LYNPARZA®
(olaparib)

1. NAME OF THE MEDICINAL PRODUCT

Lynparza (olaparib), 150 mg, film-coated tablets

Lynparza (olaparib), 100 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

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.

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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ovarian cancer

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

chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a *BRCA*1/2 mutation and/or genomic instability (see section 5.1).

Breast cancer

Lynparza is indicated:
- for the adjuvant treatment of adult patients with germline *BRCA*-mutated HER2-negative high risk early breast cancer who have previously been treated with neoadjuvant or adjuvant chemotherapy (see sections 4.2 and 5.1).
- 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 deleterious or suspected deleterious germline *BRCA*-mutated (g*BRCA*m) metastatic adenocarcinoma of the pancreas whose disease has not progressed on a minimum of 16 weeks of first-line platinum-based chemotherapy. Germline *BRCA* mutation must be confirmed before LYNPARZA treatment is initiated.

Prostate cancer

Lynparza is indicated as monotherapy for the:
- treatment of adult patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene *BRCA1/2* and/or ataxia telangiectasia (*ATM*)-mutations (germline and/or somatic) who have progressed following a prior new hormonal agent.

Lynparza in combination with abiraterone and prednisone or prednisolone is indicated for the:
- treatment of adult patients with metastatic castration-resistant prostate cancer in whom chemotherapy is not clinically indicated (see Section 5.1).

4.2 Posology and method of administration

Treatment with Lynparza should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Detection of *BRCA, ATM* gene mutations and/or genomic instability: Gene mutation and/or genomic instability status should be determined by an experienced laboratory using a validated test method.

Monotherapy maintenance treatment of newly diagnosed 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.

First-line maintenance treatment of HRD positive advanced ovarian cancer in combination with bevacizumab: Patients must have confirmation of either deleterious or

suspected deleterious *BRCA1/2* mutation and/or genomic instability before Lynparza treatment is initiated.

Adjuvant treatment of germline *BRCA*-mutated HER2-negative high risk early breast cancer: Patients must have confirmation of a *BRCA* mutation (identified by germline 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 treatment of patients with g*BRCA*m metastatic adenocarcinoma of the pancreas who are in response to first-line platinum-based chemotherapy: Patients must have confirmation of a deleterious or suspected deleterious *BRCA* mutation (identified by germline testing) before LYNPARZA treatment is initiated.

Monotherapy treatment of HRR-gene *BRCA1/2* and/or *ATM*-mutated metastatic castration-resistant prostate cancer (mCRPC): Patients must have confirmation of *BRCA1/2* and/or *ATM* 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. *BRCA1/2* and/or *ATM* genetic status should be determined by an experienced laboratory using a validated test method.

Dosage in adults

Lynparza is available as 100 mg and 150 mg tablets.

The recommended dose of Lynparza as monotherapy and in combination with bevacizumab for ovarian cancer or in combination with abiraterone and prednisone or prednisolone for prostate cancer 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 newly diagnosed advanced *BRCA*-mutated ovarian cancer: patients can continue treatment for 2 years or until 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 physician 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.

First-line maintenance treatment of HRD positive advanced ovarian cancer in combination with bevacizumab: patients can continue treatment for 2 years or until 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 physician 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).

Adjuvant treatment of germline *BRCA*-mutated HER2-negative high risk early breast cancer: it is recommended that patients are treated for a total of 1 year, or until disease recurrence, or unacceptable toxicity, whichever occurs first. Patients with hormone receptor-positive breast cancer should continue concurrent treatment with endocrine therapy as per local guidelines.

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

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

Monotherapy treatment of HRR-gene *BRCA1/2* and/or *ATM*-mutated metastatic castration-resistant prostate cancer: it is recommended that treatment be continued until progression of the underlying disease.

Treatment of metastatic castration-resistant prostate cancer in combination with abiraterone and prednisone or prednisolone: it is recommended that treatment be continued until progression of the underlying disease or unacceptable toxicity. When Lynparza is used in combination with abiraterone, refer to the Prescribing Information for abiraterone for recommended dosing information (see section 5.1).

Lynparza is also available as a 50 mg capsule. Refer to the capsules label for specific dosing information. Lynparza capsules (50 mg) should not be substituted for Lynparza tablets (100 mg and 150 mg) on a milligram-to-milligram basis due to differences in the dosing and bioavailability of each formulation.

Missing dose

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

Dose adjustments

For adverse events

Treatment may be interrupted to manage adverse events and dose reduction can be considered.

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.

Concomitant use of strong or moderate CYP3A inhibitors is not recommended and alternative agents 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

None.

4.4 Special warnings and special precautions for use

Haematological toxicity

Haematological toxicity has been reported in patients treated with Lynparza, including clinical diagnoses and/or laboratory findings of generally mild or moderate (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

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 agents. 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.

Venous Thromboembolic Events

Venous thromboembolic events, including pulmonary embolism, have occurred in patients treated with Lynparza and had no consistent clinical pattern. A higher incidence was observed in patients with metastatic castration-resistant prostate cancer, who also received androgen deprivation therapy, compared with other approved indications (see section 4.8). Monitor patients for clinical signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate.

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 olaparib 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 this drug, the patient should be apprised of the potential hazard to a foetus. Women of childbearing potential should be advised that they must use effective contraception during Lynparza treatment and for one month after receiving the last dose of Lynparza. 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).

Breast-feeding

The excretion of olaparib in milk has not been studied in animals or in breast-feeding mothers. Breast-feeding mothers are advised not to breast-feed during treatment with Lynparza and for one month after receiving the last dose of Lynparza (see section 4.6).

Interactions with other medicinal products

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 medicinal products and other forms of interaction

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

Effect of other drugs on olaparib

Strong and moderate CYP3A inhibitors

CYP3A4/5 are the isozymes predominantly responsible for the metabolic clearance of olaparib. Co-administration of olaparib with a strong CYP3A inhibitor (itraconazole) increased olaparib 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 olaparib 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).

Avoid grapefruit, grapefruit juice, Seville oranges, and Seville orange juice during Lynparza treatment since they are CYP3A inhibitors.

Strong and moderate CYP3A inducers

Co-administration of olaparib with a strong CYP3A inducer (rifampicin) decreased olaparib 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, phenobarbital 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 olaparib 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 olaparib on other drugs

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 olaparib *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, cyclosporine, 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

Olaparib 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 Pregnancy and lactation

Olaparib should not be used during pregnancy due to the teratogenic and genotoxic potential of olaparib. 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).

Contraception and pregnancy testing

Women of childbearing potential must use effective contraception during therapy and for one month 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 one month after receiving the last dose.

It is not known whether olaparib 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.

Breast-feeding

There are no data on the use of Lynparza in breast-feeding women. The excretion of olaparib in milk has not been studied in animals or in breast-feeding mothers. A risk to the newborn breast-feeding child cannot be excluded. Breast-feeding mothers are advised not to breast-feed during treatment with Lynparza and for one month after receiving the last dose (see section 4.4).

4.7 Effects on ability to drive and use machines

No studies to establish the effects of olaparib on the ability to drive and use machinery have been conducted. However, 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

Overall summary of adverse drug reactions

Lynparza has been associated with laboratory findings and/or clinical diagnoses generally of mild or moderate severity (CTCAE grade 1 or 2) and generally not requiring treatment discontinuation.

Tabulated list of adverse drug reactions from clinical trials

The safety profile is based on pooled data from 4098 patients with solid tumours treated with Lynparza monotherapy, 535 patients treated with Lynparza in combination with bevacizumab and 469 patients treated with Lynparza in combination with abiraterone and prednisone or prednisolone in clinical trials at the recommended dose.

When Lynparza is used in combination with bevacizumab for ovarian cancer or in combination with abiraterone and prednisone or prednisolone for prostate cancer, 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 <1/1000); 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/ Overall Frequency (All CTCAE grades)	Frequency of 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]	Common	Common
	Lymphopenia[a]	Common	Common
Immune system disorders	Hypersensitivity[a]	Uncommon	Rare
	Angioedema*	Rare	-
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

MedDRA SOC	MedDRA Term	CIOMS descriptor/ Overall Frequency (All CTCAE grades)	Frequency of CTCAE grade 3 and above
	Dyspnoea[a]	Very common	Common
Gastrointestinal disorders	Vomiting	Very common	Common
	Diarrhoea	Very common	Uncommon
	Nausea	Very common	Common
	Dyspepsia	Very common	Rare
	Stomatitis[a]	Common	Uncommon
	Upper abdominal pain	Common	Rare
Skin and subcutaneous tissue disorders	Rash[a]	Common	Uncommon
	Dermatitis[a]	Uncommon	Rare
	Erythema nodosum	Rare	-
General disorders	Fatigue (including asthenia)	Very common	Common
Investigations	Blood creatinine increased	Common	Rare
	Mean cell volume increased	Uncommon	-
Vascular disorders	Venous Thromboembolism[a]	Common	Common

[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.
Venous thromboembolism includes PTs of embolism, pulmonary embolism, thrombosis, deep vein thrombosis, vena cava thrombosis and venous thrombosis.

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

Haematological toxicity

Anaemia and other haematological toxicities are generally low grade (CTCAE grade 1 or 2), however, there are reports of CTCAE grade 3 and higher events. 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 olaparib 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 21%, absolute neutrophils 17%, platelets 5%, lymphocytes 26% and leucocytes 19% (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 51%. 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, with no apparent clinical sequelae. 90% of patients had creatinine values of CTCAE grade 0 at baseline and 10% were CTCAE grade 1 at baseline.

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.

4.9 Overdose

Symptoms of overdose are not established and there is no specific treatment in the event of Lynparza overdose. In the event of an overdose, physicians should follow general supportive measures and should treat the patient symptomatically.

5.   PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 or new hormonal agents (NHA).

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 non-homologous end joining (NHEJ) pathway, leading to increased genomic instability. After a number of rounds of replication, genomic instability can reach insupportable levels and result in cancer cell death, as cancer cells already have a high DNA damage load relative to normal cells. In the absence of 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 *BRCA*-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.

Pre-clinical studies in prostate cancer models reported a combined anti-tumour effect when PARP inhibitors and next-generation hormonal agents are administered together. PARP is involved in positive co-regulation of androgen receptor (AR) signalling, which leads to enhanced AR target gene suppression when PARP/AR signalling is co-inhibited. Other pre-clinical studies reported that treatment with NHAs inhibit the transcription of some HRR genes, therefore, inducing HRR deficiency and increased sensitivity to PARP inhibitors via non-genetic mechanisms.

Clinical data:

<u>Maintenance treatment of newly diagnosed advanced ovarian cancer</u>

SOLO1 Study in newly diagnosed advanced patients with a BRCA mutation

SOLO1 was a Phase III randomised, double-blind, placebo-controlled, multicentre trial that compared the efficacy of Lynparza maintenance treatment (300 mg [2 x 150 mg tablets] twice daily) with placebo in advanced (FIGO Stage III-IV) high-grade serous or endometrioid *BRCA*-mutated (*BRCAm*) ovarian cancer. The study randomised 391 patients (2:1 randomisation: 260 olaparib and 131 placebo) who were in response (CR [complete response] or PR [partial response]) following completion of first-line platinum-containing chemotherapy. Patients were stratified by response to first-line platinum chemotherapy (CR or PR). Treatment was continued for 2 years or until progression of the underlying disease. 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 *BRCA* mutations were identified either from germline testing in blood via a local test or central test (i.e. Myriad Integrated BRAC*Analysis*® test, Myriad BRACAnalysis CDx®, China BGI test) or from testing a tumour sample using a local test. 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 CDx™ 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).

