib vs 45 days for comparator.

The median duration of response was 6.4 months for olaparib vs 7.1 months for comparator. Overall survival was 64 % mature at the time of the final OS analysis (DCO 25 September 2017). The OS HR comparing olaparib with comparator was 0.90 (95 % CI 0.66-1.23; p=0.5131; median 19.3 months for olaparib vs. 17.1 months for comparator). The median follow-up time in censored patients was 25.3 months for olaparib vs 26.3 months for comparator. Consistent results were observed across patient subgroups.

Table 8 Summary of key efficacy findings for patients with *gBRCAm* HER2-negative metastatic breast cancer in OlympiAD

	Olaparib 300 mg bd	**Physician's choice chemotherapy[a]**
PFS (77% maturity) – DCO 09 December 2016		
Number of events: Total number of patients (%)	163:205 (80)	71:97 (73)
Median time (months)	7.0	4.2
HR (95% CI)		0.58 (0.43-0.80)
P value (2-sided)		p=0.0009
PFS2 (52% maturity) - DCO 09 December 2016		
Number of events: Total number of patients (%)	104:205 (51)	53:97 (55)
Median time (months)	13.2	9.3
HR (95% CI)		0.57 (0.40-0.83)
P value (2-sided)		p=0.0033
OS (64% maturity) – DCO 25 September 2017		
Number of events: Total number of patients (%)	130:205 (63)	62:97 (64)[b]
Median time (months)	19.3	17.1
HR (95% CI)		0.90 (0.66-1.23)
P value (2-sided)		p=0.5131
ORR - DCO 09 December 2016		
Number of objective responders: Total number of patients with measurable disease (%)	100:167 (60)	19:66 (29)
95% CI	52.0 to 67.4	18.3 to 41.3
Complete response (%)	15:167 (9)	1:66 (2)
Partial response (%)	85:167 (51)	18:66 (27)

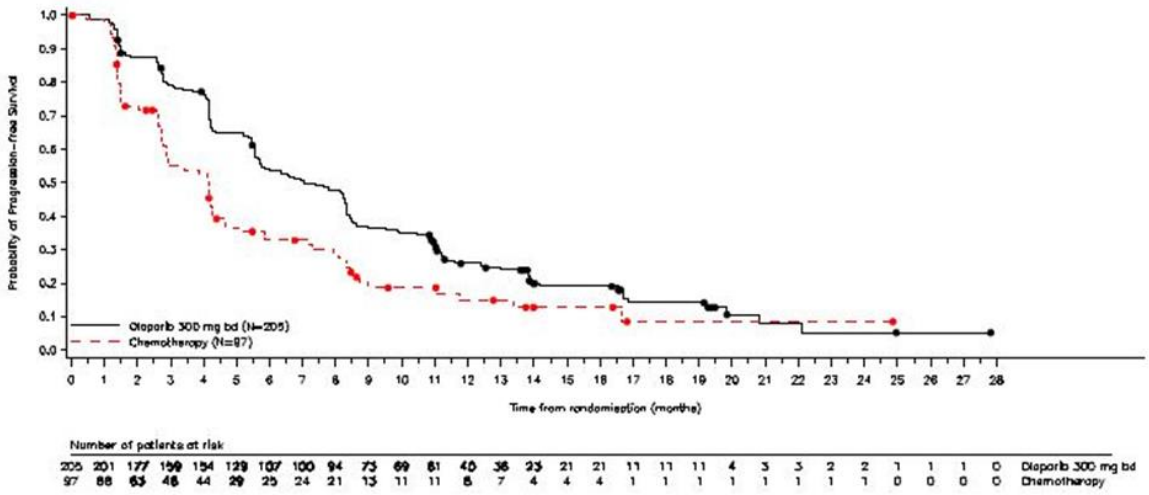
[a] Physician's choice of chemotherapy consisting of either capecitabine, eribulin or vinorelbine.

[b] Approximately a tenth of patients in the physician's choice group (8/97; 8.2 %) received a subsequent

PARP inhibitor

[bd] Twice daily; CI Confidence interval; DCO Data cut off; HR Hazard ratio; ORR Objective response rate; OS Overall survival; PFS Progression-free survival; PFS2 Time to second progression or death.

Figure 5 OlympiAD: Kaplan-Meier plot of PFS in patients with gBRCAm HER2-negative metastatic breast cancer (77 % maturity)



A significant difference in global health status/QoL (assessed using the EORTC QLQ-C30 questionnaire which uses a 0-100 point scale) in favour of olaparib was observed (adjusted mean difference in change from baseline score was 7.5 points [95% CI: 2.48-12.44; p=0.0035]).

Time to deterioration (≥10 points decrease from baseline) in global health status/QoL score was statistically significantly longer on the olaparib arm (HR 0.44; 95 % CI: 0.25-0.77; p=0.0043; median not reached for olaparib vs. 15.3 months for comparator arm). Over the treatment period, the proportion of patients with clinically significant improvement (≥10 points increase from baseline) in global health status/QoL score was 33.7 % (n=69) in the olaparib arm and 13.4 % (n=13) in the comparator arm.

Maintenance following first-line treatment of germline *BRCA*-mutated metastatic adenocarcinoma of the pancreas

POLO was a Phase III, randomised, double-blind, placebo-controlled, multicentre trial that compared the efficacy and safety of LYNPARZA maintenance treatment (300 mg [2 x 150 mg tablets] twice daily) with placebo in g*BRCA1/2*-mutated metastatic adenocarcinoma of the pancreas. The study randomised 154 patients with germline BRCA1/2 (3:2 randomisation: 92 olaparib and 62 placebo) whose disease had not

progressed following at least 16 weeks of first-line platinum-based chemotherapy. There was no upper limit to the duration of chemotherapy received. After 16 weeks of continuous platinum-based chemotherapy, the platinum could be discontinued at any time for toxicity and the other agents continued; the patients were eligible for randomisation as long as there was no evidence of progression at any time during chemotherapy treatment. All toxicities from previous anti-cancer therapy must have been resolved to CTCAE grade 1, except for alopecia, grade 3 peripheral neuropathy and Hgb ≥ 9 g/dL. LYNPARZA treatment was continued until progression of the underlying disease.

Patients with germline *BRCA* mutations were identified from prior local testing results or by central testing using the Myriad BRAC*Analysis*® or Myriad BRACAnalysis CDx® test. The *BRCAm* status of all patients identified using prior local testing results was confirmed, where sent, using the Myriad BRAC*Analysis*® or Myriad BRACAnalysis CDx® test.

