NEW ZEALAND DATA SHEET

1. PRODUCT NAME

LYNPARZA® 150 mg film-coated Tablets
LYNPARZA® 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 the full list of 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, 14.5 mm x 7.25 mm, 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, 14.5 mm x 7.25 mm, 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 newly diagnosed advanced *BRCA*-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to first-line platinum-based chemotherapy

- maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) after platinum-based chemotherapy. Prior treatment must have included at least 2 courses of platinum-based regimens.

LYNPARZA in combination with bevacizumab is indicated for the:

- maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either:

- a deleterious or suspected deleterious *BRCA* mutation (germline or somatic), and/or
- genomic instability

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

Breast Cancer

LYNPARZA is indicated as

- monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline *BRCA1/2*-mutations who have HER2-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy (see sections 4.2 and 5.1).

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

Adenocarcinoma of the pancreas

LYNPARZA is indicated as monotherapy for the

- maintenance treatment of adult patients with germline *BRCA1/2*-mutations who have metastatic adenocarcinoma of the pancreas and have not progressed after a minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen.

Prostate cancer

LYNPARZA is indicated as monotherapy for the:

- treatment of adult patients with *BRCA*-mutated (germline and/or somatic) metastatic castration-resistant prostate cancer who have progressed following prior therapy that included a new hormonal agent. *BRCA* mutation status should be determined by an experienced laboratory using a validated test method.

LYNPARZA in combination with abiraterone and prednisone or prednisolone is indicated for the:

- treatment of adult patients with metastatic castration-resistant prostate cancer

4.2 DOSE 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* and other HRR gene mutations

Gene mutation 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.

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

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

Metastatic HER2-negative breast cancer:

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

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

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

Monotherapy treatment of *BRCA*-mutated metastatic castration-resistant prostate cancer(mCRPC):

Patients must have confirmation of a deleterious or suspected deleterious *BRCA* mutation (using either tumour DNA from a tumour tissue sample, circulating tumour DNA [ctDNA] obtained from a plasma sample or germline DNA obtained from a non-tumour sample) before LYNPARZA treatment is initiated (see section 5.1). If a ctDNA test is used and the result is negative, this does not rule out the presence of a *BRCA* mutation.

Dosage in adults

LYNPARZA is available as 100 mg and 150 mg tablets.

The recommended dose of LYNPARZA in monotherapy or in combination with bevacizumab for ovarian cancer or in combination with abiraterone and prednisone or prednisolone for prostate cancer or endocrine therapy 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. There are no data to support retreatment with olaparib as maintenance following subsequent relapse.

Maintenance treatment of newly diagnosed 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 Data Sheet for bevacizumab for recommended dosing information (see section 5.1).

Adjuvant treatment of *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, 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 *BRCA*-mutated metastatic castration-resistant prostate cancer (mCRPC): 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. When LYNPARZA is used in combination with abiraterone, refer to the Prescribing Information for abiraterone for recommended dosing information (see section 5.1).

<u>Missing dose</u>

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

<u>Dose adjustments</u>

For adverse events

Treatment may be interrupted to manage adverse reactions such as nausea, vomiting, diarrhoea and anaemia, and dose reduction can be considered.

Gastrointestinal toxicities are frequently reported with olaparib therapy (see section 4.8) and are generally low grade (CTCAE grade 1 or 2) and intermittent. In addition to dose interruption or reduction, concomitant medicinal products (e.g. antiemetic therapy) may also be considered. Antiemetic prophylaxis is not required.

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 reduce to 200 mg (two 100 mg tablets) twice daily (equivalent to a total daily dose of 400 mg) is recommended.

Co-administration with CYP3A inhibitors

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.

Non-Caucasian patients

There are limited clinical data available in non-Caucasian patients. However, no dose adjustment is required on the basis of ethnicity (see section 5.2).

Patients with performance status 2 to 4

There are very limited clinical data available in patients with performance status 2 to 4.

Method of administration

For oral use. LYNPARZA tablets should be swallowed whole and not chewed, crushed, dissolved or divided. LYNPARZA tablets can be taken with or without food.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance (olaparib) or to any of the excipients listed in section 6.1.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Assessment of mutation status

Only robust, reliable and sensitive tests with demonstrated utility for the determination of gene mutation status should be used to select patients for treatment with olaparib (see Section 4.2**)**

Haematological toxicity

Haematological toxicity occurs commonly in patients treated with LYNPARZA. While the majority were generally mild or moderate (CTCAE Grade 1 or 2), Grade 3 or higher events of anaemia (decrease in haemoglobin) occurred in 7.4% of patients in Study 19, and one patient died from a haemorrhagic stroke associated with thrombocytopenia. 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 *BRCAm* 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 (g*BRCA*m*)* 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 patients treated with LYNPARZA monotherapy in clinical studies (see section 4.8). 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.

Drug-Induced Liver Injury

Rare cases of drug-induced liver injury (DILI) have been reported in patients treated with LYNPARZA in the post-marketing setting (see section 4.8). If DILI is suspected, treatment should be interrupted. If DILI is confirmed, treatment should be discontinued.

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 6 months 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 INTERACTIONS WITH OTHER MEDICINES 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

<u>Strong and moderate CYP3A inhibitors</u>

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 clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, and boceprevir 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).

Patients should avoid star fruit, grapefruit and Seville oranges while on LYNPARZA therapy as these foods are known to inhibit CYP3A enzymes.

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), 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 and modafinil 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, 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, statins and valsartan), OCT1 (e.g. metformin), OCT2 (e.g. serum creatinine), OAT3 (e.g. furosemide and methotrexate), MATE1 (e.g. metformin and cisplatin) and MATE2K (e.g. metformin). In particular, caution should be exercised if LYNPARZA is administered in combination with any statin.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Category D

LYNPARZA 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.

Based on its mechanism of action (PARP inhibition), LYNPARZA could cause foetal harm when administered to a pregnant woman. Studies in rats have shown that olaparib causes embryofoetal lethality and induces major fetal malformations (major eye and vertebral/rib malformations) at exposures below those expected at the recommended human dose of 300 mg twice daily.

If a female patient or a female partner of a male patient receiving LYNPARZA becomes pregnant, she should be informed 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 child-bearing potential must use effective contraception during therapy and for 6 months after receiving the last dose of LYNPARZA (see section 4.4). A pregnancy test should be performed on all women of childbearing potential prior to treatment, and pregnancy tests should be performed at regular intervals during treatment and at 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.

Effects on fertility

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. Exposures achieved in these studies were subclinical and the full effects on fertility may not have been revealed.

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 machines 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 4499 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	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

MedDRA SOC	MedDRA Term	CIOMS descriptor/ Overall Frequency (All CTCAE grades)	Frequency of CTCAE grade 3 and above
Respiratory, thoracic and mediastinal disorders	Cough[a]	Very common	Uncommon
	Dyspnoea[a]	Very common	Common
	Pneumonitis[a]	Uncommon	Uncommon
Nervous system disorders	Dizziness	Very common	Uncommon
	Headache	Very common	Uncommon
	Dysgeusia	Very common	-
Gastrointestinal disorders	Vomiting	Very common	Common
	Diarrhoea	Very common	Uncommon
	Nausea	Very common	Common
	Dyspepsia	Very common	Rare
	Stomatitis	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
Hepatobiliary disorders	Drug-induced liver injury[*]	Rare	-
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 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 ;
Cough includes PTs of cough and productive cough;
Dyspnoea includes PTs of dyspnoea and dyspnoea exertional;
Pneumonitis includes PTs of pneumonitis, interstitial lung disease, acute interstitial pneumonitis, eosinophilic pneumonia, eosinophilic pneumonia acute and hypersensitivity pneumonitis.
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.

* As observed in the post-marketing setting

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 to 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. Ninety percent (90%) of patients had creatinine values of CTCAE grade 0 at baseline and 10% were CTCAE grade 1 at baseline.

Nausea and vomiting

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

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.

Contact the National Poisons Centre on 0800 POISON (0800 764 766) for advice on management.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacological actions

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 mice either as a standalone treatment or in combination with established chemotherapies or new hormonal agents (NHA).

PARP enzymes 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 adduct. In normal cells, homologous recombination repair (HRR), which requires functional *BRCA*1 and 2 genes, 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 animal 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.

There was no correlation between the dose and degree of PARP-1 inhibition observed in the pharmacodynamic studies, with maximal inhibition achieved at relatively low doses. Therefore, the dose selection was based upon the higher clinical response rates observed at higher doses.

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 efficacy and safety

Maintenance treatment of newly diagnosed advanced ovarian cancer

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 (*BRCA*m) 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 *BRCA*m 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 *BRCA*m and 2 who were somatic *BRCA*m 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, a clinically meaningful and statistically significant improvement in TFST was observed for olaparib-treated patients. A descriptive analysis performed at seven years after the last patient was randomized demonstrated a clinically meaningful benefit in OS that numerically favoured the olaparib arm (Table 2, Figure 3).

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	
OS (38% maturity)		
Number of events: Total number of patients (%)	84:260 (32)	65:131 (50)[c]
Median time (months)	NR	75.2
Alive at 36 months (%)[a]	84	81
Alive at 60 months (%)[a]	73	63
Alive at 84 months (%)[a]	67	47
HR (95% CI)[b]	0.55 (0.40-0.76)	
TFST (60% maturity)		
Number of events: Total number of patients (%)	135:260 (52)	98:131 (75)
Median time (months)	64.0	15.1
HR (95% CI)[b]	0.37 (0.28-0.48)	

[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 97 patients on the placebo arm who received subsequent therapy, 58 (60%) received a PARP inhibitor.

bd Twice daily; NR not reached; CI Confidence interval; PFS Progression-free survival; PFS2 Time to second progression or death; OS Overall survival; TFST Time from randomisation to first subsequent anti-cancer therapy or death.