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	

|	Olaparib 300 mg bd	Placebo
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 including response 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)
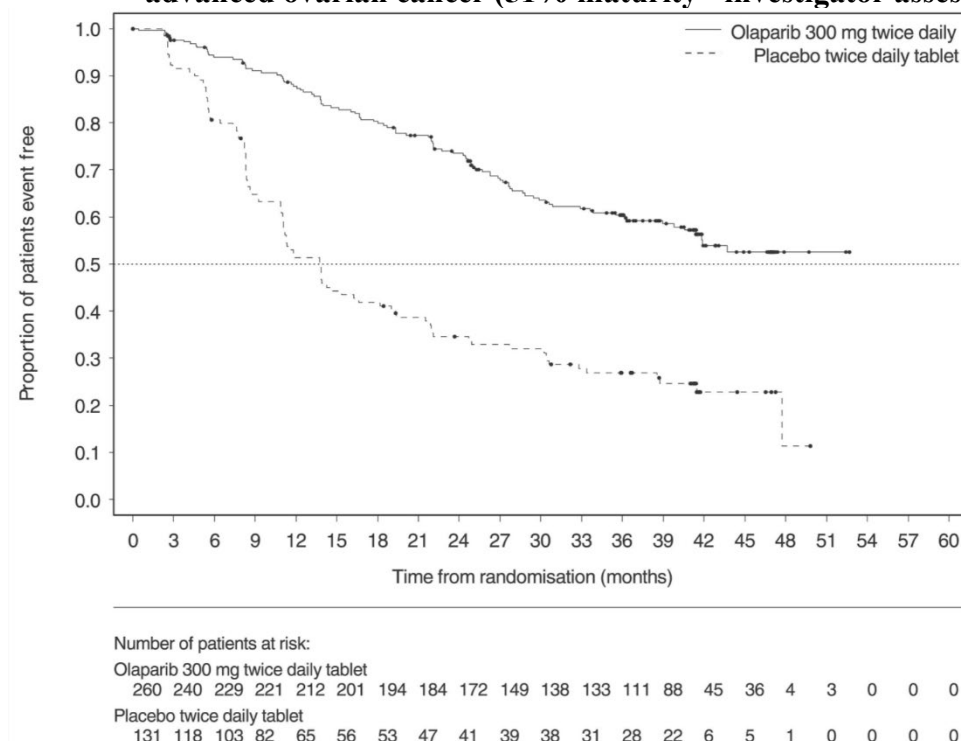
There was no decrease in HRQoL from baseline for olaparib-treated patients over the 24-month treatment period and no clinically relevant differences in HRQoL compared with placebo-treated patients as assessed by the change from baseline in the Trial Outcome Index (TOI) of the Functional Assessment of 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 PSR patients with a BRCA mutation

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.

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 (%)	139:196 (71)	86:99 (87)
Median time (months)	27.4	7.2
HR (95% CI)[a]	0.37 (0.28-0.48)	
P value* (2-sided)	p<0.0001	
TDT		
Number of events: Total number of patients (%)	152:196 (78)	91:99 (92)
Median time (months)	19.4	5.6
HR (95% CI)[a]	0.37 (0.28-0.49)	
P value* (2-sided)	p<0.0001	
TSST		
Number of events: Total number of patients (%)	130:196 (66)	79:99 (80)
Median time (months)	35.8	18.9
HR (95% CI)[a]	0.51 (0.39-0.68)	
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)

Number of patients at risk:

| 196 | 182 | 156 | 134 | 118 | 104 | 89 | 82 | 32 | 29 | 3 | 2 | 0 | Olaparib 300 mg bd |
| 99 | 70 | 37 | 22 | 18 | 17 | 14 | 12 | 7 | 6 | 0 | 0 | 0 | Placebo bd |
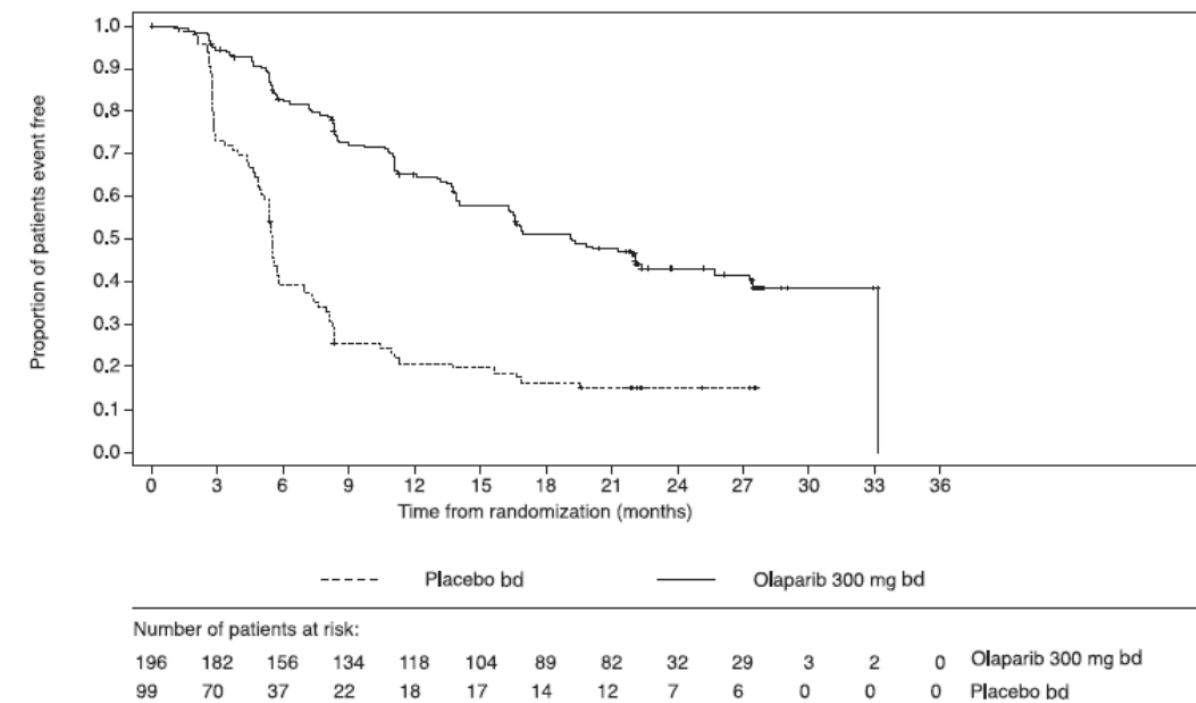
bd Twice daily; PFS Progression-free survival

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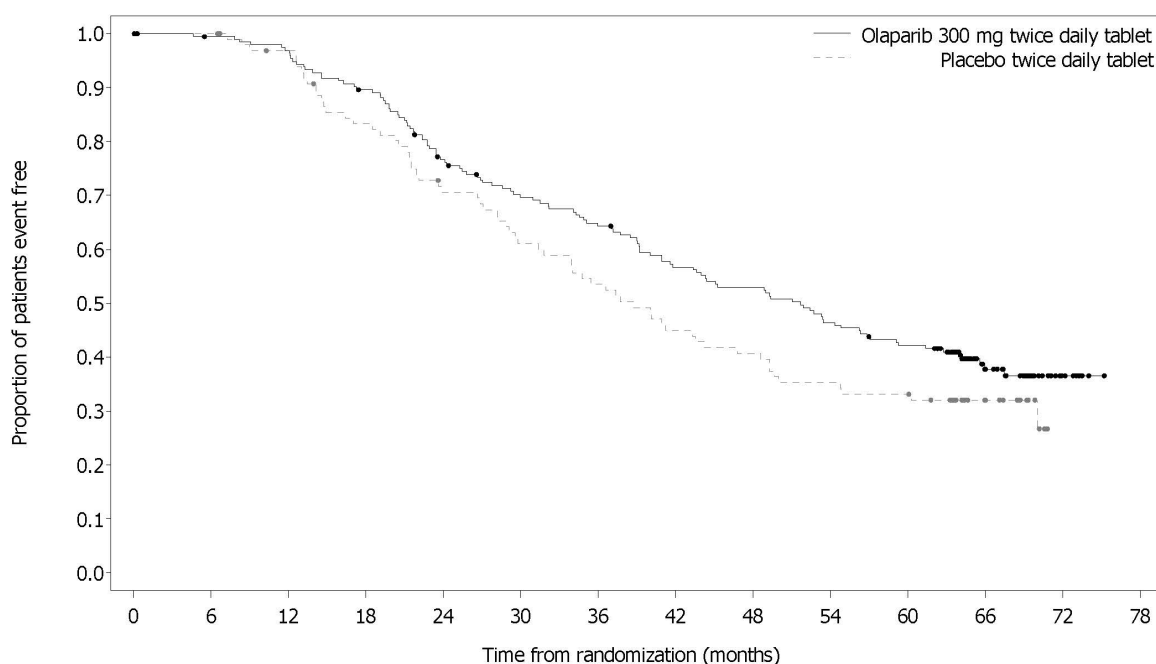
Number of patients at risk:

Olaparib 300 mg twice daily tablet													
196	192	187	172	145	130	120	105	98	86	77	39	7	0

Placebo twice daily tablet													
99	99	93	79	66	57	50	42	38	33	31	16	0	0

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, patients with *BRCAm* and patients with *BRCAwt/VUS* PSR ovarian cancer in Study 19 is presented in Table 4.