Demographic and baseline characteristics were generally well balanced between the olaparib and placebo arms. Median age was 57 years in both arms; 30 % of patients in the olaparib arm were ≥ 65 years compared to 21 % in the placebo arm. Fifty-eight per-cent (58 %) of patients in the olaparib arm and 50% of patients in the placebo group were male. In the olaparib arm 89% were white and 11% were non-white. Most patients were ECOG performance status 0 (67 %). Overall, the sites of metastasis prior to chemotherapy were liver (72%), lung (10%) and other sites (50%). Ninety-six per-cent (96 %) of patients were randomised within 8 weeks of their last dose of platinum-based chemotherapy. The median time from initiation of first-line platinum-based chemotherapy to randomisation was 5,8 months (range 3,4 to 33,4 months) and 49 % of patients were in complete or partial response to their most recent platinum-based regimen.

The primary endpoint was progression-free survival (PFS), defined as time from randomisation to progression determined by BICR using modified Response Evaluation Criteria in Solid Tumors (RECIST) 1,1, or death. Secondary efficacy endpoints included overall survival (OS), time from randomisation to second progression or death (PFS2), time from randomisation to first subsequent anti-cancer therapy or death (TFST), time from randomisation to discontinuation of treatment or death (TDT), objective response rate (ORR), duration of response (DoR), response rate, time to response and health related quality of life (HRQoL). Patients had tumour assessments at baseline and every 8 weeks for 40 weeks, and then every 12 weeks relative to the date of randomisation, until objective radiological disease progression. For PFS, the median follow-up time for censored patients was 9,1 months in the olaparib arm and 3,8 months in the

placebo arm. For OS, the median follow-up time for censored patients was 31,3 months in the olaparib arm and 23,9 months in the placebo arm.

The study demonstrated a clinically meaningful and statistically significant improvement in PFS for olaparib compared to placebo, with a HR of 0,53 (95 % CI 0,35 – 0,82; p=0,0038; the median was 7,4 months for olaparib vs 3,8 months for placebo). The sensitivity analysis of PFS by investigator assessment (HR 0,51; 95 % CI 0,34 to 0,78; p=0,0017; median 6,3 months vs 3,7 months for olaparib vs placebo, respectively) was consistent with the PFS analysis by BICR. Based on Kaplan–Meier estimates, the proportion of patients that were alive and progression-free at 12, 24 and 36 months were 34 %, 28 % and 22 % for olaparib vs 15 %, 10 % and 10 % for placebo.

At the time of PFS analysis the median DoR was longer in the olaparib arm (24,9 months) compared to the placebo arm (3,7 months), with a longer median time to onset of response (5,4 months for olaparib vs 3,6 months for placebo).

At the final analysis of OS (70 % maturity) the HR for OS was 0,83 (95 % CI 0,56 to 1,22; p=0,3487; median 19,0 months for olaparib vs 19,2 months for placebo) which did not reach statistical significance. The percentage of patients that were alive and in follow-up were 28 % in the olaparib arm and 18 % in the placebo arm.

At the time of final OS analysis, the HR for PFS2 (60 % maturity, not controlled for multiplicity) was 0,66 (95 % CI 0,42 – 1,02; p=0,0613) with a difference in median of 7,6 months in favour of olaparib (median 16,9 months for olaparib vs 9,3 months for placebo). A clinically meaningful and statistically significant improvement in TFST and TDT was observed for olaparib-treated patients.

Table 9 Summary of key efficacy findings for patients with g*BRCAm* metastatic adenocarcinoma of the pancreas in POLO

	Olaparib 300 mg bd	**Placebo**
PFS (68 % maturity)		
Number of events: Total number of	60:92 (65)	44:62 (71)

patients (%)		
Median time (months)	7,4	3,8
HR (95 % CI)[a,b]	0,53 (0,35-0,82)	
P value (2-sided)	p=0,0038	
OS (70 % maturity)		
Number of events: Total number of patients (%)	61:92 (66)	47:62 (76)[c]
Median time (months)	19,0	192
HR (95 % CI)[b,c]	0,83 (0,56-1,22)	
P value (2-sided)	p=0,3487	
PFS2 (60 % maturity)		
Number of events: Total number of patients (%)	52:92 (57)	40:62 (65)
Median time (months)	16,9	9,3
HR (95 % CI)[a,b]	0,66 (0,43-1,02)	
P value* (2-sided) [b]	p=0,0613	
TFST (82 % maturity)		
Number of events: Total number of patients (%)	72:92 (78)	55:62 (89)
Median time (months)	9,0	5,4
HR (95 % CI)[b,c]	0,44 (0,30-0,66)	
P value* (2-sided)	p<0,0001	
TDT (88 % maturity)		
Number of events: Total number of patients (%)	77:92 (84)	59:62 (95)
Median time (months)	7,5	3,8
HR (95 % CI)[b]	0,43 (0,29-0,63)	
P value* (2-sided)	p<0,0001	
ORR		
Number of objective responders: total number of patients with measurable disease at baseline (%)	18:78 (23,1)	6:52 (11,5)

Complete response (%)	2 (2,6)	0
Partial response (%)	16 (20,5)	6 (11,5)
Odds ratio (95 % CI)	2,30 (0,89; 6,76)	
P value* (2-sided)	p=0,1028	
DoR		
Median time (months) (95 % CI)	24,9 (14,75; NC)	3,7 (2,10; NC)

[a] A value <1 favours olaparib.

[b] The analysis was performed using a log-rank test.

[c] Six (6.5 %) patients in the olaparib arm received subsequent PARP inhibitor and 16 (26 %) patients on the placebo arm received a PARP inhibitor in any subsequent line.

* Not controlled for multiplicity.

[bd] Twice daily; CI Confidence interval; HR Hazard Ratio; NC Not calculable; ORR Objective Response Rate; OS Overall survival; PFS Progression-free survival; PFS2 Time to second progression or death; TDT Time from randomisation to discontinuation of treatment or death; TFST Time from randomisation to start of first subsequent therapy or death.