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

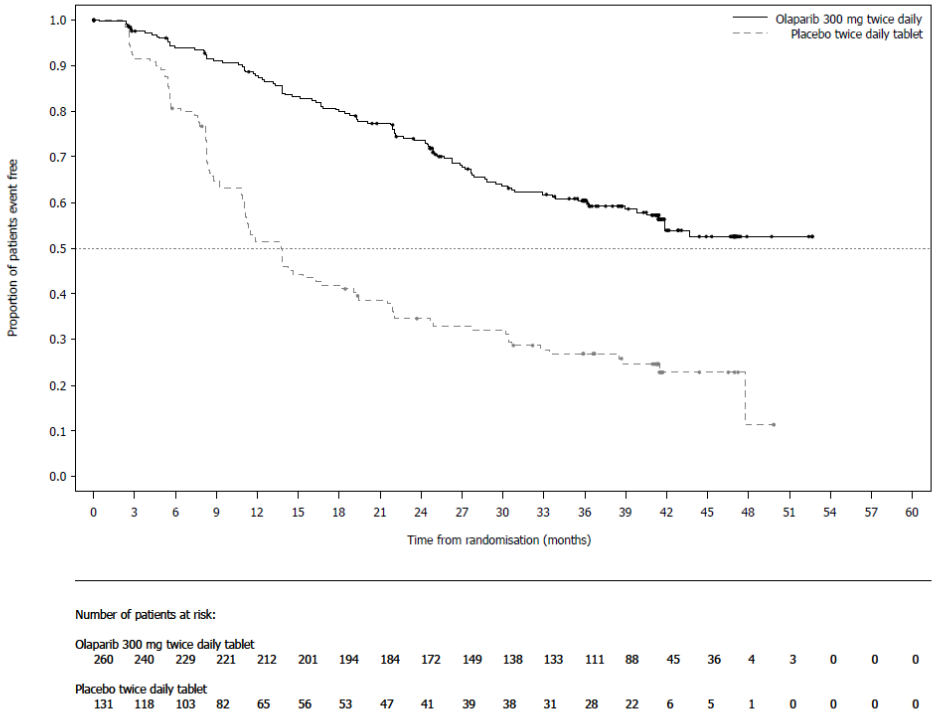
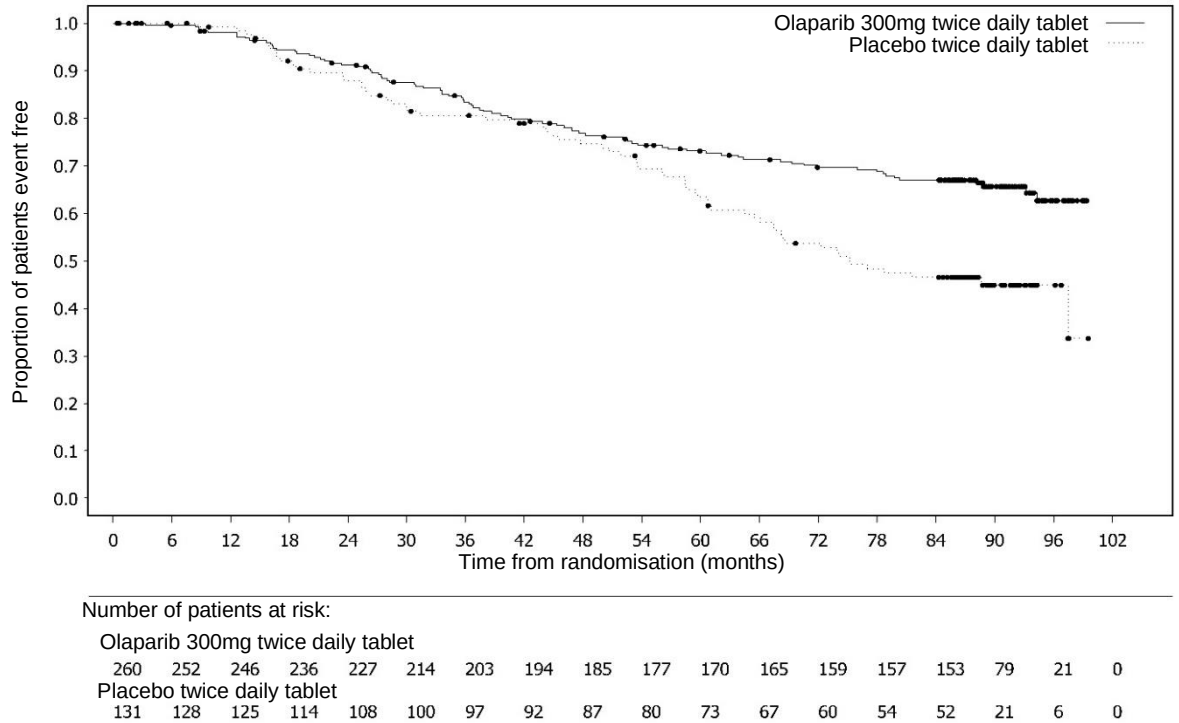


Figure 2 **SOLO1: KaplanMeier plot of OS in newly diagnosed patients with BRCA1/2m advanced ovarian cancer (38% maturity)**



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 (g*BRCA*m) 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 g*BRCA*m PSR ovarian cancer in SOLO2 is presented in Table 3.

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

	Olaparib 300 mg tablet bd		Placebo
PFS (63% maturity)			
Number of events: Total number of patients (%)	107:196 (55)		80:99 (81)
Median time (months)	19.1		5.5
HR (95% CI) [a]		0.30 (0.22-0.41)	
P value (2-sided)		p<0.0001	
PFS2 (40% maturity)			
Number of events: Total number of patients (%)	70:196 (36)		49:99 (50)
Median time (months)	NR		18.4
HR (95% CI) [a]		0.50 (0.34-0.72)	
P value (2-sided)		p=0.0002	
OS (61% maturity)			
Number of events: Total number of patients (%)	116:196 (59)		65:99 (66)[b]
Median time (95% CI) months	51.7 (41.5, 59.1)		38.8 (31.4,48.6)
HR (95% CI) [a]		0.74 (0.54-1.00)	
P value (2-sided)		p=0.0537	
TFST			
Number of events: Total number of patients (%)	92:196 (47)		79:99 (80)
Median time (months)	27.9		7.1
HR (95% CI) [a]		0.28 (0.21-0.38)	
P value* (2-sided)		p<0.0001	
TDT			
Number of events: Total number of patients (%)	112:196 (57)		86:99 (87)
Median time (months)	19.4		5.6
HR (95% CI) [a]		0.31 (0.23-0.42)	
P value* (2-sided)		p<0.0001	
TSST			
Number of events: Total number of patients (%)	68:196 (35)		60:99 (61)
Median time (months)	NR		18.2
HR (95% CI) [a]		0.37 (0.26-0.53)	
P value* (2-sided)		p<0.0001	