Table 4   Summary of key efficacy findings for all patients, patients with *BRCAm* and patients with *BRCAwt/VUS* PSR ovarian cancer in Study 19

	Full Analysis Set		*BRCAm*		*BRCAwt*/VUS	
	Olaparib 400 mg bd	Placebo	Olaparib 400 mg bd	Placebo	Olaparib 400 mg bd	Placebo
PFS – DCO 30 June 2010 – Full Analysis Set						
Number of events: total number of patients (%)	60:136 (44)	94:129 (73)	26:74 (35)	46:62 (74)	32:57 (56)	44:61 (72)
Median PFS (months)	8.4	4.8	11.2	4.3	7.4	5.5
HR (95% CI)[a]	0.35 (0.25-0.49)		0.18 (0.10-0.31)		0.54 (0.34-0.85)	
P-value[*] (2-sided)	p<0.00001		p<0.00001		p=0.00745	
OS (79% maturity) – 09 May 2016 – Full Analysis Set						
Number of events: total number of patients (%)	98:136 (72)	112:129 (87)	49:74 (66)	50:62 (81)[b]	45:57 (79)	57:61 (93)
Median time (months)	29.8	27.8	34.9	30.2	24.5	26.6
HR (95% CI)[a]	0.73 (0.55-0.95)		0.62 (0.42-0.93)		0.84 (0.57-1.25)	
Nominal P-value[*] (2-sided)	p=0.02138		p=0.02140		p=0.39749	
TFST – DCO 09 May 2016 – Safety Analysis Set						
Number of events: total number of patients (%)	106:136 (78)	124:128 (97)	55:74 (74)	59:62 (95)	47:57 (83)	60:61 (98)

	Full Analysis Set		BRCAm		BRCAwt/VUS	
	Olaparib 400 mg bd	Placebo	Olaparib 400 mg bd	Placebo	Olaparib 400 mg bd	Placebo
Median time (months)	13.3	6.7	15.6	6.2	12.9	6.9
HR (95% CI)[a]	0.39 (0.30-0.52)		0.33 (0.22-0.49)		0.45 (0.30-0.66)	
Nominal P-value* (2-sided)	p<0.00001		p<0.00001		p=0.00006	
TSST – DCO 09 May 2016 – Safety Analysis Set						
Number of events: total number of patients (%)	104:136 (77)	119:128 (93)	53:74 (72)	56:62 (90)	47:57 (83)	59:61 (97)
Median time (months)	19.1	14.8	21.4	15.3	17.0	14.7
HR (95% CI)[a]	0.53 (0.40-0.69)		0.43 (0.29-0.64)		0.63 (0.43-0.94)	
Nominal P-value* (2-sided)	p<0.00001		p=0.00003		p=0.02263	

* 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 Twice daily; BRCAm Breast cancer susceptibility gene mutated; CI Confidence interval; CSR Clinical study report; DCO Data cut-off; HR Hazard ratio; NC not calculable; OS Overall survival; PFS Progression-free survival; TFST Time to first subsequent therapy (or death); TSST Time to second subsequent therapy (or death); VUS Variant of uncertain significance; wt Wild type.

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 gBRCA 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.

Based on central retrospective germline blood testing, 90.7% of patients were confirmed with a non-g*BRCA*m status, 2.2% with g*BRCA*m status and 7.2% of patients had no confirmatory g*BRCA* result. Based on retrospective central blood and tumour testing, 9.7% of patients were identified as s*BRCA*m and 13.3% of patients had a HRD/*BRCA* status of unknown.

The primary endpoint was investigator-assessed PFS according to modified RECIST v1.1. Secondary endpoints included OS.

Olaparib when used as maintenance therapy, demonstrated clinical activity in patients with non-g*BRCA*m PSR ovarian cancer. 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 HRD positive advanced ovarian cancer

PAOLA-1 study in newly-diagnosed advanced ovarian cancer patients

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.

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 or until progression of the underlying disease. 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 the study and placebo arms in the Intention to Treat (ITT) population and also in the HRD-positive subgroup. The median age of patients was 61 years overall. Most patients in both arms were ECOG performance status 0 (70%). Ovarian cancer was the primary tumour in 86% of the patients. 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. In the HRD-positive subgroup, 65% of patients had complete cytoreduction and 35% of patients had 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)

	Olaparib/bevacizumab (n=537)	Placebo/bevacizumab (n=269)
NED/CR with complete macroscopic resection at interval debulking surgery	166 (31)	84 (31)
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 met its primary end-point in the ITT population demonstrating a statistically significant improvement in investigator assessed PFS for olaparib/bevacizumab compared to placebo/bevacizumab (HR 0.59, 95% CI 0.49-0.72, p<0.0001 with a median of 22.1 months for olaparib/bevacizumab vs 16.6 months for placebo/bevacizumab). Final analysis of PFS2 (DCO 22 March 2020, 53% maturity) in the overall population was statistically significant (HR 0.78, 95% CI 0.64-0.95, p=0.0125 with a median of 36.5 months for olaparib/ bevacizumab vs 32.6 months for placebo/bevacizumab).

Efficacy results from a biomarker subgroup analysis of 387 patients with HRD-positive tumours, identified post-randomization, who received olaparib/bevacizumab (n=255) or placebo/bevacizumab (n=132), are summarized in Table 7 and Figure 4. Results from a blinded independent review of PFS were consistent. Overall survival data in this subpopulation were immature with 27% deaths.

Table 7   Summary of key efficacy findings for patients with homologous recombination deficiency (HRD) positive status in advanced ovarian cancer patients in PAOLA-1

	Olaparib/ bevacizumab	Placebo/ bevacizumab

PFS, investigator assessment (46% maturity) DCO 22 March 2019[a]		
Number of events: Total number of patients (%)	87/255 (34)	92/132 (70)
Median time (months)	37.2	17.7
HR (95%) CI[b]	0.33 (0.25, 0.45)	
Final PFS2, investigator assessment (40% maturity) DCO 22 March 2020		
Number of events: Total number of patients (%)	85/255 (33)	70/132 (53)
Median time (months)	50.3	35.4
HR (95%) CI[b]	0.56 (0.41, 0.77)	
Interim OS (27% maturity) DCO 22 March 2020		
Number of events: Total number of patients (%)	61/255 (24)	42/132 (32)
Median time (months)	NR	NR
HR (95%) CI[b]	0.70 (0.47, 1.04)	

[a] Based on Kaplan-Meier estimates, the proportion of patients that were progression free at 12 and 24 months were 89% and 66% for olaparib/bevacizumab versus 71% and 29% for placebo/bevacizumab.
[b] A value <1 favours olaparib. The analysis was performed using a Cox proportional hazards model stratified by first line treatment outcome at screening and screening laboratory t*BRCA* status.
CI Confidence interval; HR Hazard ratio; NR not reached

Figure 4   Kaplan-Meier Curves of Investigator-Assessed Progression-Free Survival – PAOLA-1 (HRD-positive status)
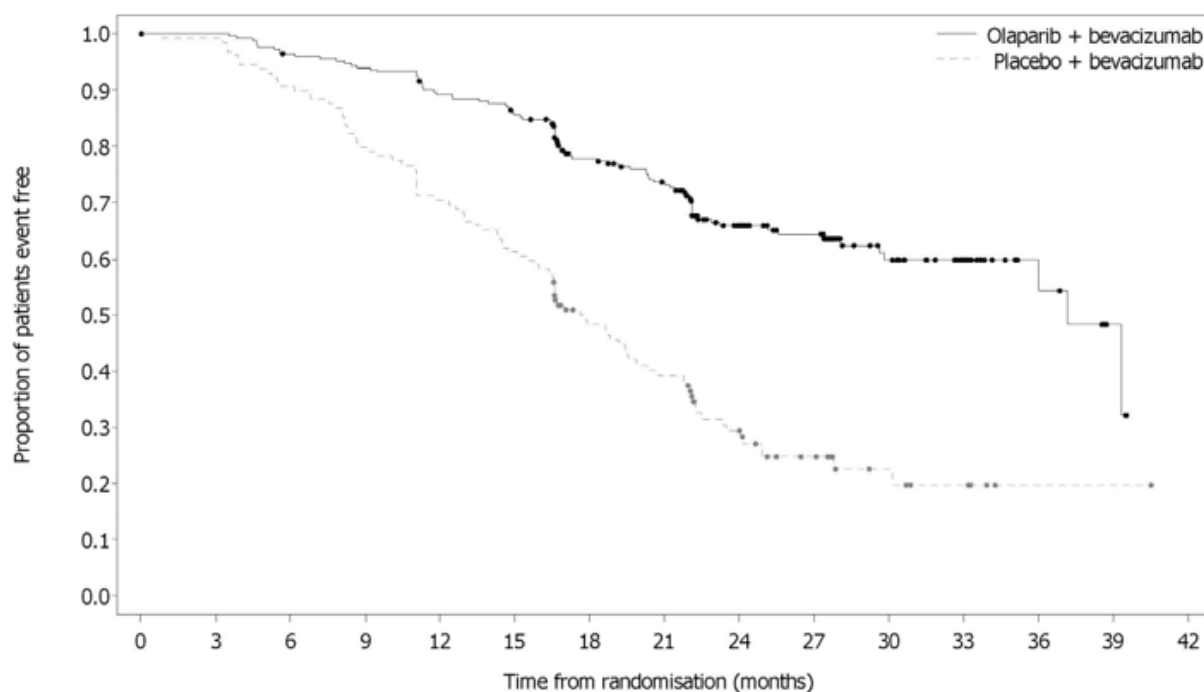
Number of patients at risk:

Olaparib + bevacizumab															
255	252	242	236	223	213	169	155	103	85	46	29	11	3	0
Placebo + bevacizumab															
132	128	117	103	91	79	54	44	28	18	8	5	1	1	0

Adjuvant treatment of germline BRCA-mutated HER2-negative high risk early breast cancer

OlympiA study in HER2-negative high risk early breast cancer patients with a germline BRCA mutation

OlympiA was a Phase III randomised, double-blind, parallel group, placebo-controlled, multicentre study to assess the efficacy and safety of olaparib (300 mg [2 x 150 mg tablets] twice daily) vs placebo as adjuvant treatment in patients with germline _BRCA1/2_ mutations and HER2-negative high risk early breast cancer who had completed definitive local treatment and neoadjuvant or adjuvant chemotherapy. Patients were required to have completed at least 6 cycles of neoadjuvant or adjuvant chemotherapy containing anthracyclines, taxanes or both. Prior platinum for previous cancer (e.g. ovarian) or as adjuvant or neoadjuvant treatment for breast cancer was allowed. High risk early breast cancer patients were defined as follows:

- patients who received prior neoadjuvant chemotherapy: patients with either triple negative breast cancer (TNBC) or hormone receptor positive breast cancer must have had residual invasive cancer in the breast and/or the resected lymph nodes (non-pathologic complete response) at the time of surgery. Additionally, patients with hormone receptor positive breast cancer must have had a score of ≥3 based on pre-treatment clinical and post-

treatment pathologic stage (CPS), estrogen receptor (ER) status and histologic grade as shown in Table 8.

Table 8   Early Breast Cancer Stage, Receptor Status and Grade Scoring Requirements for Study Enrolment*

Stage/feature		Points
Clinical Stage (pre-treatment)	I/IIA	0
	IIB/IIIA	1
	IIIB/IIIC	2
Pathologic Stage (post-treatment)	0/I	0
	IIA/IIB/IIIA/IIIB	1
	IIIC	2
Receptor status	ER positive	0
	ER negative	1
Nuclear grade	Nuclear grade 1-2	0
	Nuclear grade 3	1

* Total score of ≥3 required for patients with hormone receptor positive breast cancer.

- patients who have received prior adjuvant chemotherapy: triple negative breast cancer (TNBC) patients must have had node positive disease or node negative disease with a ≥2cm primary tumor; ER and/or PgR positive, HER2-negative patients must have had ≥4 pathologically confirmed positive lymph nodes.

Patients were randomised in a 1:1 ratio to either olaparib (n=921) or placebo (n=915). Randomisation was stratified by hormone receptor status (ER and/or PgR positive/ HER2 negative versus TNBC), by prior neoadjuvant versus adjuvant chemotherapy, and by prior platinum use for breast cancer (yes versus no). Treatment was continued for 1 year, or until disease recurrence, or unacceptable toxicity.

The primary endpoint was invasive disease free survival (IDFS), defined as the time from randomisation to date of first recurrence, where recurrence is defined as loco-regional, distant recurrence, contralateral invasive breast cancer, new cancer or death from any cause. Secondary objectives included OS, distant disease free survival [(DDFS, defined as the time from randomisation until evidence of first distant recurrence of breast cancer or death from any cause), the incidence of new primary contralateral breast cancers (invasive and non-invasive), new primary ovarian cancer, new primary fallopian tube cancer and new primary peritoneal cancer], and patient reported outcomes using the FACIT-Fatigue and EORTC QLQ-C30 questionnaires.