Figure 6 POLO: Kaplan-Meier plot of PFS for patients with g*BRCAm* metastatic adenocarcinoma of the pancreas (68 % maturity – BICR)

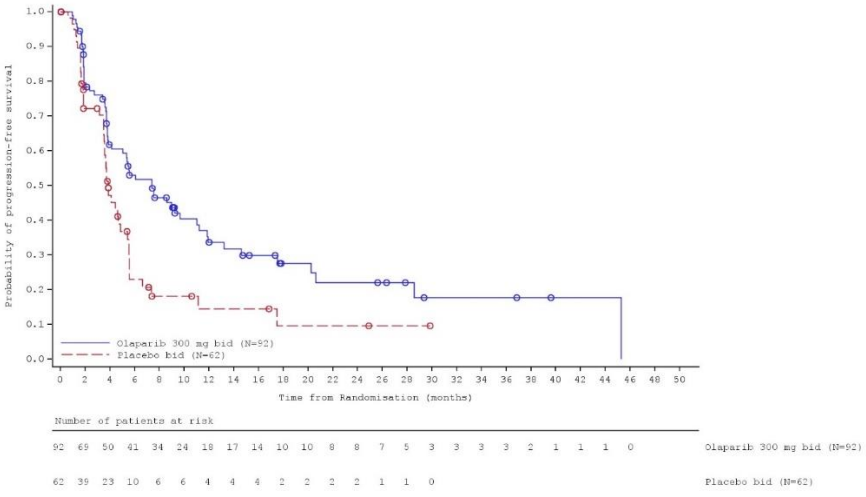
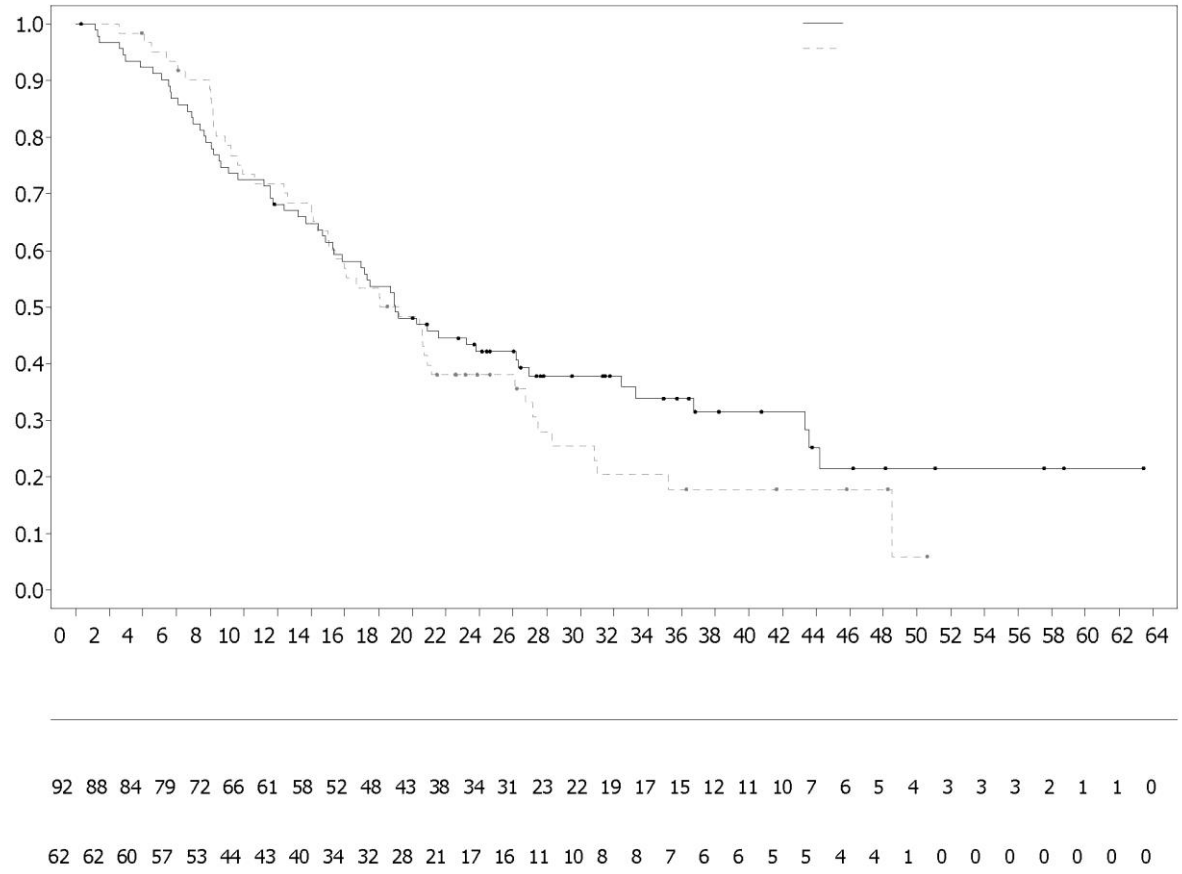


Figure 7 POLO: Kaplan-Meier plot of OS for patients with g*BRCAm* metastatic adenocarcinoma of the pancreas (70 % maturity)



Patient-reported HRQoL was assessed using the EORTC QLQ-C30 and its pancreatic cancer module (EORTC QLQ-PAN26). A 10-point change was pre-defined as clinically meaningful on a 0-100 points global HRQoL scale. The adjusted mean change from baseline in global HRQoL score across all timepoints up to 6 months was -1,20 ± 1,42 in the olaparib group (n=84) and 1,27 ± 1,95 in the placebo group (n=54), with a corresponding estimated difference of −2,47 points (95 % CI, −7,27 to 2,33), demonstrating no worsening in olaparib treated patients and no clinically meaningful differences in global HRQoL over the treatment period between arms. Median time to clinically meaningful deterioration (≥10 points decrease from baseline sustained at the next timepoint) in global HRQoL score was numerically longer in the olaparib arm compared to placebo (HR 0,72; 95 % CI: 0,41-1,27; medians: 21,2 months olaparib vs. 6,0 months placebo). Over the treatment period, the proportion of patients with clinically significant improvement (≥10 points increase from baseline) in global HRQoL score was 29,2 % in the olaparib arm and 22,4 % in the placebo arm.

Homologous recombination repair gene mutated metastatic castration-resistant prostate cancer

PROfound was a Phase III randomised, open-label, multicentre trial that evaluated the efficacy of LYNPARZA (300 mg [2 x 150 mg tablets] twice daily) versus a comparator arm of investigator's choice of NHA ([new hormonal agent] enzalutamide or abiraterone acetate) in men with metastatic castration-resistant

prostate cancer (mCRPC). Patients needed to have progressed on prior NHA for the treatment of metastatic prostate cancer and/or CRPC and have a tumour mutation in one of 15 genes involved in the homologous recombination repair (HRR) pathway. All patients continued on a luteinising hormone releasing hormone (LHRH) analogue or had prior bilateral orchiectomy.