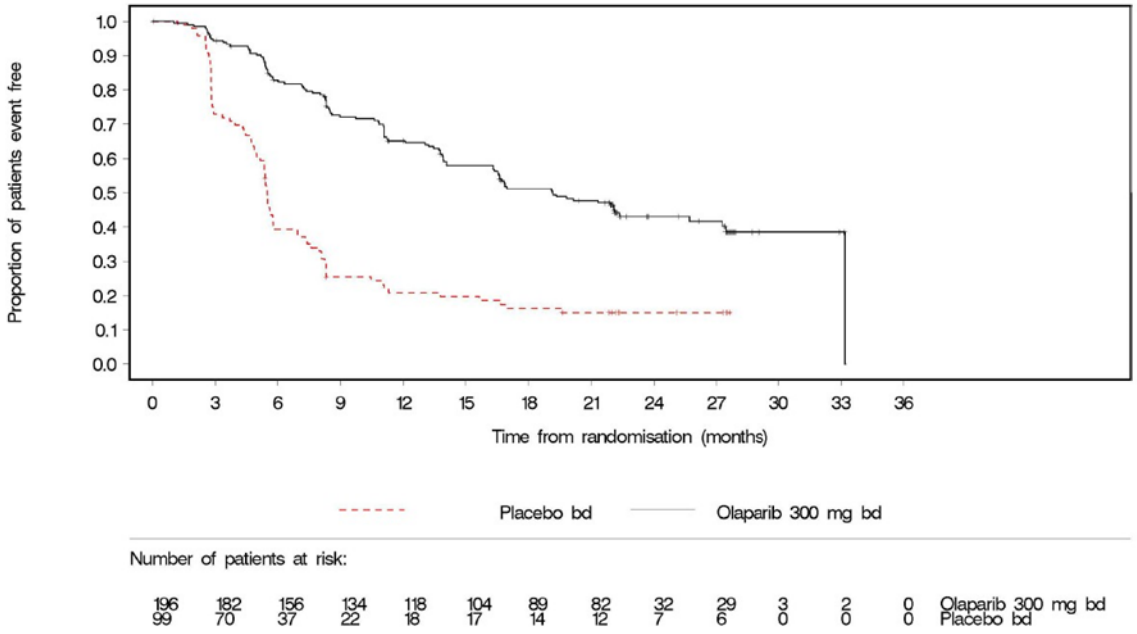
* Not controlled for multiplicity

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

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

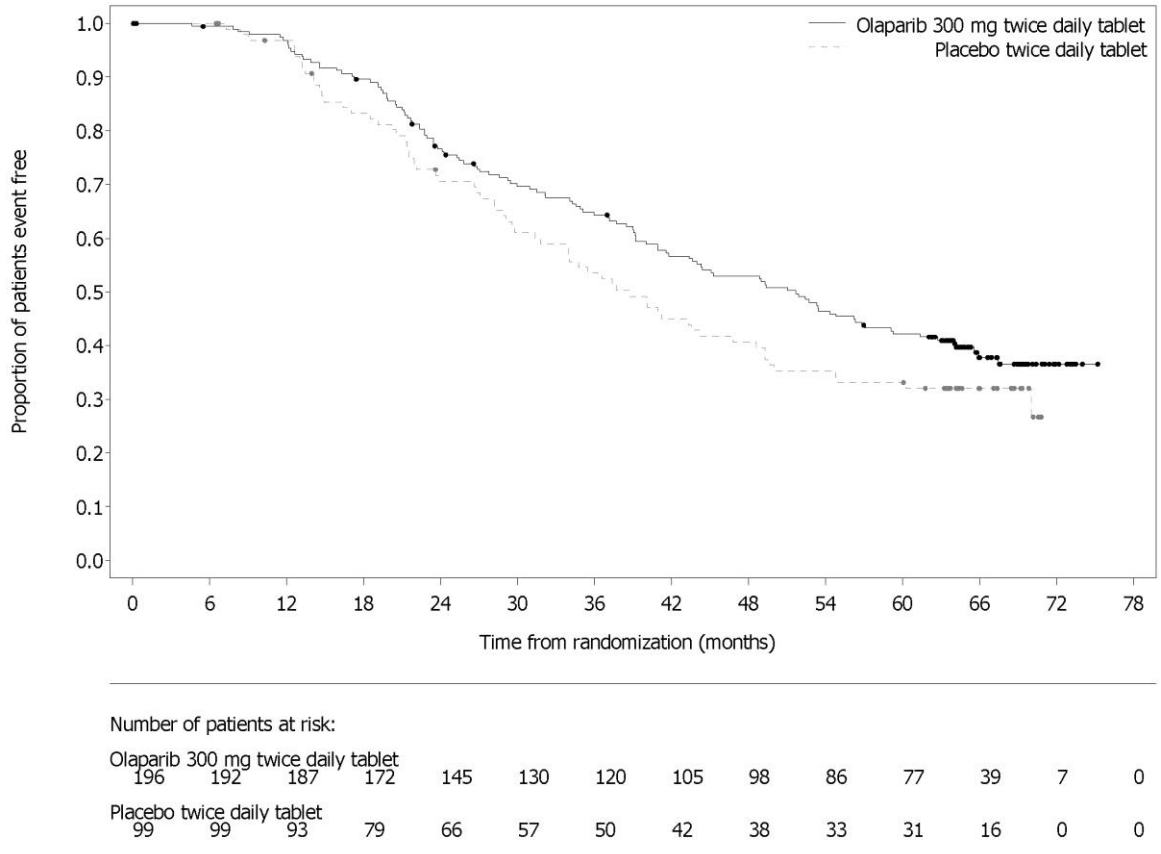
bd Twice daily; NR Not Reached; OS overall survival; PFS Progression-free survival; CI Confidence interval; TDT Time from randomisation to discontinuation of treatment or death; TFST Time from randomisation to start of first subsequent therapy or death; PFS2 Time from randomisation to second progression;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

Figure 3 SOLO2: Kaplan-Meier plot of PFS in patients with g*BRCA*m PSR ovarian cancer (63% maturity - investigator assessment)



bd Twice daily; PFS Progression-free survival

Figure 4 SOLO2: Kaplan-Meier plot of OS in patients with g*BRCA*m PSR ovarian cancer (61% maturity)



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

Study 19 in PSR patients

The study compared the efficacy of LYNPARZA capsule maintenance treatment (400 mg [8 x 50 mg capsules] twice daily) taken to progression with placebo in 265 (136 LYNPARZA and 129 placebo) PSR patients who were in response (CR [complete response] or PR [partial response]) following completion of platinum containing chemotherapy. The primary endpoint was PFS based on investigator assessment using RECIST 1.0. Secondary efficacy endpoints included OS (overall survival), DCR (disease control rate) defined as confirmed CR/PR + SD (stable disease), HRQoL (health related quality of life), and disease related symptoms. Exploratory analyses of time to first subsequent therapy or death (TFST) and time to second subsequent therapy or death (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 0.35 (95% CI 0.25-0.49; p<0.00001; median 8.4 months olaparib vs 4.8 months 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 olaparib versus 27.8 months placebo). TFST and TSST were also longer for olaparib-treated patients (Table 4)

Preplanned subgroup analysis identified patients with *BRCA*-mutated 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 *BRCA*-mutated 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 versus 30.2 months for placebo). In the olaparib-treated group, 28.4% of patients remained on treatment for ≥2 years and 14.9% for ≥5 years. In the placebo-treated group, 8.1% of patients remained on treatment for ≥2 years and 1.6% for ≥5 years. TFST and TSST were also longer for olaparib-treated patients (Table 4).

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

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

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

	All patients		*BRCA*-mutated	
	Olaparib 400 mg capsule bd	**Placebo**	**Olaparib 400 mg capsule bd**	**Placebo**
Number of events: Total number of patients (%)	98:136 (72)	112:129 (87)	49:74 (66)	50:62 (81)[b]
Median time (months)	29.8	27.8	34.9	30.2
HR (95% CI)[a]	0.73 (0.55–0.95)		0.62 (0.42–0.93)	
P value* (2-sided)	p=0.02138		p=0.02140	
TFST – DCO 09 May 2016				
Number of events: Total number of patients (%)	106:136 (78)	124:128 (97)	55:74 (74)	59:62 (95)
Median time (months)	13.3	6.7	15.6	6.2
HR (95% CI)[a]	0.39 (0.30-0.52)		0.33 (0.22–0.49)	
P value* (2-sided)	p<0.00001		p<0.00001	
TSST – DCO 09 May 2016				
Number of events: Total number of patients (%)	104:136 (77)	119:128 (93)	53:74 (72)	56:62 (90)
Median time (months)	19.1	14.8	21.4	15.3
HR (95% CI)[a]	0.53 (0.40-0.69)		0.43 (0.29-0.64)	
P value* (2-sided)	p<0.00001		p= 0.00003	

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

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

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

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

Within the overall population, the disease control rate (DCR) at 24 weeks was 53% and 25% for patients in the olaparib and placebo groups, respectively and in the *BRCA*-mutated population DCR 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-g*BRCA*m PSR ovarian cancer patients*

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

The primary endpoint was investigator-assessed PFS 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 final overall survival analysis (DCO 17 September 2021), the OS data were 52.3% 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)
OS (52.3% maturity) (DCO 17 September 2021)	
Number of events: total number of patients (%)	146: 279 (52.3)
Median OS (95% CI), months[a]	32.7 (29.5, 35.3)

[a] Calculated using the Kaplan-Meier technique.
Confidence intervals for median PFS and OS were derived based on Brookmeyer Crowley method.
bd Twice daily; PFS Progression-free survival; OS Overall survival, DCO Data cut off; CI Confidence interval.

First-line maintenance treatment of 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 and safety 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) versus placebo plus bevacizumab for the maintenance treatment of advanced (FIGO Stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer following first-line platinum-based chemotherapy and bevacizumab. Treatment with bevacizumab was for a total of up to 15 months/22 cycles, including the period given with chemotherapy and given as maintenance.

The study randomised 806 patients (2:1 randomisation: 537 olaparib/bevacizumab: 269 placebo/bevacizumab) who had no evidence of disease (NED) due to complete surgical resection, or who were in complete response (CR), or partial response (PR) following completion of first-line platinum-containing chemotherapy and bevacizumab. Patients had completed a minimum of 4 and a maximum of 9 cycles, with the majority (63%) having received 6 cycles of first line platinum-taxane based chemotherapy, including a minimum of 2 cycles of bevacizumab in combination with the 3 last cycles of chemotherapy. The median number of bevacizumab cycles prior to randomisation was 5. Patients were stratified by first-line treatment outcome (timing and outcome of cytoreductive surgery and response to platinum-based chemotherapy) and t*BRCA*m 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 until progression of the underlying disease, unacceptable toxicity or for up to 2 years. Patients who in the opinion of the treating physician could derive further benefit from continuous treatment could be treated beyond 2 years.

Demographic and baseline characteristics were well balanced between both arms in the ITT population and in the biomarker-defined sub-groups by t*BRCA*m (prospectively and retrospectively defined), GIS and HRD status (defined in this study by a combination of both biomarkers). 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 63% having complete cytoreduction at initial or interval debulking surgery and 37% having residual macroscopic disease. Thirty percent (30%) of patients in both arms were t*BRCA*m at screening. Demographic and baseline characteristics in the biomarker sub-groups were consistent with those in the ITT population. In the HRD-positive subgroup, 65% of patients had complete cytoreduction and 35% of patients had residual macroscopic disease. In the overall patient population enrolled, 30% of patients in both arms were t*BRCA*m (deleterious/pathogenic mutation) at screening by local testing and for 4% of patients the *BRCA*m status was unknown. Retrospective analysis of available clinical samples was conducted in 97% of patients to confirm t*BRCA*m status and investigate genomic instability score as described above. Among non-t*BRCA*m patients, 29% (19% of the overall population) had positive GIS pre-defined in this study as composite score ≥42. When t*BRCA*m status and positive GIS were combined, patients with HRD-positive, HRD-negative and HRD unknown status in their tumours represented 48%, 34% and 18% of the overall patient population.

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). This was consistent with a BICR analysis of PFS. However, patients defined as biomarker-positive (t*BRCA*m, GIS, HRD status positive defined as t*BRCA*m and/or GIS positive) derived most of the benefit.

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).

Final analysis of OS (DCO 22 March 2022, 55.6% maturity) in the overall population demonstrated an HR of 0.92 (95% CI 0.76 to 1.12; p=0.3947; median 56.4 months for olaparib/bevacizumab vs 51.6 months for placebo/bevacizumab) which numerically favoured the olaparib/bevacizumab arm but was not statistically significant. Sixty-seven percent (67%) of patients in the olaparib/bevacizumab arm and 80.7% in the placebo/bevacizumab arm received subsequent therapy and of these patients, 29.2% and 56.7% in the olaparib/bevacizumab and placebo/bevacizumab arms, respectively, received a PARP

inhibitor. In the HRD status positive patients (t*BRCA*m and/or GIS), there was a clinically meaningful improvement in OS with olaparib/bevacizumab arm vs placebo/bevacizumab arm (see Table 6).