Central testing with Myriad BRACAnalysis® or local g*BRCA* testing, if available, was used to establish study eligibility. Patients enrolled based on local g*BRCA* test results provided a sample for retrospective confirmatory testing with BRACAnalysis® (excluding patients enrolled in China). Out of 1836 patients enrolled into OlympiA, 1539 were confirmed as g*BRCAm* by Myriad BRACAnalysis®, either prospectively or retrospectively.

Demographic and baseline characteristics were well balanced between the arms. The median age was 42 years. Sixty-seven percent (67%) of patients were White, 29% Asian and 2.6% Black. Two patients (0.2%) in the olaparib arm and four patients (0.4%) in the placebo arm were male. Sixty-one percent (61%) of patients were pre-menopausal. Eighty-nine percent (89%) of patients were ECOG performance status 0 and 11% ECOG PS 1. Eighty-two percent (82%) of patients had TNBC and 18% had hormone receptor-positive disease (defined as ER positive and/or PgR positive). Fifty percent (50%) of patients had received prior neoadjuvant and 50% received prior adjuvant chemotherapy. Ninety-four percent (94%) of patients received anthracycline and taxane. Twenty-six (26%) of patients overall had received prior platinum for breast cancer. In the olaparib and placebo arms, 87% and 92% of patients with HR positive disease were receiving concomitant endocrine therapy, respectively.

The study demonstrated a statistically significant improvement in IDFS in the olaparib arm compared with the placebo arm. Two hundred and eighty-four (284) patients had IDFS events, this represented 12% of patients in the olaparib arm (distant 8%, local/regional 1.4%, contralateral invasive breast cancer 0.9%, non-breast second primary malignancies 1.2%, death 0.2%) and 20% of patients in the placebo arm (distant 13%, local/regional 2.7%, contralateral invasive breast cancer 1.3%, non-breast second primary malignancies 2.3%, death 0%). A statistically significant improvement in DDFS in the olaparib arm compared with the placebo arm was also observed. At the next planned OS analysis, a statistically significant improvement in OS was observed in the olaparib arm compared with the placebo arm.

Efficacy results from the FAS are presented in Table 9 and for the subgroups by stratification factors in Table 10.

Table 9   Summary of key efficacy findings in HER2-negative high risk early breast cancer patients with a germline *BRCA* mutation in OlympiA

	Olaparib 300 mg bd (N=921)	Placebo (N=915)
IDFS (15% maturity) DCO 27 March 2020		
Number of events/total number of patients (%)	106/921 (12)	178/915 (20)
HR (99.5% CI) [a] p-value (2-sided) [b]	0.58 (0.41, 0.82) 0.0000073	
Percentage of patients invasive disease free at 3 years [c]	86 (83, 88)	77 (74, 80)
DDFS (13% maturity) DCO 27 March 2020		
Number of events/total number of patients (%)	89/921 (10)	152/915 (17)
HR (99.5% CI) [a] p-value (2-sided) [b]	0.57 (0.39, 0.83) 0.0000257	
Percentage (95% CI) of patients distant disease free at 3 years [c]	88 (85, 90)	80 (77, 83)
OS (10% maturity) DCO 12 July 2021		

	Olaparib 300 mg bd (N=921)	Placebo (N=915)
Number of events/total number of patients (%)	75/921 (8)	109/915 (12)
HR (98.5% CI) [a]	0.68 (0.47, 0.97)	
p-value (2-sided) [b]	0.0091	
Percentage (95% CI) of patients alive at 3 years [c]	93 (91, 94)	89 (87, 91)
Percentage (95% CI) of patients alive at 4 years [c]	90 (87, 92)	86 (84, 89)

[a]   Based on the stratified Cox's Proportional Hazards Model, <1 indicates a lower risk with olaparib compared with placebo arm.

[b]   p-value from a stratified log-rank test.

[c]   Percentages are calculated using KM estimates.

bd = twice daily; CI = confidence interval; DDFS = distant disease free survival; IDFS = invasive disease free survival; KM = Kaplan-Meier; OS = overall survival.

Figure 5   Kaplan-Meier plot of IDFS in patients with HER2-negative high risk early breast cancer patients with a germline *BRCA* mutation

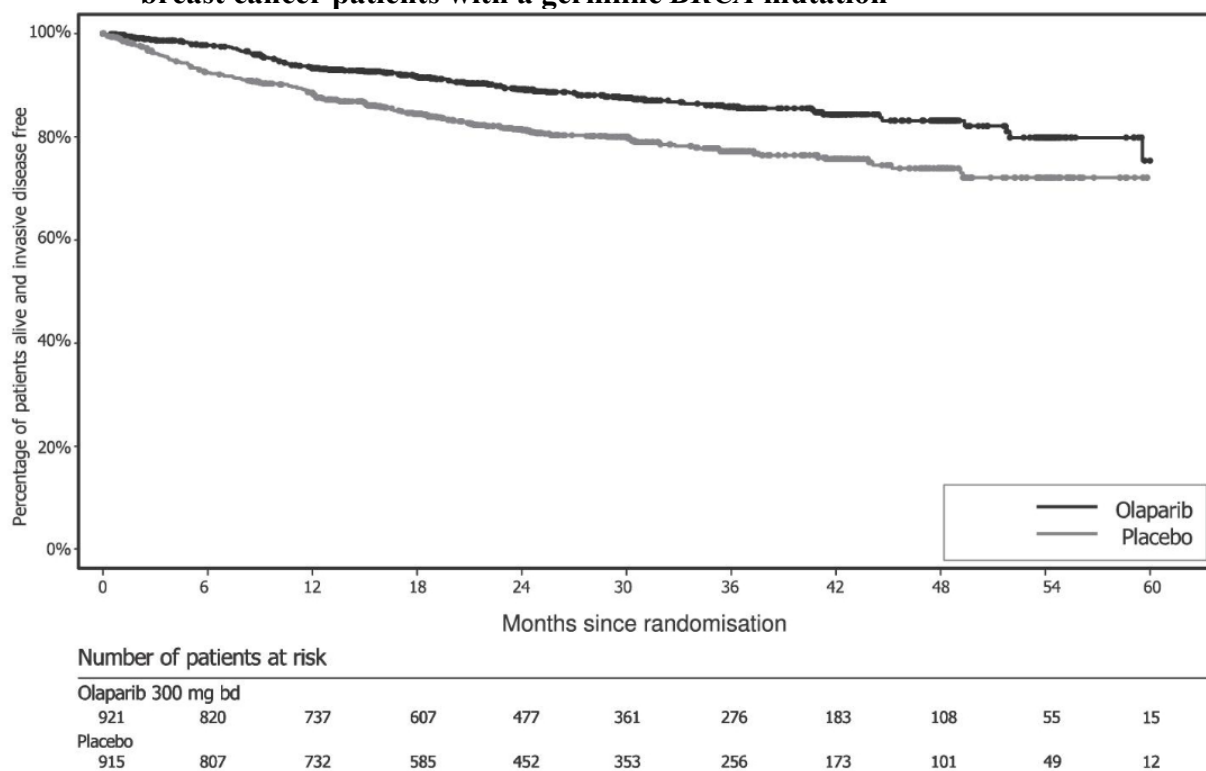| Number of patients at risk										
Olaparib 300 mg bd										
921	820	737	607	477	361	276	183	108	55	15
Placebo										
915	807	732	585	452	353	256	173	101	49	12

Figure 6   Kaplan-Meier plot of DDFS in patients with HER2-negative high risk early breast cancer patients with a germline BRCA mutation

Figure 7 **Kaplan-Meier plot of OS in patients with HER2-negative high risk early breast cancer patients with a germline *BRCA* mutation**
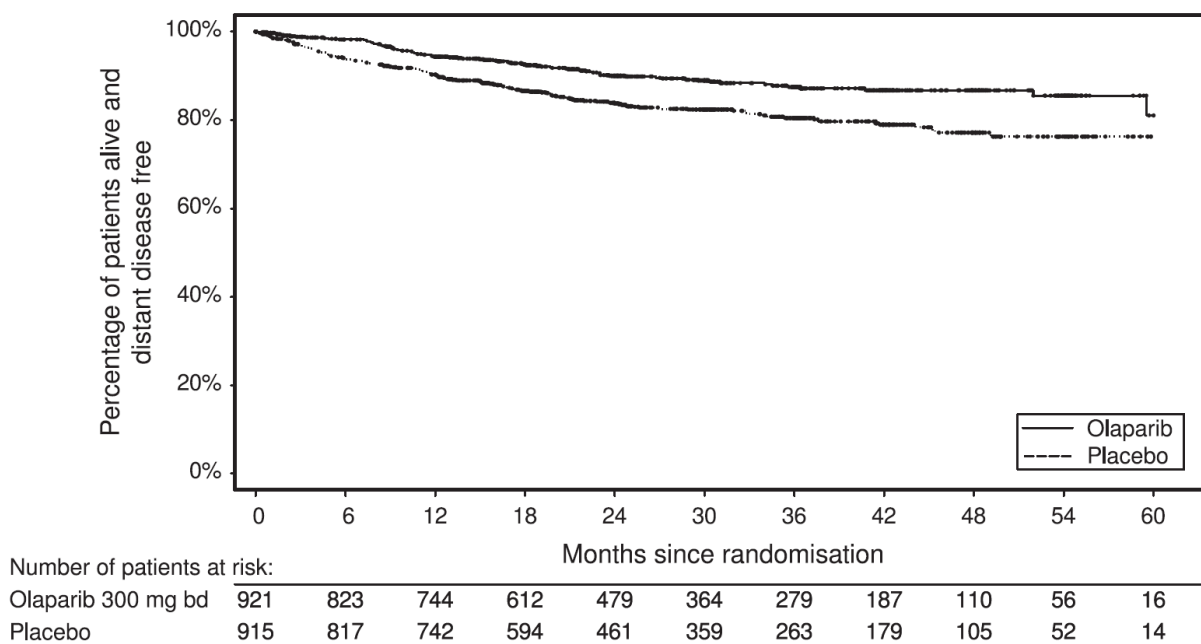
Number of patients at risk:	0	6	12	18	24	30	36	42	48	54	60
Olaparib 300 mg bd	921	823	744	612	479	364	279	187	110	56	16
Placebo	915	817	742	594	461	359	263	179	105	52	14

Number of patients at risk:

Olaparib 300 mg bd
921 862 844 809 773 672 560 437 335 228 151 70 16 6 0 0

Placebo
915 868 843 808 752 647 530 423 333 218 141 74 17 4 0 0
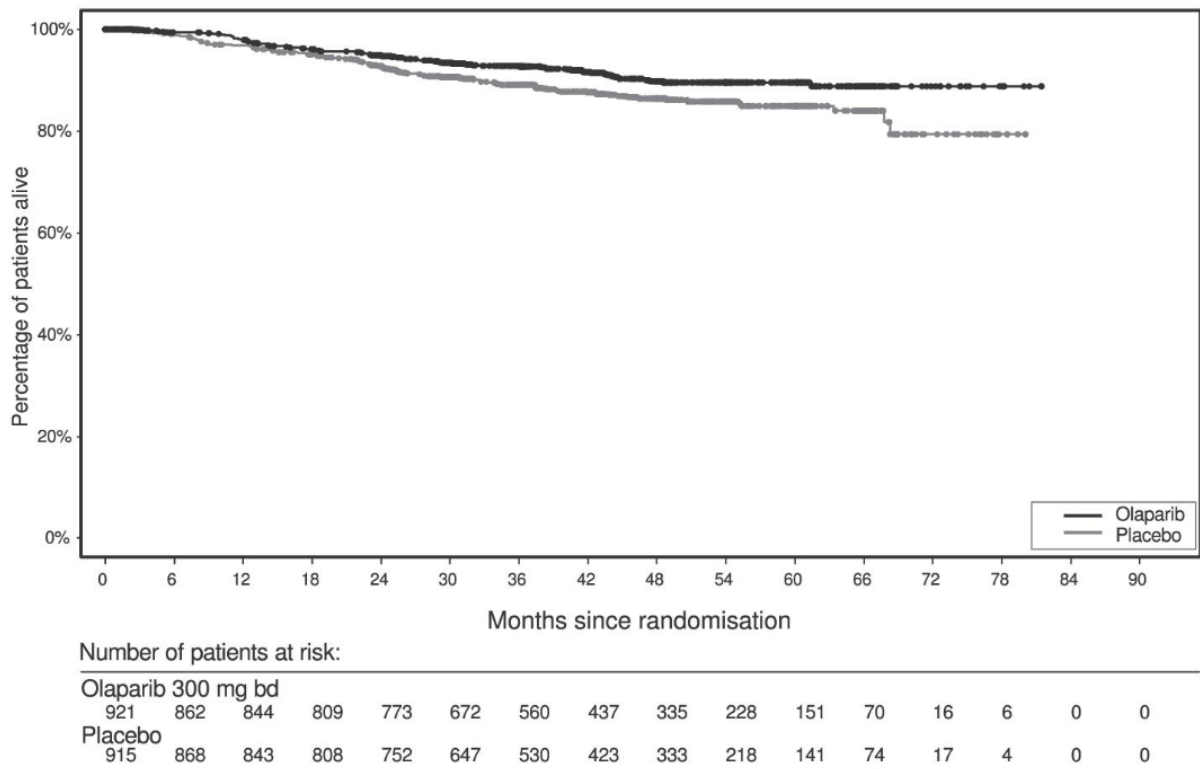
Table 10 IDFS by subgroup in HER2-negative high risk early breast cancer patients with a *BRCA* mutation in OlympiA

	Number of IDFS events/total number of patients (%)		HR (95% CI) [a]	Percentage of patients invasive disease free at 3 years [b]	
	Olaparib 300 mg bd (N=921)	Placebo (N=915)		Olaparib 300 mg bd (N=921)	Placebo (N=915)
Hormone receptor status					
HR+/HER2-	19/168 (11)	25/157 (16)	0.70 (0.38, 1.27)	84	77
TNBC	87/751 (12)	153/758 (20)	0.56 (0.43,0.73)	86	77
Prior neoadjuvant versus adjuvant chemotherapy					
Adjuvant	36/461 (8)	61/455 (13)	0.60 (0.39, 0.90)	89	85
Neoadjuvant	70/460 (15)	117/460 (25)	0.56 (0.41, 0.75)	83	68
Prior platinum					

	Number of IDFS events/total number of patients (%)		HR (95% CI) [a]	Percentage of patients invasive disease free at 3 years [b]	
	Olaparib 300 mg bd (N=921)	Placebo (N=915)		Olaparib 300 mg bd (N=921)	Placebo (N=915)
Yes	34/247 (14)	43/239 (18)	0.77 (0.49, 1.21)	82	77
No	72/674 (11)	135/676 (20)	0.52 (0.39, 0.69)	87	77

[a] Based on the stratified Cox's Proportional Hazards Model, <1 indicates a lower risk with olaparib compared with placebo arm.
[b] Percentages are calculated using KM estimates.
bd = twice daily; CI = confidence interval; IDFS = invasive disease free survival; KM = Kaplan-Meier.

The patient reported outcome assessments included the FACIT-Fatigue (to assess fatigue and its impact upon daily activities and function) which were completed at baseline prior to randomisation and at 6 months and 12 months after randomisation. A 3-point difference in FACIT-Fatigue score was predefined as clinically meaningful. Patient reported outcome data indicate no clinically meaningful differences among olaparib-treated patients as compared to placebo when measured using FACIT-Fatigue scale. These results should be interpreted cautiously as this secondary endpoint was not adjusted for multiplicity testing in the statistical analysis.

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 physician'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 physician 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 (95% CI 0.43-0.80; p=0.0009; median 7.0 months for olaparib vs. 4.2 months for comparator) (Table 11).

A clinically meaningful and statistically significant improvement in PFS2 was also observed 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 11 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		

	Olaparib 300 mg bd	Physician's choice chemotherapy[a]
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 8   OlympiAD: Kaplan-Meier plot of PFS in patients with *gBRCAm* HER2-negative metastatic breast cancer (77% maturity)
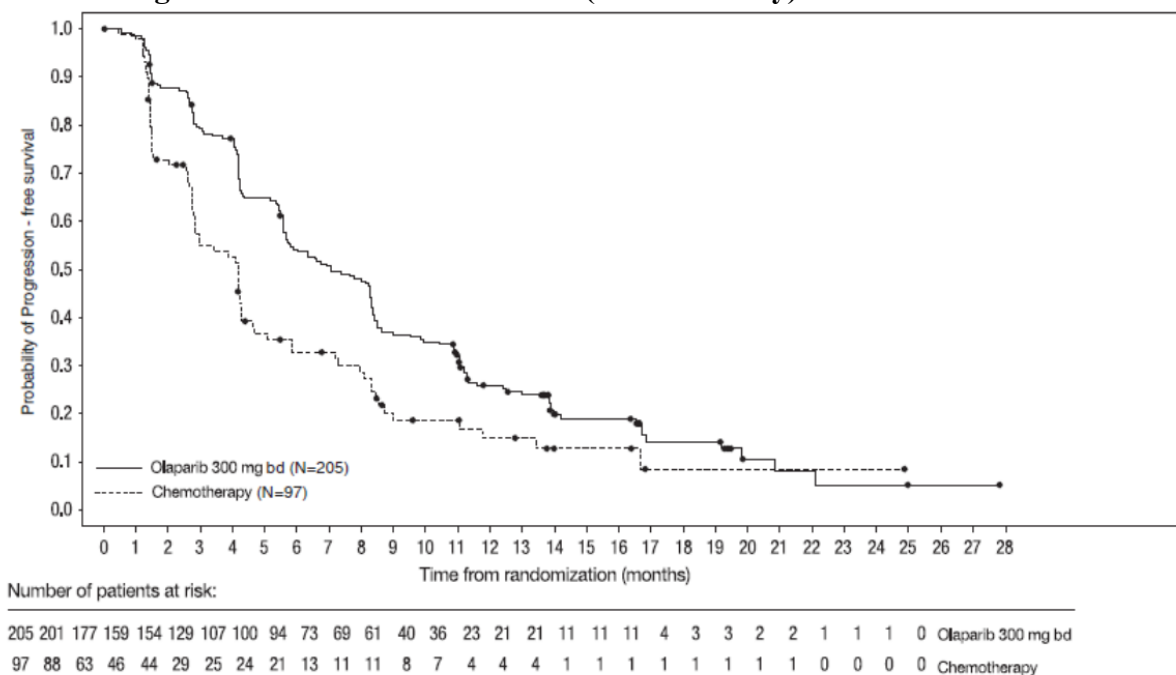
A significant difference in global health status/QoL (assessed using the EORTC QLQ-C30 questionnaire which uses a 0-100 point scale) in favour of olaparib was observed (adjusted mean difference in change from baseline score was 7.5 points [95% CI: 2.48-12.44; p=0.0035]). Time to deterioration (≥10 points 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 of Lynparza maintenance treatment (300 mg [2 x 150 mg tablets] twice daily) with placebo in g*BRCA*-mutated metastatic adenocarcinoma of the pancreas. The study randomised 154 patients (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 were male. Most patients were ECOG performance status 0 (67%). 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). The median TFST was 9.0 months in the olaparib arm and 5.4 months in the placebo arm; HR 0.44; 95% CI 0.30, 0.69; and p<0.0001 [nominal]. The median TDT was 7.5 months in the olaparib arm and 3.8 months in the placebo arm; HR 0.43; 95% CI 0.29, 0.63; and p<0.0001 [nominal].