Patients were divided into two cohorts based on HRR gene mutation status. Patients with mutations in either *BRCA1*, *BRCA2 genes* or *ATM mutations* were randomised in Cohort A; patients with mutations among 12 other genes involved in the HRR pathway (*BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D* or *RAD54L*) were randomised in Cohort B. Patients with co-mutations (*BRCA1*, *BRCA2* or *ATM* plus a Cohort B gene) were randomised in Cohort A. Although patients with *PPP2R2A* gene mutations were enrolled in the trial, LYNPARZA is not indicated for the treatment of patients with this gene mutation due to unfavourable benefit-risk.

The study randomised 387 patients (2:1 randomisation: 256 olaparib and 131 comparator); in Cohort A there were 245 patients (162 olaparib and 83 comparator) and in Cohort B there were 142 patients (94 olaparib and 48 comparator). Patients were stratified by prior taxane use and evidence of measurable disease. Treatment was continued until disease progression. Patients randomised to comparator were given the option to switch to olaparib upon confirmed radiological BICR progression.

Patients with HRR gene mutations were identified based on prostate cancer tissue specimen testing by the Foundation Medicine FoundationOne® HRR clinical trial assay performed in a CLIA certified laboratory (CLIA HRR Clinical Trial Assay) or from reanalysis of data from a prior Foundation Medicine test.

Demographics and baseline characteristics were generally well balanced between the olaparib and comparator arms in Cohort A+B. Median age was 69 years in both arms. Prior therapy in the olaparib arm was 66 % taxane, 40 % enzalutamide, 38 % abiraterone acetate and 20 % both enzalutamide and abiraterone acetate. Prior therapy in the comparator arm was 63 % taxane, 41 % enzalutamide, 41 % abiraterone acetate and 18 % both enzalutamide and abiraterone acetate. Fifty-eight percent (58 %) of patients in the olaparib arm and 55 % in the comparator arm had measurable disease at study entry. The proportion of patients with bone, distant lymph node, locoregional lymph node, liver and respiratory metastases was 85 %, 39 %, 21 %, 10 % and 17 %, respectively in the olaparib arm and 86 %, 39 %, 24 %, 14 % and 12 %, respectively in the comparator arm. Most patients in both treatment arms had an ECOG of 0

or 1 (95 %). Baseline pain scores (BPI-SF worst pain) were 0-<2 (48 %), 2-3 (12 %) or >3 (36 %) in the olaparib arm and 0-<2 (44 %), 2-3 (10 %) or >3 (43 %) in the comparator arm. Median baseline PSA was 68,22 µg/L in the olaparib arm and 106,49 µg/L in the comparator arm.

The primary endpoint of the study was radiological progression free survival (rPFS) in Cohort A determined by BICR using RECIST 1.1 (soft tissue) and Prostate Cancer Working Group (PCWG3) (bone). Key secondary endpoints included confirmed objective response rate (ORR) by BICR (Cohort A), rPFS by BICR (Cohort A+B), time to pain progression (TTPP) (Cohort A) and overall survival (OS) (Cohort A).

Other secondary endpoints in Cohort A and Cohort A+B included time to first symptomatic skeletal-related event (SSRE), duration of response (DoR), time to opiate use for cancer-related pain, confirmed soft tissue ORR, reduction of at least 50% in the concentration of prostate specific antigen (PSA_{50}-response), circulating tumour cells (CTC) conversion rate, time to second progression or death (PFS2) and disease-related symptoms and health related quality of life ([HRQoL], pain progression, pain severity progression, pain interference and pain palliation). Other secondary end-points in Cohort B included rPFS by BICR. In addition, other secondary end-points in Cohort B and Cohort A+B included confirmed ORR by BICR, OS and time to pain progression.

The study demonstrated a clinically meaningful and statistically significant improvement in BICR assessed rPFS for olaparib vs comparator in Cohort A and also in Cohort A+B.

In Cohort A there was a statistically significant and clinically meaningful improvement in confirmed radiological ORR by BICR for patients with measurable disease at baseline in the olaparib arm vs comparator and an improvement observed in confirmed radiological ORR Cohort A+B. There was a statistically significant and clinical meaningful delay in TTPP in the olaparib arm compared with the investigators choice of NHA arm in Cohort A and the results in Cohort A+B were consistent with Cohort A.

The final analysis of OS demonstrated a statistically significant improvement in OS in patients randomised to LYNPARZA compared to patients in the investigators choice of NHA arm in Cohort A.

Table 10 Summary of key efficacy in Cohort A and Cohort A + B in PROfound

	Cohort A	Cohort A	Cohort A+B	Cohort A+B

	Olaparib 300 mg bd (N=162)	Investigators choice of NHA (N=83)	Olaparib 300 mg bd (N=256)	Investigators choice of NHA (N=131)
rPFS by BICR[a,b]				
Number of events/total number of patients (%)	106/162 (65)[c]	68/83 (82) [c]	180/256 (70) [c]	99/131 (76) [c]
Median rPFS (95 % CI) [months]	7.4 (6.2, 9.3)	3.6 (1.9, 3.7)	5.8 (5.5, 7.4)	3.5 (2.2, 3.7)
HR (95 % CI)[d]	0.34 (0.25, 0.47)		0.49 (0.38, 0.63)	
P value (2-sided)[e]	<0.0001		<0.0001	
Confirmed ORR by BICR				
Number of objective responders/total number of patients with measurable disease at baseline (%)	28/84 (33)	1/43 (2)	30/138 (22)	3/67 (5)
Odds ratio (95% CI)	20.86 (4.18, 379.18)		5.93 (2.01, 25.40)	
P-value (2-sided)	<0.0001		0.0006	
DoR (patients with confirmed objective response)[f]				
N	28	1	30	3
Median (95% CI) [months]	5.9 (5.5, 9.0)	7.4 (NR, NR)	5.9 (5.5, 9.0)	7.4 (3.6, 7.4)
OS				
Number of events/total number of patients (%)	91/162 (56)	57/83 (69)	160/256 (63)	88/131 (67)
Median OS (95% CI) [months]	19.1 (17.4, 23.4)	14.7 (11.9, 18.8)	17.3 (15.5, 18.6)	14.0 (11.5, 17.1)
HR (95% CI)	0.69 (0.50, 0.97)		0.79 (0.61, 1.03)	
P-value (2-sided)	0.0175		-[f]	
PFS2 (by investigator)[f]				
Number of events/total number of patients (%)	61/162 (38)	44/83 (53)	113/256 (44)	69/131 (53)