In the t*BRCA*m as randomised subgroup (241/806 patients) median PFS for the olaparib/bevacizumab arm was 37.2 months vs 22.0 months for the placebo/bevacizumab arm (HR=0.34, 95% CI 0.23,0.51). At the final overall survival analysis (DCO 22 March 2022), the t*BRCA*m as randomised subgroup demonstrates a clinically meaningful reduction in the risk of death for olaparib/bevacizumab compared to placebo/bevacizumab (HR 0.63; 95% CI 0.41, 0.97).

Efficacy results in other biomarkers subgroup analyses based on retrospectively analysed tumour samples are presented in Table 6.

Table 6 Summary of key efficacy findings for patients with homologous recombination deficiency (HRD) positive status defined by either t*BRCA*m and/or GIS in advanced ovarian cancer in PAOLA-1

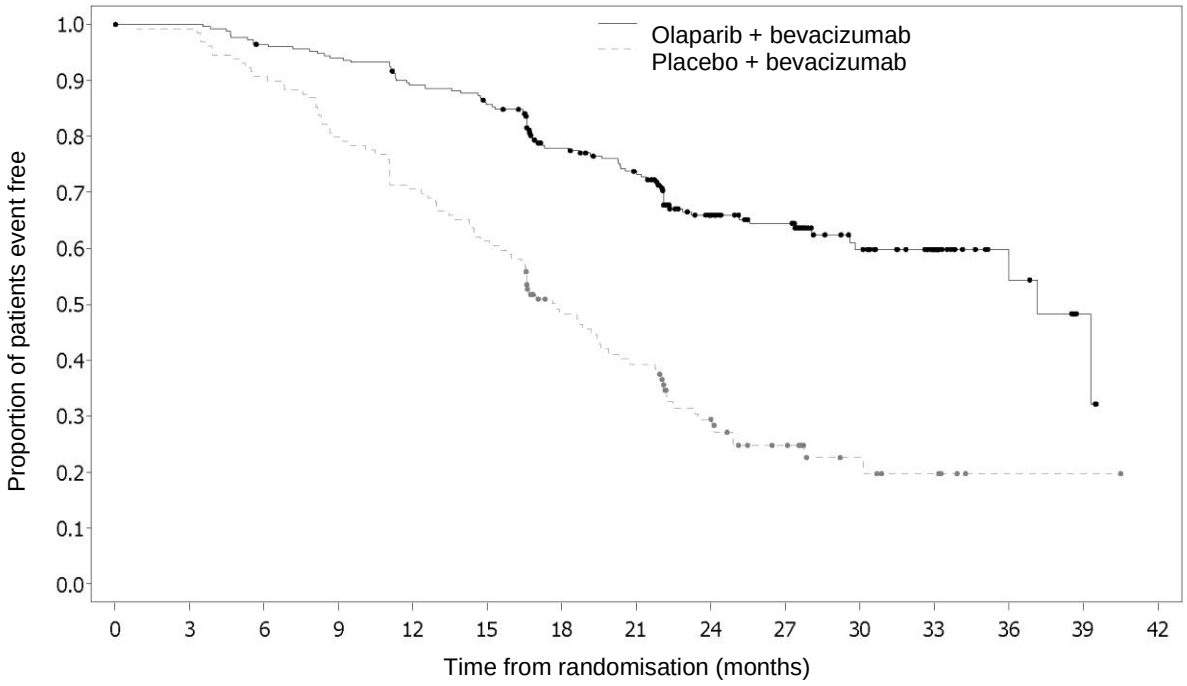
[a]

	t*BRCAm*[*, c] (n=235)		GIS positive (HRD positive excluding t*BRCA*m) [*, d] (n=152)		HRD positive[*] (n=387)	
	Olaparib/ bevacizumab	**Placebo/ bevacizumab**	**Olaparib/ bevacizumab**	**Placebo/ bevacizumab**	**Olaparib/ bevacizumab**	**Placebo/ bevacizumab**
PFS, investigator assessment (46% maturity) DCO 22 March 2019[a]						
Number of events: Total number of patients (%)	44/158 (28)	52/77 (68)	43/97 (44)	40/55 (73)	87/255 (34)	92/132 (70)
Median time (months)	37.2	18.8	28.1	16.6	37.2	17.7
HR (95% CI[b]	0.28 (0.19, 0.42)		0.43 (0.28, 0.66)		0.33 (0.25, 0.45)	
PFS2, investigator assessment (40 % maturity) DCO 22 March 2020						
Number of events: Total number of patients (%)	44/158 (28)	37/77 (48)	41/97 (50)	33 /55 (60)	85 /255 (33)	70/132 (53)
Median time (months)	NR	42.2	50.3	30.1	50.3	35.4
HR (95% CI[b]	0.53 (0.34, 0.82)		0.60 (0.38, 0.96)		0.56 (0.41, 0.77)	
Final OS (55.6% maturity) DCO 22 March 2022						

	t*BRCAm*[*, c] (n=235)		GIS positive (HRD positive excluding t*BRCA*m) [*, d] (n=152)		HRD positive[*] (n=387)	
	Olaparib/ bevacizumab	**Placebo/ bevacizumab**	**Olaparib/ bevacizumab**	**Placebo/ bevacizumab**	**Olaparib/ bevacizumab**	**Placebo/ bevacizumab**
Number of events: Total number of patients (%)	49/158 (31.0)	37/77 (48.1)	44/97 (45.4)	32/55 (58.2)	93/255 (36.5)	69/132 (52.3)
Median time (months)	75.2	66.9	NR	52.0	75.2	57.3
HR (95%) CI[b]	0.57 (0.37, 0.88)		0.71 (0.45, 1.13)		0.62 (0.45, 0.85)	
Percentage of patients alive at 5 years	72.0	51.6	54.7	44.2	65.5	48.4

* Pre-planned subgroup
[a] Based on Kaplan-Meier estimates, the proportion of patients that were progression free at 12 and 24 months were 89% and 66% for olaparib/bevacizumab versus 71% and 29% for placebo/bevacizumab.
[b] A value <1 favours olaparib. The analysis was performed using a Cox proportional hazards model stratified by first line treatment outcome at screening and screening laboratory t*BRCA* status.
[c] t*BRCA*m status by Myriad
[d] HRD positive excluding t*BRCA*m was defined as Genomic instability score (GIS) by Myriad ≥42 (pre-specified cut-off)
CI Confidence interval; HR Hazard ratio; NR not reached

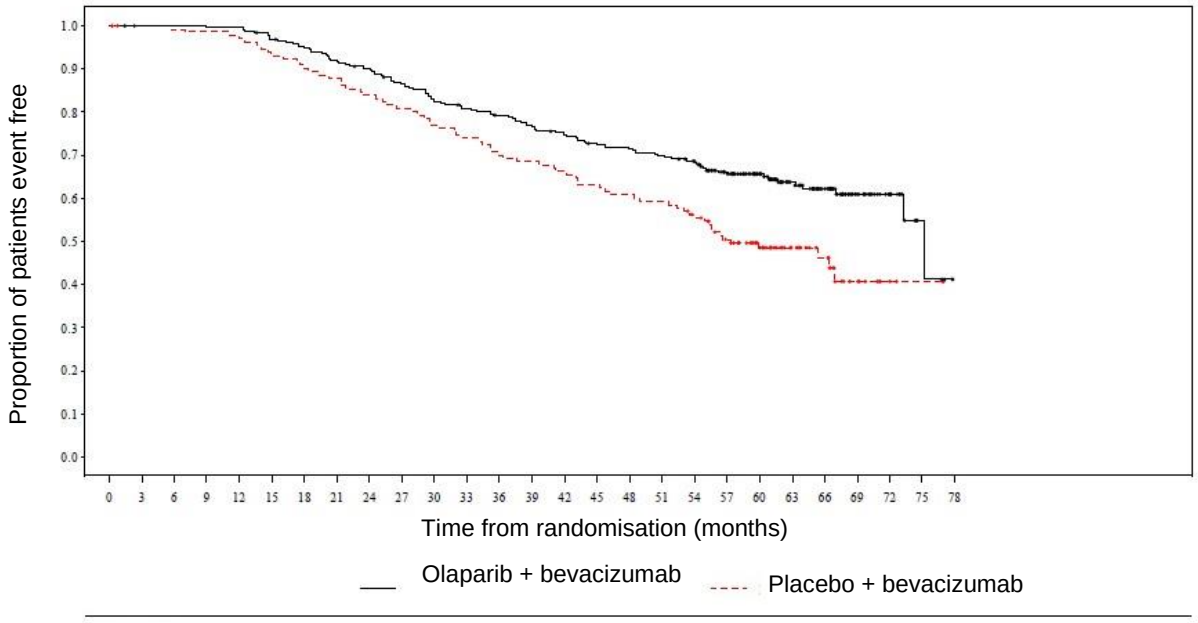
Figure 5 PAOLA-1: Kaplan-Meier plot of PFS for patients with advanced ovarian cancer defined as HRD positive in PAOLA-1 (46% maturity - investigator assessment)



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

Figure 6 PAOLA-1: Kaplan-Meier Plot, Final Overall Survival by HRD Status Positive (including *tBRCAm*) (DCO 22 March 2022)



Number of patients at risk:

255	253	253	252	252	244	238	231	225	215	205	200	195	189	183	176	174	170	164	142	116	83	62	32	17	4	0	Olaparib + bevacizumab
132	130	129	128	126	121	117	114	109	105	100	96	91	89	86	82	79	77	70	59	44	29	21	9	2	1	0	Placebo + bevacizumab

Adjuvant treatment of *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 7.