Table 12 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 patients (%)	60:92 (65)	44:62 (71)
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	19.2
HR (95% CI)[b,c]	0.83 (0.56-1.22)	
P value (2-sided)	p=0.3487	
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 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 9 POLO: Kaplan-Meier plot of PFS for patients with g*BRCAm* metastatic
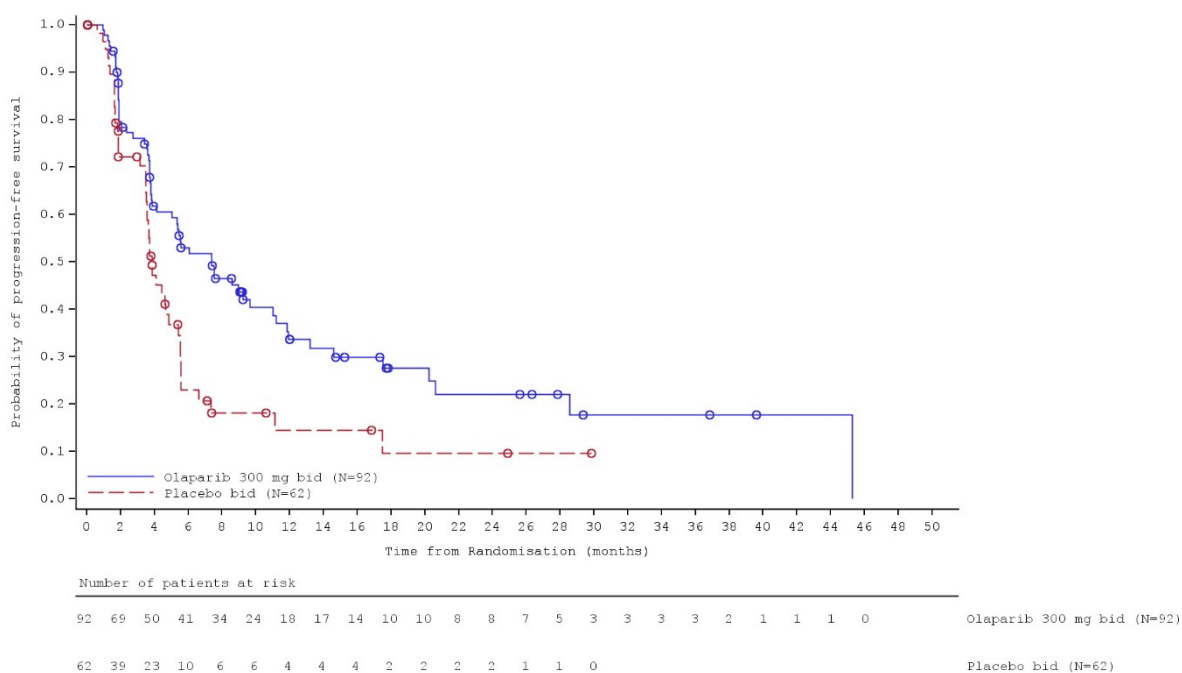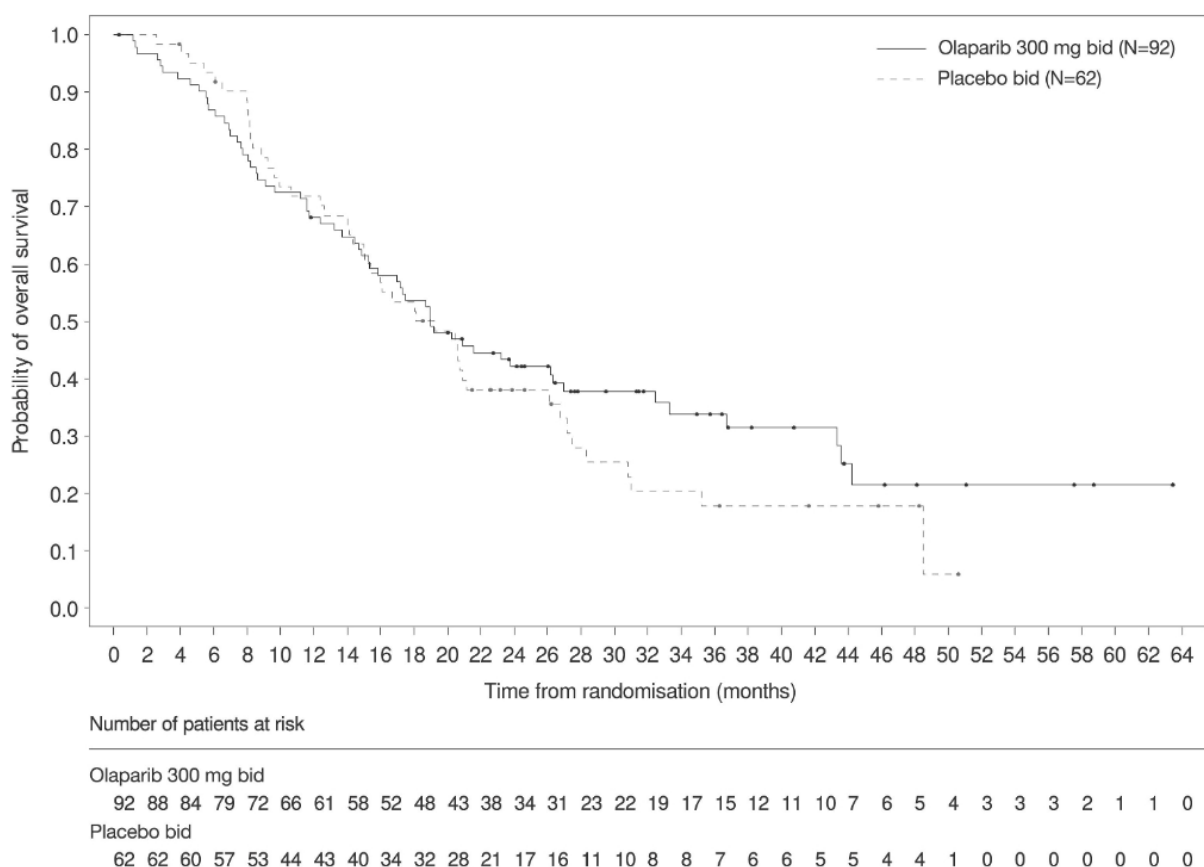adenocarcinoma of the pancreas (68% maturity – BICR)**

**Figure 10 POLO: Kaplan-Meier plot of OS for patients with g*BRCAm* metastatic
adenocarcinoma of the pancreas (70% maturity)**

Number of patients at risk

Olaparib 300 mg bid

92 88 84 79 72 66 61 58 52 48 43 38 34 31 23 22 19 17 15 12 11 10 7 6 5 4 3 3 3 2 1 1 0

Placebo bid

62 62 60 57 53 44 43 40 34 32 28 21 17 16 11 10 8 8 7 6 6 5 5 4 4 1 0 0 0 0 0 0 0

Patient-reported HRQoL was assessed using the EORTC QLQ-C30. 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). These results should be interpreted cautiously as this secondary endpoint was not adjusted for multiplicity testing in the statistical analysis.

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* or *ATM* 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 has an unfavourable benefit-risk in patients with this gene mutation.

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 64% 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, 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 13 Summary of key efficacy findings in Cohort A and Cohort A + B in PROfound

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

	Cohort A Olaparib 300 mg bd (N=162)	Cohort A Investigators choice of NHA (N=83)	Cohort A+B Olaparib 300 mg bd (N=256)	Cohort A+B Investigators choice of NHA (N=131)
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 single visit response (n)	69	9	78	17
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.

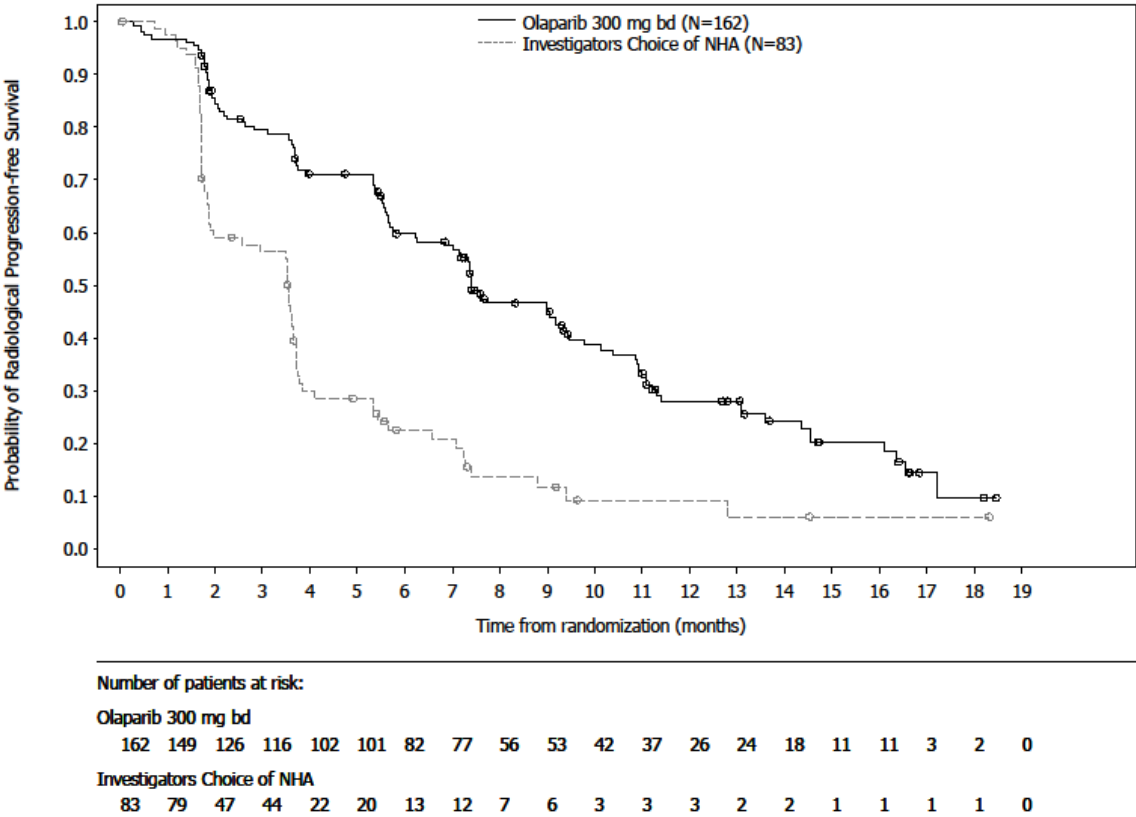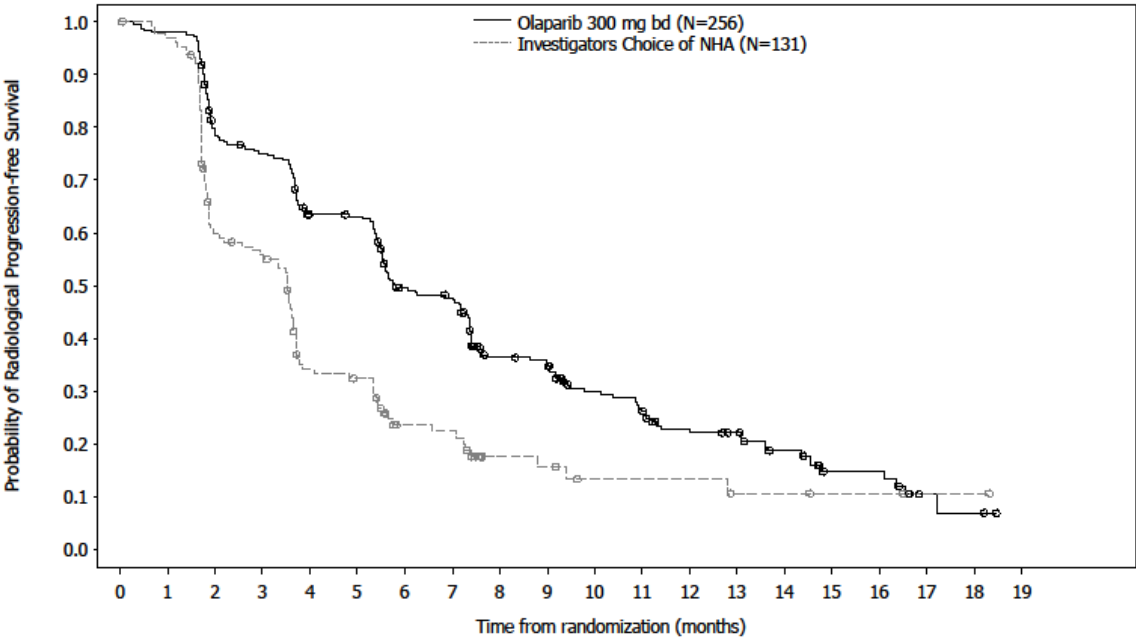**Figure 11 Cohort A: Kaplan-Meier plot of rPFS (by BICR)**

| Number of patients at risk:																				
Olaparib 300 mg bd																				
162	149	126	116	102	101	82	77	56	53	42	37	26	24	18	11	11	3	2	0	
Investigators Choice of NHA																				
83	79	47	44	22	20	13	12	7	6	3	3	3	2	2	1	1	1	1	0	

Figure 12 Cohort A+B: Kaplan-Meier plot of rPFS (by BICR)

Number of patients at risk:

Olaparib 300 mg bd

| 256 | 239 | 188 | 176 | 145 | 143 | 106 | 100 | 67 | 63 | 48 | 43 | 31 | 28 | 21 | 11 | 11 | 3 | 2 | 0 |

Investigators Choice of NHA

| 131 | 123 | 73 | 67 | 38 | 35 | 20 | 19 | 9 | 8 | 5 | 5 | 5 | 3 | 3 | 2 | 2 | 1 | 1 | 0 |