Median PFS2 (95% CI) [months]	17.2 (12.7,18.3)	10.6 (9.1, 11.2)	13.0 (11.4, 15.8)	9.7 (8.2, 11.0)
HR (95% CI)	0.53 (0.36, 0.79)		0.61 (0.45, 0.83)	
P-value (2-sided) [nominal]	p=0.0003		p=0.0003	
Time to first SSRE[f]				
Number of events/total number of patients (%)	25/162 (15)	19/83 (23)	41/256 (16)	25/131 (19)
Median (95% CI) [months]	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)
HR (95% CI)	0.37 (0.20, 0.70)		0.48 (0.29, 0.82)	
P-value (2-sided) [nominal]	0.0013		0.0050	
Time to pain progression[g]				
Number of events/total number of patients (%)	21/162 (13)	14/83 (17)	32/256 (13)	16/131 (12)
Median (95% CI) [months]	NR (NR, NR)	9.9 (5.4, NR)	NR (NR, NR)	NR (NR, NR)
HR (95% CI)	0.44 (0.22, 0.91)		0.64 (0.35, 1.21)	
P-value (2-sided)	0.0192		0.1490	
Time to opiate use for cancer-related pain[f]				
Number of events/total number of patients (%)	42/113 (37)	29/58 (50)	65/175 (37)	44/92 (48)
Median (95% CI) [months]	18.0 (12.7, NR)	7.5 (3.2, NR)	18.0 (11.6, NR)	9.0 (5.4, NR)
Opiate-free use at 6 months (%)	75.6	56.7	74.8	61.0
Opiate-free use at 12 months (%)	61.5	45.6	58.8	47.7
HR (95% CI)	0.61 (0.38, 0.99)		0.67 (0.46, 0.99)	
P-value (2-sided) [nominal]	0.0443		0.0229	
PSA_{50} response[f]				
Number of patients with	69	9	78	17

single visit response (n)				
Single visit response (%) [95% CI]	42.6 (34.87, 50.59)	10.8 (5.08, 19.59)	30.5 (24.89, 36.51)	13.0 (7.74, 19.96)
Number of patients with confirmed response (n)	66	6	73	12
Confirmed response (%) [95% CI]	40.7 (33.10, 48.73)	7.2 (2.70, 15.07)	28.5 (23.07, 34.47)	9.2 (4.82, 15.45)
CTC conversion rate[f,h]				
Number of patients with CTC conversion (n)	29	5	41	7
CTC conversion (%) [95% CI]	17.9 (12.33, 24.69)	6.0 (1.98, 13.50)	16.0 (11.74, 21.09)	5.3 (2.18, 10.70)

[a] rPFS (Cohort A), rPFS (Cohort A+B), ORR (Cohort A), TTPP (Cohort A) and OS (Cohort A) were tested for multiplicity. The multiplicity strategy for primary endpoint and key secondary endpoints was that upon achieving statistical significance on the primary endpoint rPFS in Cohort A, testing of each of the secondary endpoints, ORR (Cohort A), rPFS (Cohort A + B), TTPP (Cohort A) and OS (Cohort A) were performed sequentially.

[b] Cohort A - the sensitivity analysis of rPFS by investigator assessment (HR=0.24, 95% CI 0.17, 0.34, p<0.0001 [nominal]; median rPFS 9.8 months vs 3.6 months for olaparib vs investigators choice of NHA, respectively) was consistent with the rPFS analysis by BICR assessment. Cohort A+B - the sensitivity analysis of rPFS by investigator assessment (HR=0.36, 95% CI 0.27, 0.47, p<0.0001 [nominal]; median rPFS 7.5 months vs 3.5 months for olaparib vs investigators choice of NHA, respectively) was consistent with the rPFS analysis by BICR.

[c] rPFS 71% maturity (Cohort A), 72% maturity (Cohort A+B)

[d] The HR and CI were calculated using a Cox proportional hazards model adjusted for prior taxane use and measurable disease. The Efron approach was used for handling ties. HR <1 favours olaparib

[e] The analysis was performed using the log-rank test stratified by prior taxane use and measurable disease using the Breslow method for handling ties

[f] Not controlled for multiplicity

[g] Time to pain progression was defined as the time from randomisation to the first date of a clinically meaningful worsening (≥2 points increase from baseline on a scale of 0-10) in average BPI-SF worst pain [Item 3] score and/or an increase in or initiation of opioid analgesic use.

[h] Circulating tumour cell conversion was defined as the proportion of patients achieving a decline in the number of CTCs from ≥5 cells/7.5 mL at baseline to <5 cells/7.5 mL at any visit post baseline

bd Twice daily; BICR Blinded independent central review; CI Confidence interval; CTC Circulating tumour cells; DoR Duration of response; HR Hazard ratio; NHA New hormonal agent; ORR Objective response rate; OS Overall survival; PFS2 Time from randomisation to second progression or death; PSA Prostate specific antigen; rPFS Radiological progression-free survival; SSRE Symptomatic skeletal-related event; TTPP Time to pain progression.

Figure 8 Cohort A: Kaplan-Meier plot of rPFS (by BICR)

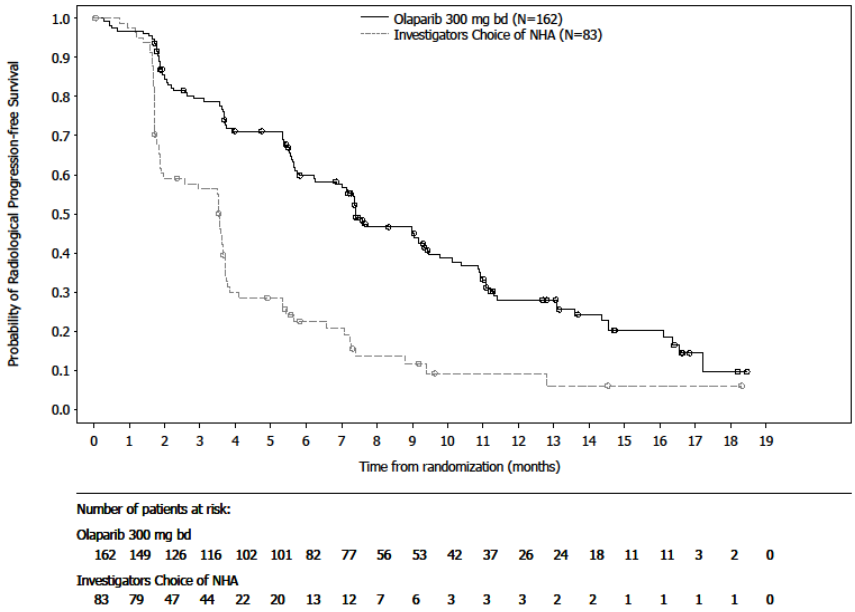


Figure 9 Cohort A+B: Kaplan-Meier plot of rPFS (by BICR)