Table 7 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
	0/I	0

Stage/feature		Points
Pathologic Stage (post-treatment)	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 ≥2 cm 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. Patients with HR positive (ER and/or PgR positive) tumours also received endocrine therapy.

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), 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*BRCA*m 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 and clinically meaningful 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 and clinically meaningful 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 8 and for the subgroups by stratification factors in Table 9.

Table 8 Summary of key efficacy findings in HER2-negative high risk early breast cancer patients with a *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,]	0.58 (0.41, 0.82)	
p-value (2-sided) [b]	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]	0.57 (0.39, 0.83)	
p-value (2-sided) [b]	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		
Number of events/total number of patients (%)	75/921 (8)	109/915 (12)
HR (99% 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.
p-value from a stratified log-rank test.
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 7 Kaplan-Meier plot of IDFS in patients with HER2-negative high risk early breast cancer patients with a *BRCA* mutation

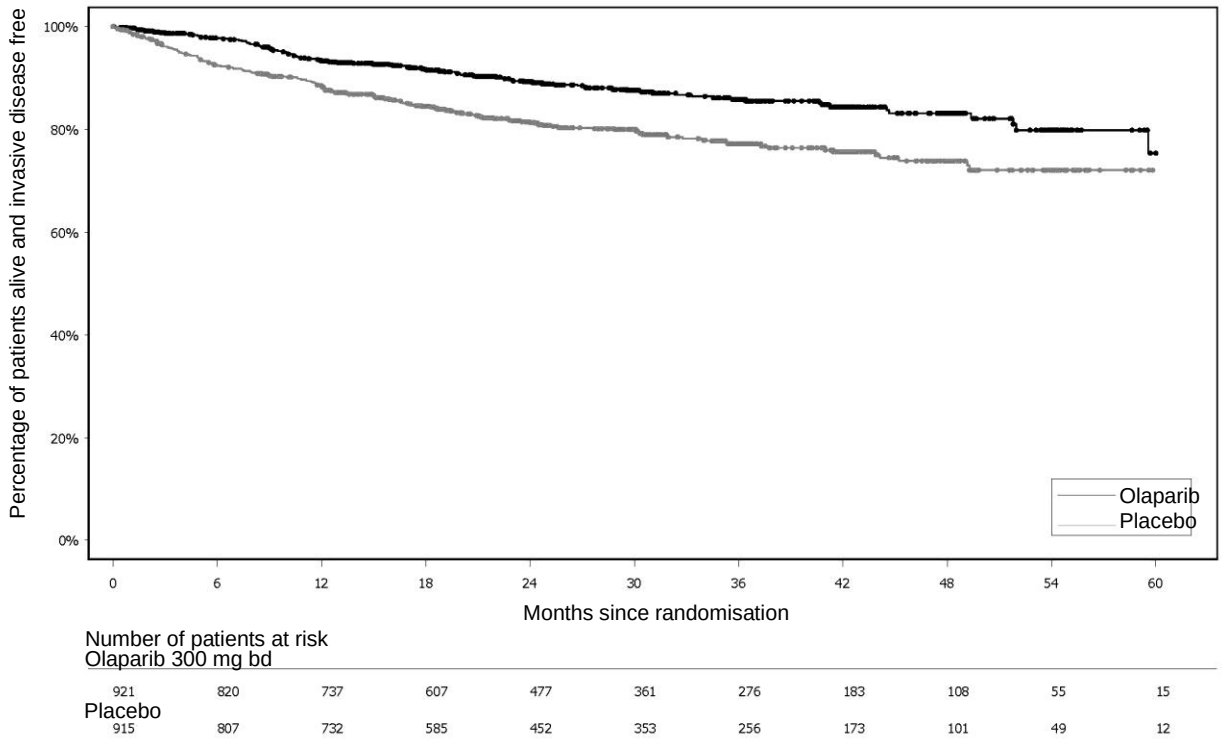


Figure 8 Kaplan-Meier plot of DDFS in patients with HER2-negative high risk early breast cancer patients with a *BRCA* mutation.

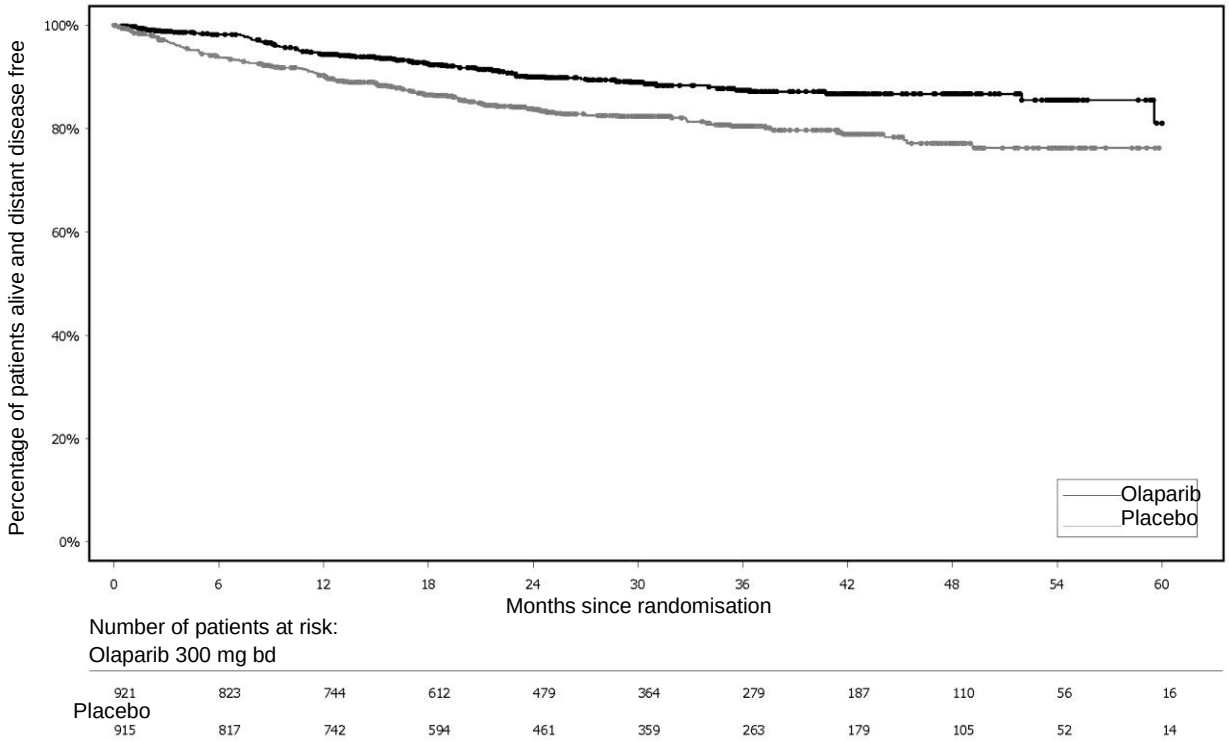


Figure 9 Kaplan-Meier plot of OS in patients with HER2-negative high risk early breast cancer patients with a *BRCA* mutation

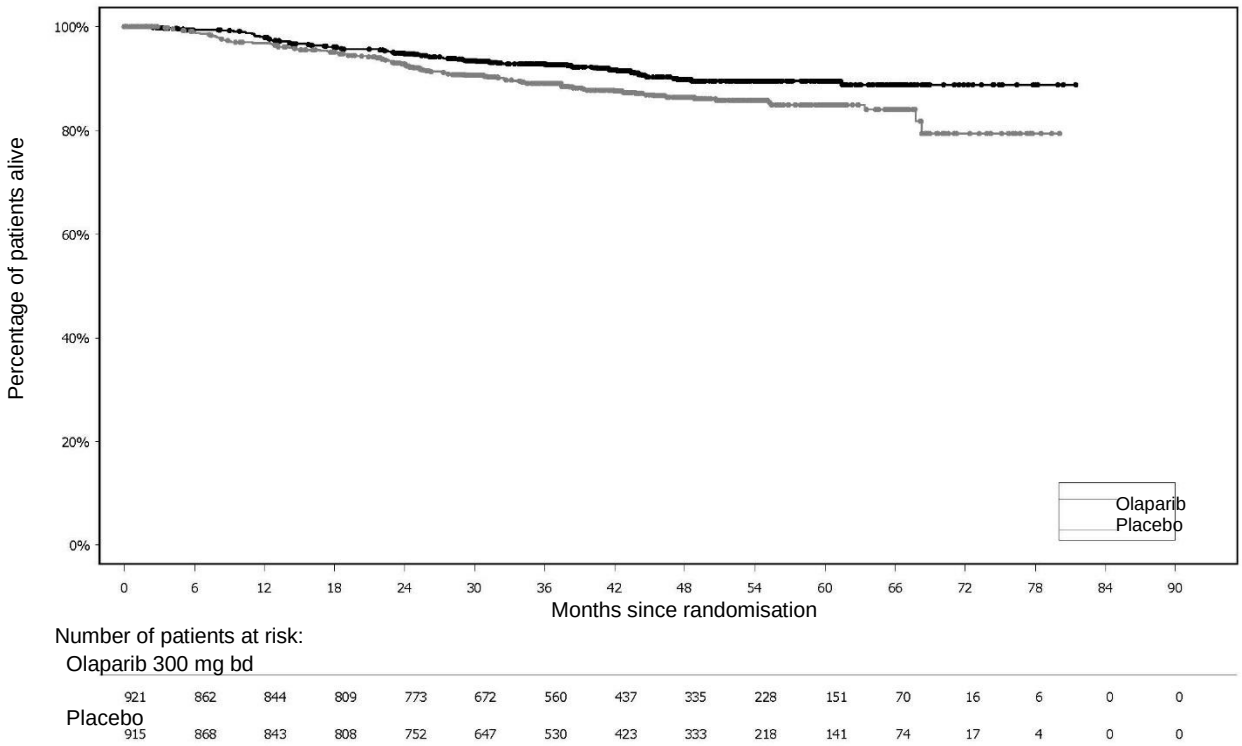


Table 9 IDFS by subgroup in HER2-negative high risk early breast cancer patients with a *BRCA* mutation in OlympiA

	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					
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) and the EORTC QLQ-C30 (to assess global health status/QoL, functioning and GI symptoms) which were completed at baseline prior to randomisation and every 6 months after randomisation for a period of 2 years. A 3-point difference in FACIT-fatigue score and a 10-point difference in EORTC QLQ-C30 scores were considered clinically meaningful. Patient reported outcome data indicate no clinically meaningful differences among olaparib-treated patients as compared to placebo when measured using FACIT-Fatigue and EORTC QLQ-C30 global health status/QoL and functioning scales. Olaparib-treated patients had worse EORTC QLQ-C30 nausea/vomiting scores during the initial assessments (at 6 and 12 months) which returned to baseline levels and were comparable to placebo-treated patients at the later assessments (18 and 24 months).