Figure 13 Cohort A: Kaplan-Meier plot of OS
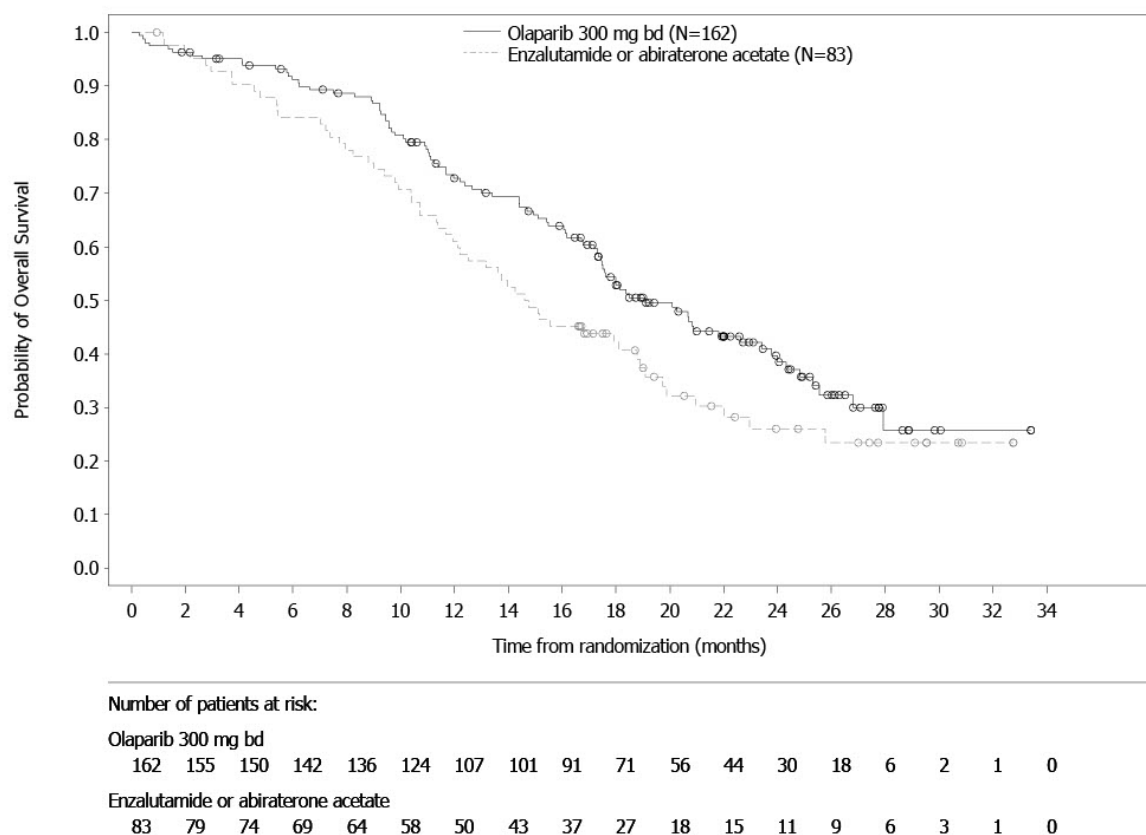
In Cohort A and Cohort A+B the benefit of olaparib over investigators choice of NHA was maintained across all pre-defined subgroups, with clinically meaningful reductions in the risk of progression or death in olaparib-treated patients (ranging from 39% to 75% in Cohort A and from 23% to 88% in Cohort A+B).

The prevalence of the mutations in Cohort B did not provide sufficient power to test independently. In Cohort B exploratory analysis, 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. 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).

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.

Treatment of metastatic castration-resistant prostate cancer

The efficacy of Lynparza in the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) was investigated in a randomized, double-blind, placebo-controlled trial in the mCRPC setting (PROpel). In this study, Lynparza was used in combination with abiraterone and prednisone or prednisolone.

PROpel Study in the mCRPC setting

PROpel was a Phase III randomised, double-blind, placebo-controlled, multicentre study that compared the efficacy of Lynparza (300 mg [2 x 150 mg tablets] twice daily) in combination with abiraterone (1000 mg [2 x 500 mg tablets] once daily) compared with placebo plus abiraterone for the treatment of patients with mCRPC. Patients in both arms also received either prednisone or prednisolone 5 mg twice daily. Prior to the mCRPC stage, treatment with NHAs (except abiraterone) without PSA progression (clinical or radiological) during treatment was allowed, provided the treatment was stopped at least 12 months before randomisation. Treatment with first-generation antiandrogen agents (e.g., bicalutamide, nilutamide, flutamide) was also allowed, provided there was a washout period of 4 weeks. Docetaxel treatment was allowed during neoadjuvant/adjuvant treatment for localised prostate cancer and at metastatic hormone-sensitive prostate cancer (mHSPC) stage, as long as no signs of disease progression occurred during or immediately after such treatment. All patients continued on a gonadotropin-releasing hormone (GnRH) analogue or had prior bilateral orchiectomy.

The study randomised 796 patients (1:1 randomisation; 399 olaparib/abiraterone:397 placebo/abiraterone) who had evidence of histologically confirmed prostate adenocarcinoma and metastatic status defined as at least one documented metastatic lesion on either a bone or CT/MRI scan. Patients were stratified by metastases (bone only, visceral or other) and docetaxel treatment at mHSPC stage (yes or no). Treatment was continued until disease progression or unacceptable toxicity.

Demographic and baseline characteristics were well balanced between the two treatment arms. The median age of patients was 69 years, and the majority (71%) of patients were in the ≥65 years age group. Twenty-one (21) (3%) patients had prior docetaxel treatment during neoadjuvant/adjuvant treatment for localised prostate cancer and 189 (24%) patients had prior docetaxel treatment at mHSPC stage. In total, 434 (55%) patients had bone metastases (metastases in the bone and no other distant site), 105 (13%) patients had visceral metastases (distant soft tissue metastases in an organ e.g., liver, lung) and 257 (32%) patients had other metastases (this could include, for example, patients with bone metastases and distant lymph nodes or patients with disease present only in distant lymph nodes). The majority of patients in both arms were ECOG performance status 0 (70%).

HRR gene mutation status was assessed retrospectively by ctDNA and tumour tissue tests on 14 HRR genes: *ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D*, and *RAD54L*. Of the patients in PROpel tested, 198 (24.9%) and 118 (14.8%) were HRRm as determined by ctDNA and tumour tissue, respectively. Majority of the HRRm patients were with mutations in *BRCA2* (7.3%), *ATM* (7.5%), *CDK12* (4.6%), or *CHEK2* (4.4%) as determined by ctDNA test, and in *BRCA2* (5.7%), *ATM* (3.9%), or *CDK12* (4.4%) as determined by tumour tissue test. The distribution of HRRm patients was well balanced between the two arms.

The primary endpoint was rPFS, defined as time from randomisation to progression determined by investigator assessment based on RECIST 1.1 and PCWG-3 criteria (bone), or death from any cause, whichever occurred first. The key secondary efficacy endpoint was overall survival (OS). Additional secondary endpoints included PFS2, TFST and HRQoL.

At the time of interim rPFS analysis, there was a statistically significant and clinically meaningful improvement in the risk of radiological disease progression or death for olaparib/abiraterone compared to placebo/abiraterone as assessed by the investigator (see Table 14). The sensitivity analysis of rPFS by BICR was consistent with the investigator-based analysis with HR 0.61; 95% CI 0.49, 0.74; p<0.0001; median rPFS 27.6 months in the olaparib/abiraterone arm vs 16.4 months in the placebo/abiraterone arm, respectively.

Subgroup analysis showed rPFS improvement for olaparib/abiraterone compared to placebo/abiraterone in all pre-defined sub-groups, including patients with or without prior taxane at mHSPC, patients with different metastatic disease at baseline (bone only vs visceral vs other) and patients with or without HRRm.

There were improvements in PFS2 and TFST in the olaparib/abiraterone arm vs. placebo/abiraterone arm.

At the second interim analysis, the percentage of patients alive at 36 months in the olaparib/abiraterone arm and the placebo/abiraterone arm was 57% and 52%, respectively.

Table 14 Summary of key efficacy findings in the mCRPC setting in PROpel

	Olaparib/abiraterone N = 399	Placebo/abiraterone N = 397
rPFS (by investigator assessment) (50% maturity) (30 July 2021)		
Number of events/total number of patients (%)	168/399 (42.1)	226/397 (56.9)
Median time (95% CI) (months)[d]	24.8 (20.5, 27.6)	16.6 (13.9, 19.2)
HR (95% CI)[a]	0.66 (0.54, 0.81)	
p-value[b]	<0.0001	
Interim OS (40% maturity) (14 March 2022)		

	Olaparib/abiraterone N = 399	Placebo/abiraterone N = 397
Number of events/total number of patients (%)	148/399 (37.1)	171/397 (43.1)
Median time (95% CI) (months)[d]	NC (NC, NC)	NC (NC, NC)
HR (95% CI)[a]	0.83 (0.66, 1.03)	
p-value[b]	p=0.1126	
PFS2 (21% maturity) (30 July 2021)		
Number of events/total number of patients (%)	70/399 (17.5)	94/397 (23.7)
Median time (95% CI) (months)[d]	NC (NC, NC)	NC (NC,NC)
HR (95% CI)[a]	0.69 (0.51, 0.94)	
p-value[b,c]	p=0.0184	
TFST (51% maturity) (30 July 2021)		
Number of events/total number of patients (%)	183/399 (45.9)	221/397 (55.7)
Median time (95% CI) (months)[d]	25.0 (22.2, NC)	19.9 (17.1, 22.0)
HR (95% CI)[a]	0.74 (0.61, 0.90)	
p-value[b,c]	p=0.0040	

[a] The HR and CI were calculated using a Cox proportional hazards model adjusted for the variables selected in the primary pooling strategy: metastases, docetaxel treatment at mHSPC stage. The Efron approach was used for handling ties. A HR <1 favours olaparib 300 mg bd.
[b] The 2-sided p-value was calculated using the log-rank test stratified by the same variables selected in the primary pooling strategy.
[c] The p-value presented is nominal as the endpoint is not alpha controlled.
[d] Calculated using the Kaplan-Meier technique.

Efficacy results are presented in Figure 14, Figure 15, Table 15 and Table 16.