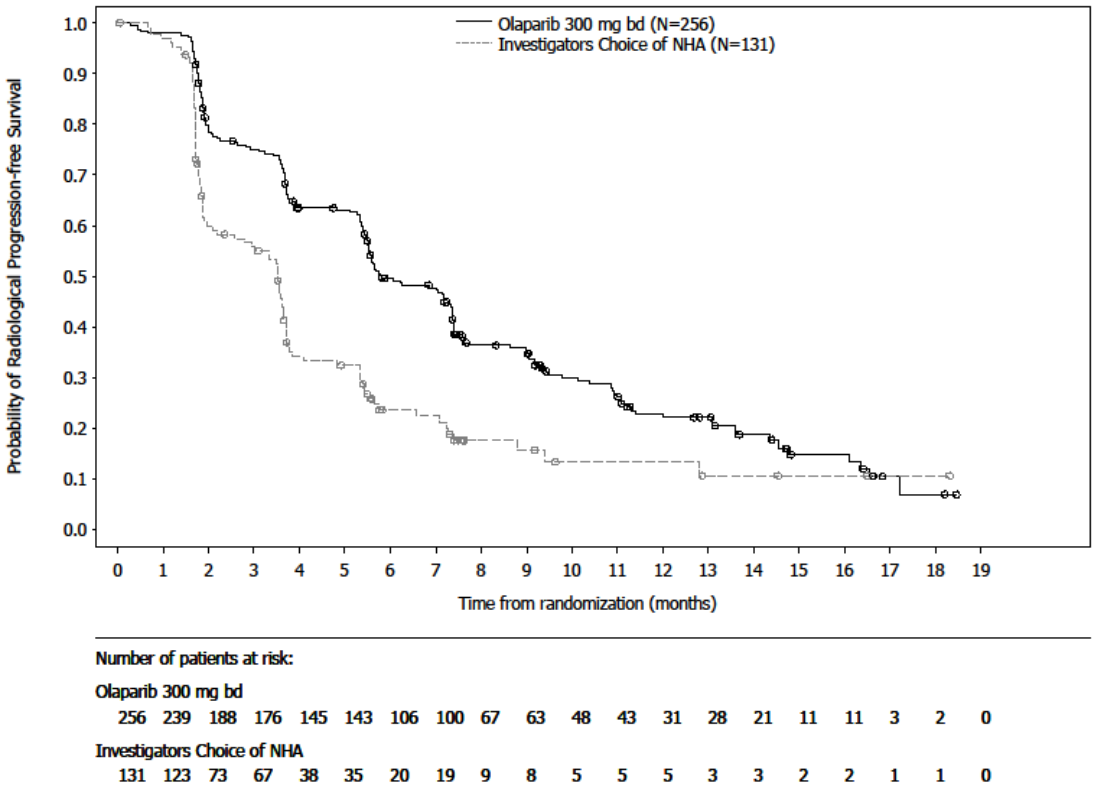
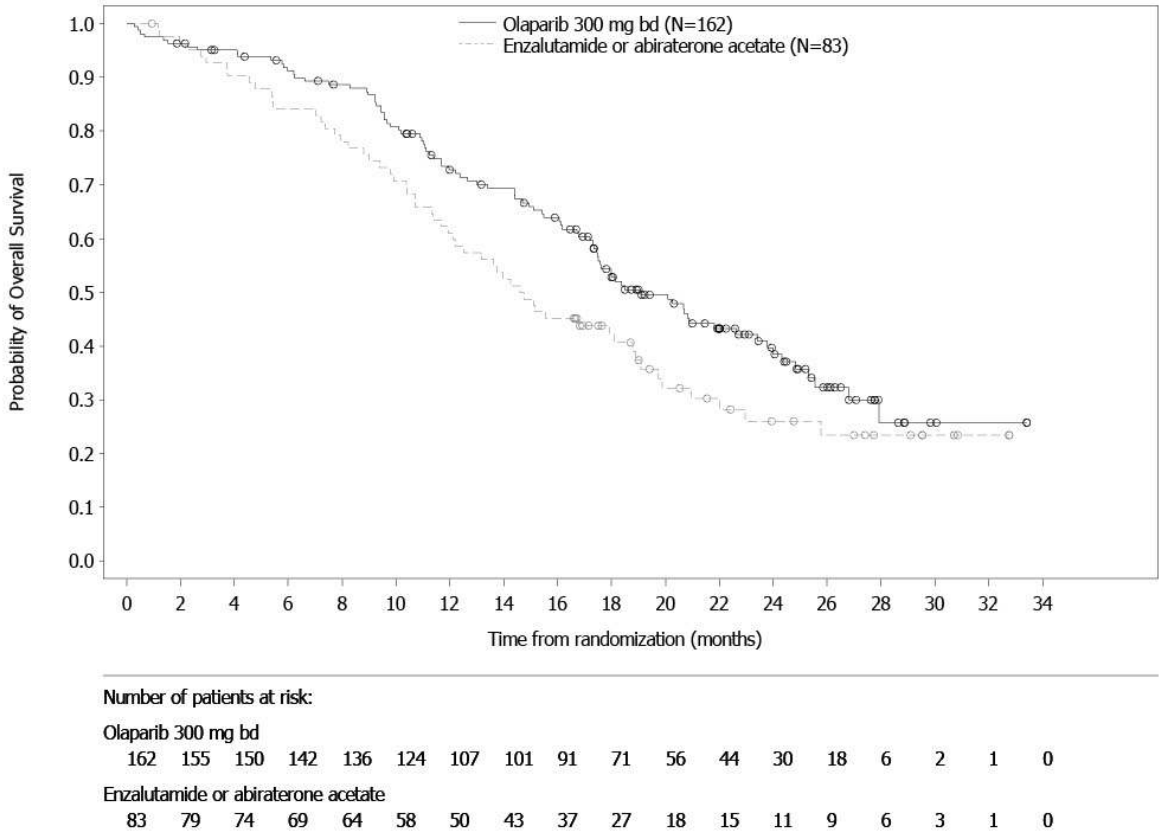


Figure 10 Cohort A: Kaplan-Meier plot OS



In Cohort A and Cohort A+B the benefit of olaparib over investigators choice of NHA was maintained across

all pre-defined subgroups, with clinically meaningful reductions in the risk of progression or death in olaparib-treated patients (ranging from 39 % to 75 % in Cohort A and from 23 % to 88 % in Cohort A+B).