VIOLETTE study in metastatic triple negative breast cancer

VIOLETTE was a Phase II, open-label, multicentre study to assess the safety and efficacy of agents targeting DNA damage repair in combination with olaparib versus olaparib monotherapy in the treatment of second or third line metastatic TNBC patients stratified by alterations in HRR-related genes (including *BRCA1/2*).

Thirty-six patients with t*BRCA*m were enrolled to the olaparib monotherapy arm. Confirmed responses were reported in 11 of 33 patients receiving olaparib monotherapy (ORR, 33% CI 18-52%); median PFS was 6.1 months (95% CI, 5.1 to 8.9 months). Four patients had somatic *BRCA*m tumours and 2 out of 4 (50%) had confirmed responses on olaparib.

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

*OlympiAD in HER2-negative metastatic breast cancer patients with a g*BRCA *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 g*BRCA*m 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 neo adjuvant, 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 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 10).

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.

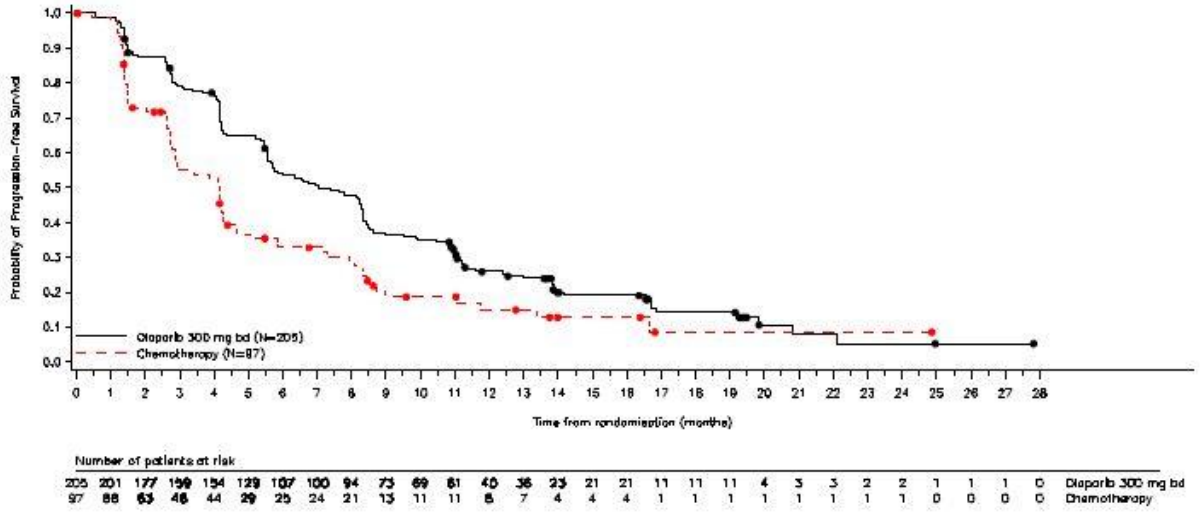
Table 10 Summary of key efficacy findings for patients with g*BRCA*m HER2-negative metastatic breast cancer in OlympiAD

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

a Physician's choice of chemotherapy consisting of either capecitabine, eribulin or vinorelbine.
b Approximately a tenth of patients in the physician's choice group (8/97; 8.2%) received a subsequent PARP inhibitor

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

Figure 10 OlympiAD: Kaplan-Meier plot of PFS in patients with g*BRCA*m 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.

<u>Maintenance following first-line treatment of germline *BRCA*-mutated metastatic adenocarcinoma of the pancreas</u>

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 *BRCA*m 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). A clinically meaningful and statistically significant improvement in TFST and TDT was observed for olaparib-treated patients.

Table 11 Summary of key efficacy findings for patients with g*BRCA*m 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)	46:62 (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	
PFS2 (60% maturity)		
Number of events: Total number of patients (%)	52:92 (57)	40:62 (65)
Median time (months)	16.9	9.3
HR (95% CI)[a,b]	0.66 (0.43-1.02)	
P value[*] (2-sided)	p=0.0613	
TFST (82% maturity)		
Number of events: Total number of patients (%)	72:92 (78	55:62 (89)
Median time (months)	9.0	5.4
HR (95% CI)[b,c]	0.44 (0.30-0.66)	
P value[*] (2-sided)	p<0.0001	
TDT (88% maturity)		
Number of events: Total number of patients (%)	77:92 (84)	59:62 (95)
Median time (months)	7.5	3.8
HR (95% CI)[b]	0.43 (0.29-0.63)	
P value[*] (2-sided)	p<0.0001	
ORR		
Number of objective responders: total number of patients with measurable disease at baseline (%)	18:78 (23.1)	6:52 (11.5)
Complete response (%)	2 (2.6)	0
Partial response (%)	16 (20.5)	6 (11.5)
Odds ratio (95% CI)	2.30 (0.89, 6.76)	
P value[*] (2-sided)	p=0.1028	
DoR		
Median time (months) (95% CI)	24.9 (14.75, NC)	3.7 (2.10, NC)

[a] A value <1 favours olaparib.

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

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

[*] Not controlled for multiplicity.

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

Figure 11 POLO: Kaplan-Meier plot of PFS for patients with g*BRCA*m metastatic adenocarcinoma of the pancreas (68% maturity – BICR)

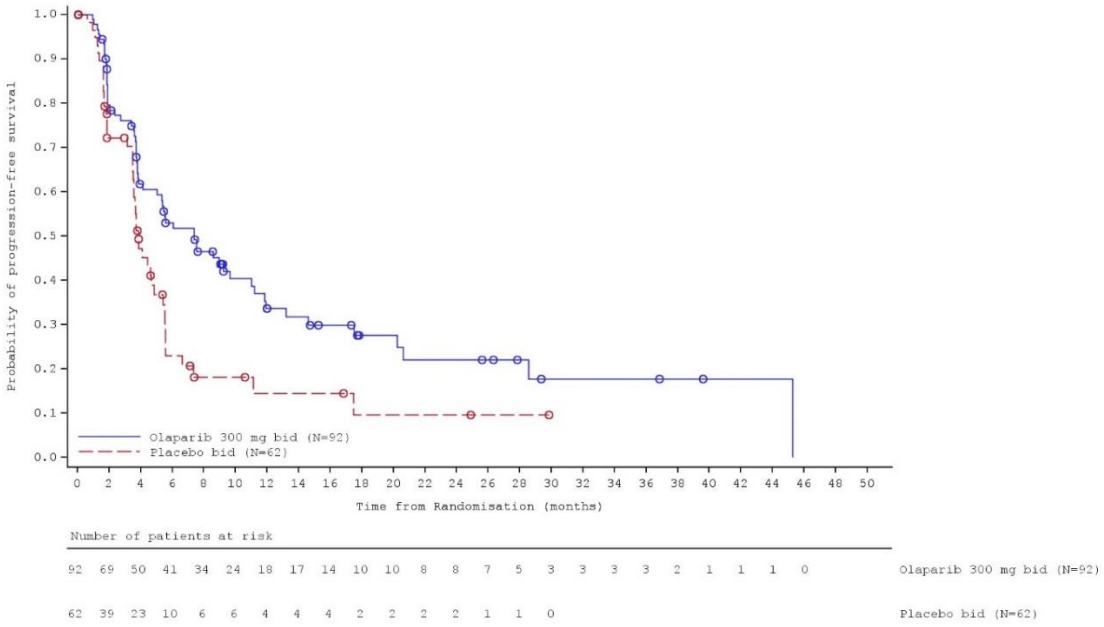
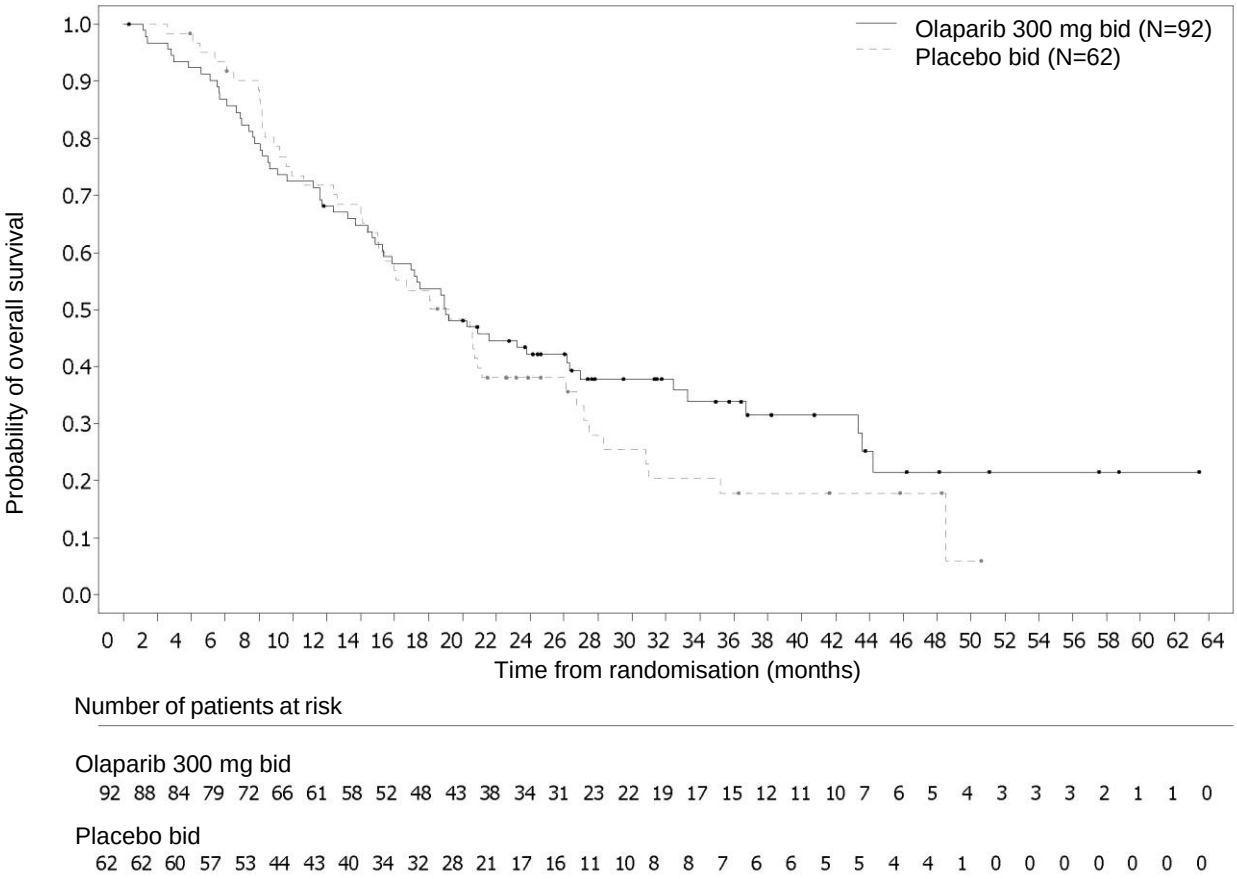