Figure 14 PROpel: Kaplan-Meier plot of rPFS (by investigator assessment)
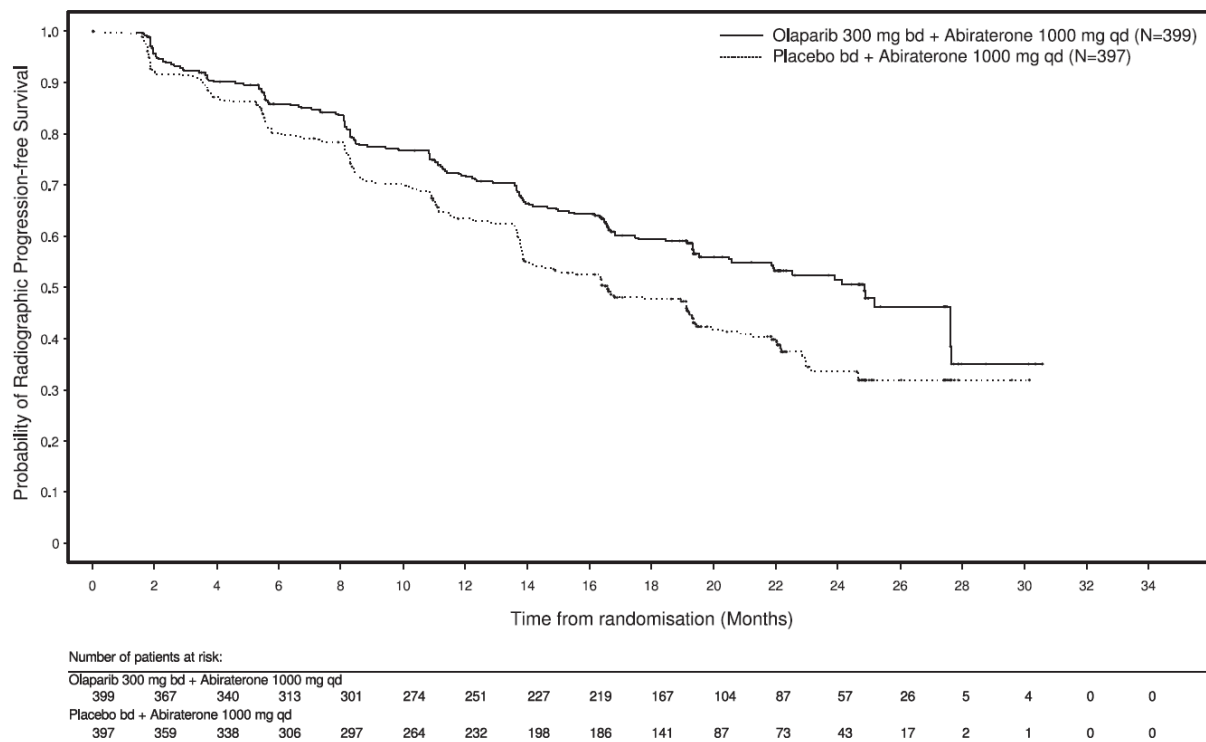
Number of patients at risk:

Olaparib 300 mg bd + Abiraterone 1000 mg qd

| 399 | 367 | 340 | 313 | 301 | 274 | 251 | 227 | 219 | 167 | 104 | 87 | 57 | 26 | 5 | 4 | 0 | 0 |

Placebo bd + Abiraterone 1000 mg qd

| 397 | 359 | 338 | 306 | 297 | 264 | 232 | 198 | 186 | 141 | 87 | 73 | 43 | 17 | 2 | 1 | 0 | 0 |

Figure 15 PROpel: Kaplan-Meier plot of OS

Number of patients at risk:

Olaparib 300 mg bd + Abiraterone 1000 mg qd

| 399 | 398 | 391 | 385 | 374 | 365 | 350 | 335 | 318 | 313 | 298 | 284 | 274 | 232 | 188 | 135 | 93 | 53 | 23 | 5 | 1 | 0 |

Placebo bd + Abiraterone 1000 mg qd

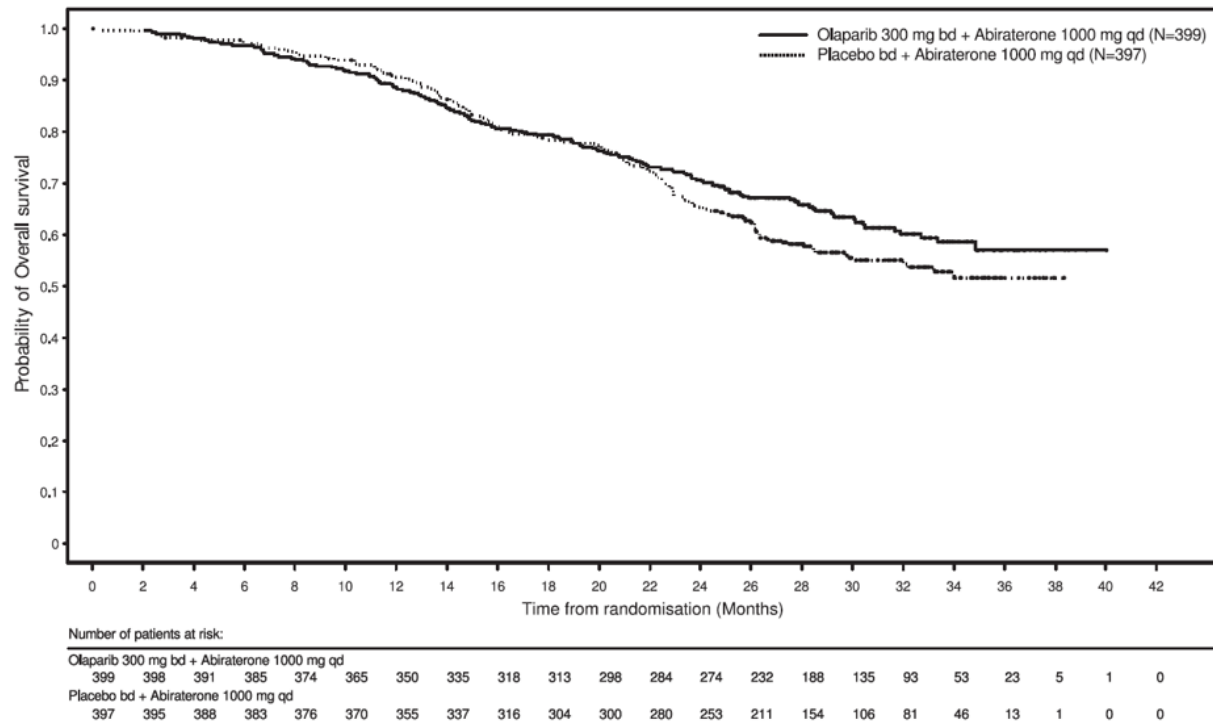| 397 | 395 | 388 | 383 | 376 | 370 | 355 | 337 | 316 | 304 | 300 | 280 | 253 | 211 | 154 | 106 | 81 | 46 | 13 | 1 | 0 | 0 |

Table 15   rPFS by investigator assessment and OS subgroup analyses – PROpel (DCO 30 July 2021)

	Olaparib/ abiraterone	Placebo/ abiraterone
Radiological Progression-Free Survival (rPFS) by investigator assessment		
Aggregate HRRm Subgroup Analyses[a]		
HRRm	**N=111**	**N=115**
Number of events: Total number of patients (%)	43:111 (38.7)	73:115 (63.5)
Median (months)	NC	13.86
Hazard Ratio (95% CI)[b]	0.50 (0.34, 0.73)	
Non-HRRm	**N=279**	**N=273**
Number of events: Total number of patients (%)	119:279 (42.7)	149:273 (54.6)
Median (months)	24.11	18.96
Hazard Ratio (95% CI)[b]	0.76 (0.60, 0.97)	
Overall Survival		
Aggregate HRRm Subgroup Analyses[a]		
HRRm	**N=111**	**N=115**
Number of events: Total number of patients (%)	28/111 (25.2)	35/115 (30.4)
Median (months)	NC	NC
Hazard Ratio (95% CI)[b]	0.82 (0.50, 1.35)	
Non-HRRm	**N=279**	**N=273**
Number of events: Total number of patients (%)	77/279 (27.6)	84/273 (30.8)
Median (months)	NC	NC
Hazard Ratio (95% CI)[b]	0.89 (0.65,1.21)	

[a] Aggregate subgroups were derived from ctDNA and tissue-based groupings.

[b] The analysis was performed using a Cox proportional hazards model including terms for treatment group, the subgroup factor, and a treatment by subgroup interaction. Confidence interval calculated using the profile likelihood method. An HR< 1 favors olaparib 300 mg bd.

CI, confidence interval; HR, hazard ratio; HRRm, homologous recombination repair gene mutation; NC, not calculable; OS, overall survival; rPFS radiological progression-free survival.

Table 16 Summary of rPFS by investigator assessment and OS results, by baseline pain subgroups (DCO2 14 March 2022)

	Asymptomatic[a] baseline pain		Symptomatic[b] baseline pain	
	Olaparib + abiraterone (N= 266)	Placebo + abiraterone (N = 294)	Olaparib + abiraterone (N=103)	Placebo + abiraterone (N = 80)
rPFS by investigator assessment				
Number of events: Total number of patients (%)	119 (44.7)	185 (62.9)	67 (65.0)	59 (73.8)
Median time (95% CI) (months)	29.14 (27.56, 30.46)	19.12 (14.59, 19.45)	14.06 (11.20, 19.32)	13.77 (8.41, 16.39)
HR (95% CI)	0.62 (0.49, 0.78)		0.80 (0.57, 1.14)	
Overall survival				
Number of events: Total number of patients (%)	77 (28.9)	111 (37.8)	62 (60.2)	49 (61.3)
Median time (95% CI) (months)	NC (NC, NC)	NC (NC, NC)	22.90 (18.40, 29.24)	22.83 (16.36, 26.15)
HR (95% CI)	0.73 (0.54, 0.97)		0.95 (0.66, 1.39)	

[a] Brief Pain Inventory-Short Form item 3 score <4 and no opiate use at baseline
[b] Brief Pain Inventory-Short Form item 3 score ≥4 and/or opiate use at baseline
Each subgroup analysis was performed using a Cox proportional hazards model including terms for treatment group, the subgroup factor, and a treatment by subgroup interaction. CIs calculated using profile likelihood method.
A hazard ratio < 1 favours Olaparib + Abiraterone.
BICR = Blinded Independent Central Review; BPI-SF = Brief Pain Inventory-short form; CI = Confidence interval;
DCO = Data cut-off; HR = Hazard ratio; NC = Not calculated; rPFS = Radiographic progression-free survival.

The results from the analyses of PRO measures, including change from baseline for the FACT-P total score, the BPI-SF pain severity and pain interference scores, showed no overall detriment in the olaparib/abiraterone arm compared with the placebo/abiraterone arm. Similar findings were generally observed with the FACT-P subscale scores.

__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

General

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 (t_{max} delayed by 2.5 hours and C_{max} 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 C_{max}.

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.

Metabolism

In vitro, CYP3A4/5 were shown to be the enzymes primarily responsible for the metabolism of olaparib.

Following oral dosing of ^{14}C-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 (IC_{50}=76 µM), 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.

Excretion

Following a single dose of ^{14}C-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.

Effect of 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).

Effect of hepatic impairment

Following a single oral 300 mg dose of olaparib to patients with mild hepatic impairment (Child-Pugh classification A) AUC increased by 15% and C_{max} by 13% and to 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 in patients with mild or moderate hepatic impairment (see section 4.2).

Olaparib has not been studied 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

The names of inactive ingredients may vary according to region.

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) (150 mg tablet only)

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

Please refer to expiry date on the outer carton.

Store at or below 30°C.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Alu/Alu non-perforated blister containing 8 tablets. Cartons of 56 tablets (7 blisters) and a multipack containing 112 (2 cartons of 56) tablets.

Not all pack sizes may be marketed.

6.6 Instructions for use, handling and disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Product Owner
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