In Cohort B, the median rPFS was 4,8 months for olaparib vs 3,3 months for comparator with a HR of 0,88 (95 % CI 0,58, 1,36; p=0,3976 [nominal]). Two patients (3,7 %) in the olaparib arm and 2 patients (8,3 %) in the comparator arm with measurable disease at baseline had a confirmed radiological objective response. The odds ratio (OR) and 95 % CIs were not calculated due to the small number of responders. In the olaparib arm, the 2 patients had *CDK12* mutations and achieved a partial response. In the comparator arm, the 2 patients had co-occurring mutations (one with *PALB2*+*PPP2R2A* and one with *CDK12*+*PALB2*) and achieved a partial response. Stable disease was observed in 57,4 % of patients in the olaparib arm and 29,2 % of patients in the comparator arm. The final OS analysis had events in 100/142 patients. Median OS was 14,1 months for olaparib vs 11,5 months for comparator with a HR of 0,96 (95 % CI 0,63, 1,49; p=0,7921, nominal). The HR indicates no detriment in OS for olaparib-treated patients.

With regards to the rPFS subgroup analysis by Cohort B gene, there was a trend for benefit of olaparib over comparator for patients with a single *CDK12* mutation. For *CHEK2* and *RAD54L*, results should be interpreted with caution due to the small number of events. Hazard ratios were not calculable for some of the Cohort B genes (*BARD1*, *BRIP1*, *CHEK1*, *PALB2*, *RAD51B*, and *RAD51D*) due to the small number of events in these subgroups. In Cohort B a subgroup analysis of confirmed ORR for each individual gene in patients with single HRR gene mutations only, 2/34 *CDK12*m patients (5,9 %) in the olaparib arm and no patients in the comparator arm (N=12) had a response The OR and 95 % CIs were not calculable.

Table 11 Summary of rPFS in PROfound for Cohort B genes

		Number of events/total number of patients (%)			**Median (95 % CI) [months]**	
	Patients n=142	**Olaparib 300 mg bd n=94**	**Investigator's choice of NHA n=48**	**HR (95 % CI)**	**Olaparib 300 mg bd**	**Investigator's choice of NHA**
rPFS (BICR)						
Overall Cohort B		74/94 (78,7)	31/48 (64,6)	0,88 (0,58; 1,36)	4,8 (3,7; 5,5)	3,3 (1,9; 5,4)

CDK12	89	47/61 (77,0)	18/28 (64,3)	0,74 (0,44; 1,31)	5,1 (3,6; 5,5)	2,2 (1,7; 4,8)
PALB2	4	1/3 (33,3)	0/1 (0)	NC (NC, NC)	NC (NC, NC)	NC (NC, NC)
RAD51B	5	3/4 (75,0)	1/1 (100)	NC (NC, NC)	10,9 (1,6; 14,8)	1,77 (NC, NC)
RAD51D	1	1/1 (100)	0/0	NC (NC, NC)	1,9 (NC, NC)	NC (NC, NC)
CHEK1	2	1/1 (100)	1/1 (100)	NC (NC, NC)	1,8 (NC, NC)	3,7 (NC, NC)
CHEK2	12	6/7 (85,7)	3/5 (60,0)	0,87 (0,23; 4,13)	5,6 (1,6; 12,0)	3,4 (1,4; NC)
RAD54L	5	3/3 (100)	2/2 (100)	0,33 (0,05; 2,54)	7,2 (3,7; 7,4)	2,4 (1,8; 3,0)
PPP2R2A	10	5/6 (83,3)	2/4 (50,0)	6,61 (1,41; 46,41)	2,7 (1,8; 3,9)	NC (NC, NC)
BRIP1	3	2/2 (100)	1/1 (100)	NC (NC, NC)	3,6 (1,7; 5,4)	1,7 (NC, NC)
BARD1	1	0/0	1/1 (100)	NC (NC, NC)	NC (NC, NC)	5,8 (NC, NC)

Seven patients in Cohort B had a co-occurring mutation. Gene by gene analysis is presented for single mutations only. No patients in Cohort B had *FANCL* or *RAD51C* mutations. LYNPARZA is not indicated for patients with *PPP2R2A* mutation.

Sensitivity analysis of rPFS by investigator assessment (HR=0,60; 95 % CI 0,39; 0,93; p=0,0178 [nominal]; median rPFS 5,6 months vs 3,4 months for olaparib vs investigators choice of NHA.

bd Twice daily; BICR Blinded independent central review; CI Confidence interval; HR Hazard ratio; NC Not calculable; NHA New hormonal agent; rPFS Radiological progression-free survival.

Olaparib improved overall adjusted mean change (based in mixed model of repeated measures analysis) from baseline scores in HRQoL (FACT-P total score, FACT-General total score, Trial Outcome Index), functioning (physical well-being, functional well-being) and prostate cancer symptoms (PCS, FACT Advanced Prostate Symptom Index-6) compared with investigators choice of NHA during treatment demonstrating that patients in the olaparib arm experienced improvement in HRQoL, functioning and prostate cancer symptoms compared with patients in the investigators choice of NHA arm in Cohort A. The analysis of adjusted mean change from baseline in HRQoL, functioning and prostate cancer symptoms scores in Cohort A were consistent with results in Cohort A+B.

Effect on the QT interval

There is no clinically relevant effect of olaparib on cardiac repolarisation (as evaluated by an effect on the QT

interval) following 300 mg twice daily multiple dosing of olaparib.

5.2 Pharmacokinetic properties

The pharmacokinetics of olaparib at the 300 mg tablet dose are characterised by an apparent plasma clearance of ~7 L/h, an apparent volume of distribution of ~158 L and a terminal half-life of 15 hours. On multiple dosing, an AUC accumulation ratio of 1.8 was observed and PK appeared to be time-dependent to a small extent.

Absorption

Following oral administration of olaparib via the tablet formulation (2 x 150 mg), absorption is rapid with median peak plasma concentrations typically achieved 1.5 hours after dosing.