Figure 12 POLO: Kaplan-Meier plot of OS for patients with g*BRCA*m metastatic adenocarcinoma of the pancreas (70% maturity)



Patient-reported HRQoL was assessed using the EORTC QLQ-C30 and its pancreatic cancer module (EORTC QLQ-PAN26). A 10-point change was pre-defined as clinically meaningful on a 0-100 points global HRQoL scale. The adjusted mean change from baseline in global HRQoL score across all timepoints up to 6 months was -1.20 ± 1.42 in the olaparib group (n=84) and 1.27 ± 1.95 in the placebo group (n=54), with a corresponding estimated difference of −2.47 points (95% CI, −7.27 to 2.33), demonstrating no worsening in olaparib treated patients and no clinically meaningful differences in global HRQoL over the treatment period between arms. Median time to clinically meaningful deterioration (≥10 points decrease from baseline sustained at the next timepoint) in global HRQoL score was numerically longer in the olaparib arm compared to placebo (HR 0.72; 95% CI: 0.41-1.27; medians: 21.2 months olaparib vs. 6.0 months placebo). Over the treatment period, the proportion of patients with clinically significant improvement (≥10 points increase from baseline) in global HRQoL score was 29.2% in the olaparib arm and 22.4% in the placebo arm.

BRCA--mutated metastatic castration-resistant prostate cancer (mCRPC)

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 mCRPC.

To be eligible, patients had 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, as detected by prospective central testing using a clinical trial assay. Cohort A comprised patients with deleterious or suspected deleterious mutations in *BRCA1, BRCA2* or *ATM*. Although patients with gene mutations other than *BRCA1/2* were enrolled in the trial, LYNPARZA is not indicated for the treatment of patients with gene mutations other than *BRCA1/2* since favourable benefit-risk is not established beyond *BRCA1/2*.

All patients continued on a luteinising hormone releasing hormone (LHRH) analogue or had prior bilateral orchiectomy.

A total of 245 patients were randomised in Cohort A (162 olaparib and 83 comparator). Randomisation was stratified by prior taxane use and evidence of measurable disease. Treatment was continued until disease progression. Patients randomised to the NHA comparator were given the option to switch to olaparib upon confirmed radiological BICR progression.

Of the 160 patients with a *BRCA1* or *BRCA2* mutation enrolled in PROfound, 114 patients underwent retrospective testing to determine if the identified *BRCA1/2* mutation was germline or somatic in origin. Germline *BRCA1/2* mutations were identified in 63 patients, and for the remaining 51 patients, the *BRCA1/2* mutation was determined to be somatic in origin based on the absence of evidence of germline *BRCA1/2* mutation.

Demographics and baseline characteristics were generally well balanced between the olaparib and comparator arms in patients with *BRCA1/2* mutations. Median age was 68 years and 67 years in the olaparib and comparator arms, respectively. Prior therapy in the olaparib arm was 71% taxane, 41% enzalutamide, 37% abiraterone acetate and 20% both enzalutamide and abiraterone acetate. Prior therapy in the comparator arm was 60% taxane, 50% enzalutamide, 36% abiraterone acetate and 14% both enzalutamide and abiraterone acetate. Fifty-eight percent (58%) of patients in the olaparib arm and 55% in the comparator arm had measurable

disease at study entry. The proportion of patients with bone, lymph node, liver and respiratory metastases was 89%, 62%, 12% and 23%, respectively in the olaparib arm and 86%, 71% 17% and 16%, respectively in the comparator arm. Most patients in both treatment arms had an ECOG of 0 or 1 (93%). Baseline pain scores (BPI-SF worst pain) were 0-<2 (52%), 2-3 (10%) or >3 (34%) in the olaparib arm and 0-<2 (45%), 2-3 (7%) or >3 (45%) in the comparator arm. Median baseline PSA was 57.48 µg/L in the olaparib arm and 103.95 µg/L in the comparator 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, time to pain progression (TTPP) and overall survival (OS).

The study demonstrated a clinically meaningful and statistically significant improvement in BICR-assessed rPFS and final OS for olaparib vs comparator in Cohort A, attributable to patients with *BRCA1/2* gene mutations. Results for patients with *BRCA1/2* mutations are presented in Table 12.

Sensitivity analyses showed similar efficacy in patients for whom mutations could be identified using the Foundation Medicine F1CDx assay, the Foundation Medicine F1 Liquid CDx assay, or the Myriad BRACAnalysis CDx assay.

Table 12 Summary of key efficacy findings in patients with *BRCA1/2*-mutated mCRPC in PROfound

	Olaparib 300 mg bd (N=102)	**Investigators choice of NHA (N=58)**
rPFS by BICR[a,b,c] DCO 4 June 2019		
Number of events/total number of patients (%)	62/102 (61)[c]	51/58 (88)[c]
Median rPFS (95% CI) [months]	9.8 (7.6, 11.3)	3.0 (1.8, 3.6)
HR (95% CI)[c]	0.22 (0.15, 0.32)	
Confirmed ORR by BICR[a]		
Number of objective responders/total number of patients with measurable disease at baseline (%)	25/57 (44)	0/33 (0)
Odds ratio (95% CI)	NC (NC, NC)	
OS[a] DCO 20 March 2020[c]		
Number of events/total number of patients (%)	53/102 (52)	41/58 (71)
Median OS (95% CI) [months]	20.1 (17.4, 26.8)	14.4 (10.7, 18.9)
HR (95% CI)	0.63 (0.42, 0.95)	
Time to pain progression[a, d]		
Number of events/total number of patients (%)	9/102 (9)	10/58 (17)
Median (95% CI) [months]	NC (NC, NC)	
HR (95% CI)	0.27 (0.11, 0.69)	

[a] Not controlled for multiplicity when tested in the *BRCA1/2* subgroup (but was controlled for multiplicity when tested in Cohort A, which showed statistically significant results)
[b] rPFS 71% maturity
[c] The HR and CI were calculated using a Cox proportional hazards model that contains terms for treatment, *BRCA* mutation (positive, negative) and interaction term of treatment and *BRCA* mutation.
[d] 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.