Co-administration with food slowed the rate (tmax delayed by 2.5 hours and Cmax reduced by approximately 21 %) but did not significantly affect the extent of absorption of olaparib (AUC treatment ratio: 1.08; 90 % CI: 1.01, 1.16). Consequently, patients should take LYNPARZA without regard to food (see section 4.2).

Distribution

The in vitro plasma protein binding is approximately 82 % at 10 µg/mL which is approximately Cmax. *In vitro*, human plasma protein binding of olaparib was dose-dependent; the fraction bound was approximately 91 % at 1 µg/mL, reducing to 82 % at 10 µg/mL and to 70 % at 40 µg/mL. In solutions of purified proteins, the olaparib fraction bound to albumin was approximately 56 %, which was independent of olaparib concentrations. Using the same assay, the fraction bound to alpha-1 acid glycoprotein was 29 % at 10 µg/mL with a trend of decreased binding at higher concentrations.

Biotransformation

In vitro, CYP3A4/5 were shown to be the enzymes primarily responsible for the metabolism of olaparib. Following oral dosing of 14C-olaparib to female patients, unchanged olaparib accounted for the majority of the circulating radioactivity in plasma (70 %) and was the major component found in both urine and faeces (15 % and 6 % of the dose respectively). The metabolism of olaparib is extensive with the main site of metabolism being the piperazine and fluorobenzyl ring structures. The majority of the metabolism was attributable to oxidation reactions with a number of the components produced undergoing subsequent glucuronide or sulphate conjugation. Up to 20, 37 and 20 metabolites were detected in plasma, urine and

faeces respectively, the majority of them representing <1 % of the dosed material. A ring-open piperazin-3-ol moiety, and two mono-oxygenated metabolites (each~10 %) were the major circulating components, with one of the mono-oxygenated metabolites also being the major metabolite in the excreta (6 % and 5 % of the urinary and faecal radioactivity respectively).

In vitro, olaparib produced little/no inhibition of UGT1A4, UGT1A9, UGT2B7, or CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and is not expected to be a clinically significant time dependent inhibitor of any of these CYP enzymes. Olaparib inhibited UGT1A1 *in vitro*, however, PBPK simulations suggest this is not of clinical importance.

Based on evaluation using enzyme activity, olaparib was not an inducer of CYP2C9 or 2C19. *In vitro*, olaparib is a substrate of and inhibits the efflux transporter P-gp (IC50 = 76µM), however, this is unlikely to be of clinical significance.

In vitro, data also show that olaparib is not a substrate for OATP1B1, OATP1B3, OCT1, BCRP or MRP2, is a weak inhibitor of BCRP and not an inhibitor of OATP1B3, OAT1 or MRP2.

Elimination

Following a single dose of 14C-olaparib, ~86% of the dosed radioactivity was recovered within a 7-day collection period, ~44 % via the urine and ~42 % via the faeces. The majority of the material was excreted as metabolites.

Special populations

In population based PK analyses, patient age, gender, bodyweight, tumour location or race (including White and Japanese patients) were not significant covariates.

Renal impairment

Following a single oral 300 mg dose of olaparib to patients with mild renal impairment (creatinine clearance: 51 to 80 mL/min), AUC increased by 24 % and C_{max} by 15 % compared with patients with normal renal function. No LYNPARZA dose adjustment is required for patients with mild renal impairment.

Following a single oral 300 mg dose of olaparib to patients with moderate renal impairment (creatinine

clearance: 31 to 50 mL/min), AUC increased by 44 % and C_{max} by 26 % compared with patients with normal renal function. LYNPARZA dose adjustment is recommended for patients with moderate renal impairment (see section 4.2).

Olaparib has not been studied in patients with severe renal impairment or end-stage renal disease (creatinine clearance ≤30 ml/min).

Hepatic impairment

In patients with mild hepatic impairment (Child-Pugh classification A), AUC increased by 15 % and C_{max} by 13 % and in patients with moderate hepatic impairment (Child-Pugh classification B), AUC increased by 8 % and C_{max} decreased by 13 % compared with patients with normal hepatic function. No LYNPARZA dose adjustment is required for patients with mild or moderate hepatic impairment (see section 4.2). There are no data in patients with severe hepatic impairment (Child-Pugh classification C).

5.3 Preclinical safety data

Mutagenicity

Olaparib showed no mutagenic potential, but was clastogenic in mammalian cells *in vitro*. When dosed orally to rats, olaparib induced micronuclei in bone marrow. This clastogenicity is consistent with the primary pharmacology of olaparib and indicates potential for genotoxicity in man.

Repeat-dose toxicity

In repeat-dose toxicity studies of up to 6 months duration in rats and dogs, daily oral doses of olaparib were well-tolerated. The major primary target organ for toxicity in both species was the bone marrow, with associated changes in peripheral haematology parameters. These findings occurred at exposures below those seen clinically and were largely reversible within 4 weeks of cessation of dosing. Studies using human bone marrow cells also showed that direct exposure to olaparib can result in toxicity to bone marrow cells in ex vivo assays.

Reproductive toxicology

Olaparib had no effect on fertility in male rats. In a female fertility study in rats, extended oestrus was observed in some animals although mating performance and fertility was not)affected. Embryofoetal survival was reduced in this study.

In rat embryofoetal development studies, olaparib caused reduced embryofoetal survival, reduced foetal weight and foetal developmental abnormalities (including visceral and skeletal abnormalities, and major eye and vertebral/rib malformations) at dose levels that did not induce significant maternal toxicity.

Carcinogenicity

Carcinogenicity studies have not been conducted with Olaparib.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Copovidone

Colloidal silicon dioxide

Mannitol

Sodium stearyl fumarate

Tablet coating:

Hypromellose

Macrogol 400

Titanium dioxide (E171)

Iron oxide yellow (E172)

Iron oxide black (E172) (LYNPARZA 150 mg tablet only)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 years

6.4 Special precautions for storage

Store at or below 30 °C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Aluminium/Aluminium non-perforated blister containing 8 tablets.

Cartons of 56 tablets (7 blisters) and a multipack containing 112 (2 cartons of 56) tablets.

HDPE bottle containing desiccant with a child-resistant closure. Pack sizes of 60 or 120 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets)

7 HOLDER OF CERTIFICATE OF REGISTRATION

AstraZeneca Pharmaceuticals (Pty) Ltd

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South Africa

8 REGISTRATION NUMBERS

LYNPARZA 100: 52/26/0745

LYNPARZA 150: 52/26/0746

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10 DATE OF REVISION OF THE TEXT

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