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

Figure 13 *BRCA1/2*m patients: Kaplan-Meier plot of rPFS (by BICR)

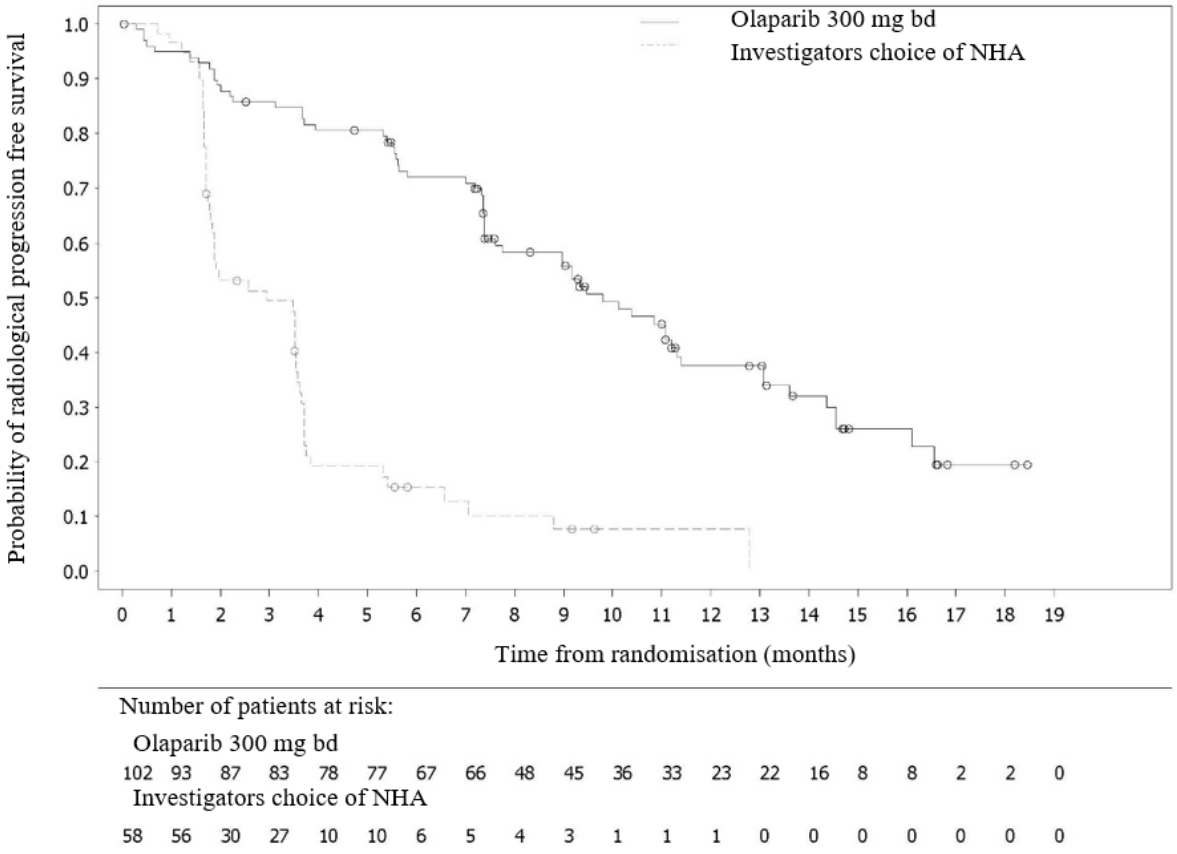
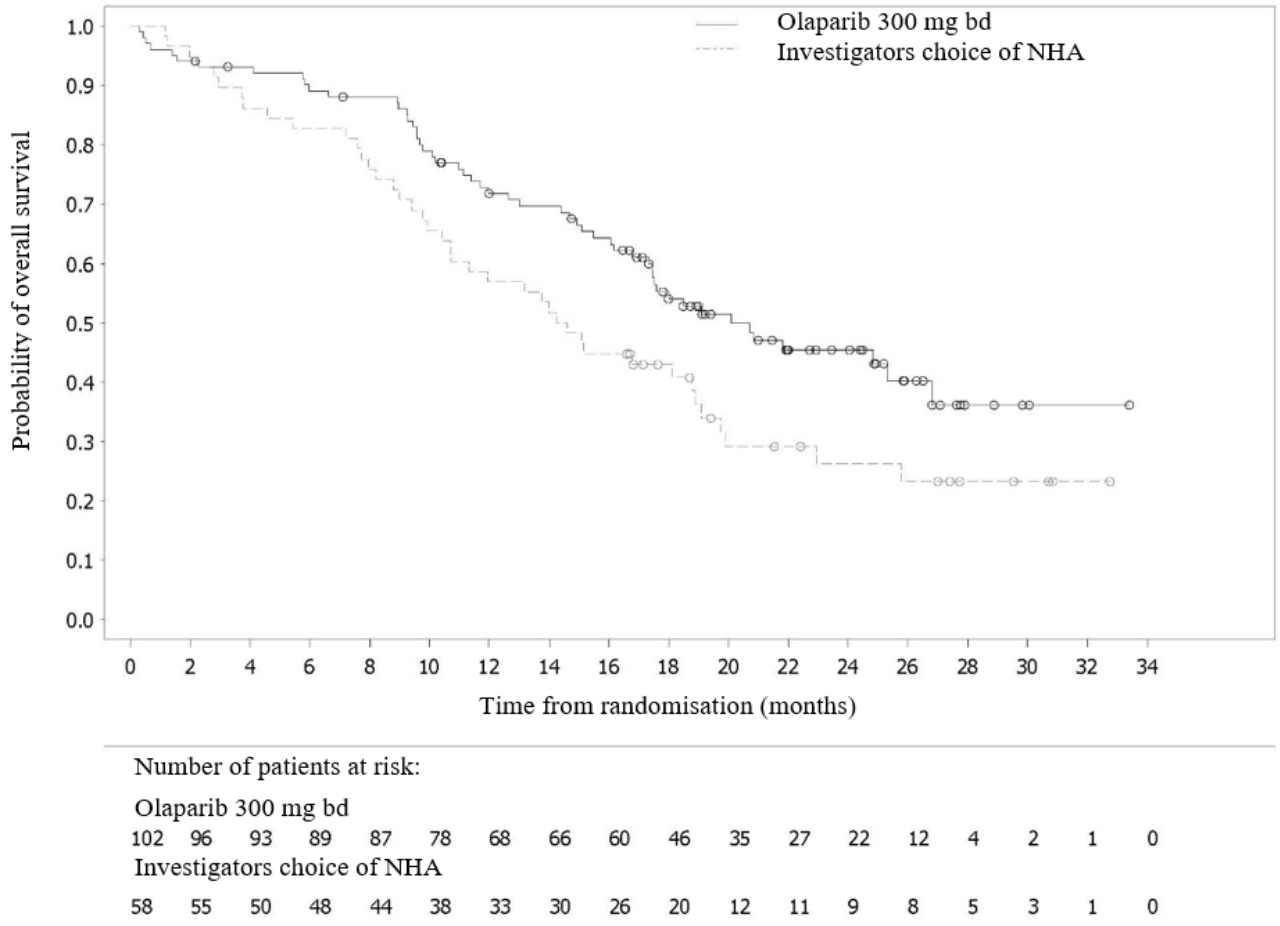


Figure 14 *BRCA1/2*m patients: Kaplan-Meier plot of OS 3



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 two randomized, double-blind, placebo-controlled trials in the first-line mCRPC setting (PROpel) and in patients who had received prior taxane (Study 8) in the mCRPC setting. In both studies, LYNPARZA was used in combination with abiraterone and prednisone or prednisolone.

PROpel Study in the first-line 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. Of the patients tested, 198 and 118 were HRRm as determined by ctDNA and tumour tissue, respectively. 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). 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. 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 final prespecified analysis, the percentage of patients alive at 36 months in the olaparib/abiraterone arm and the placebo/abiraterone arm was 57% and 50%, respectively.

Table 13 Summary of key efficacy findings in the first-line 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	
Final OS (48% maturity) (12 October 2022)		
Number of events/total number of patients (%)	176/399 (44.1)	205/397 (51.6)
Median time (95% CI) (months)[d]	42.1 (38.4, NC)	34.7 (31.0, 39.3)
HR (95% CI)[a]	0.81 (0.67, 1.00)	
p-value[b]	p=0.0544	
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 + abiraterone 1000 mg qd.

[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.

Figure 15 PROpel: Kaplan-Meier plot of rPFS

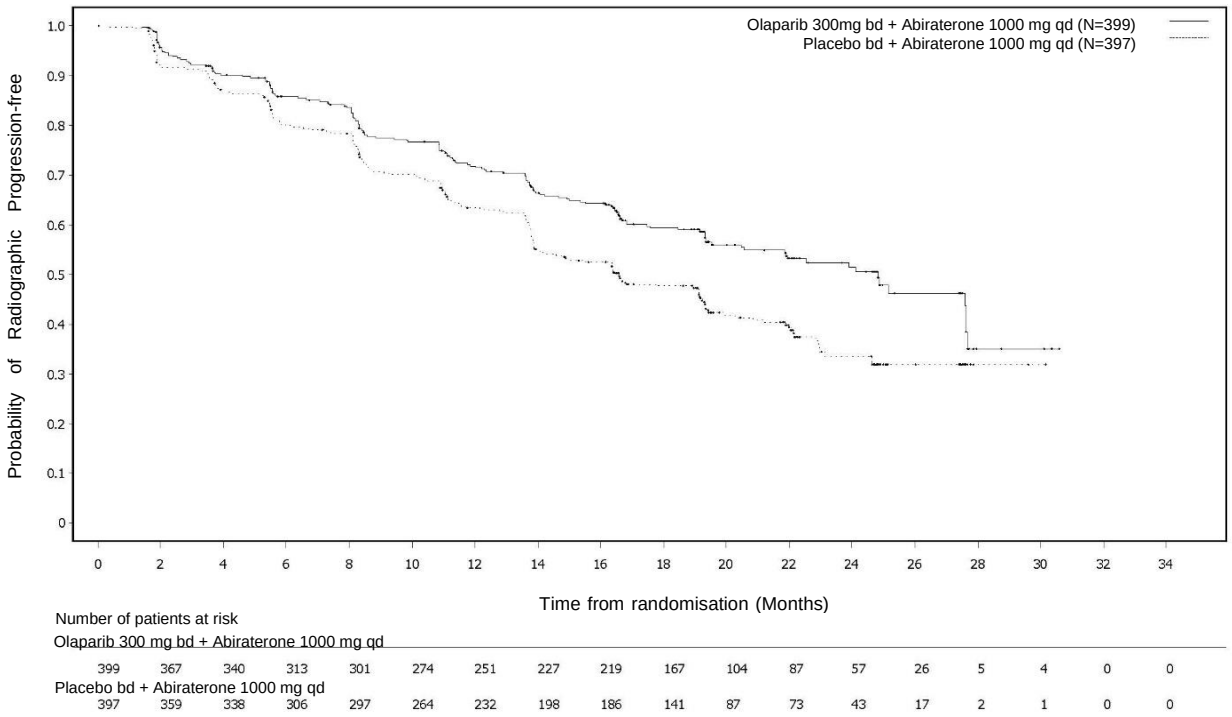
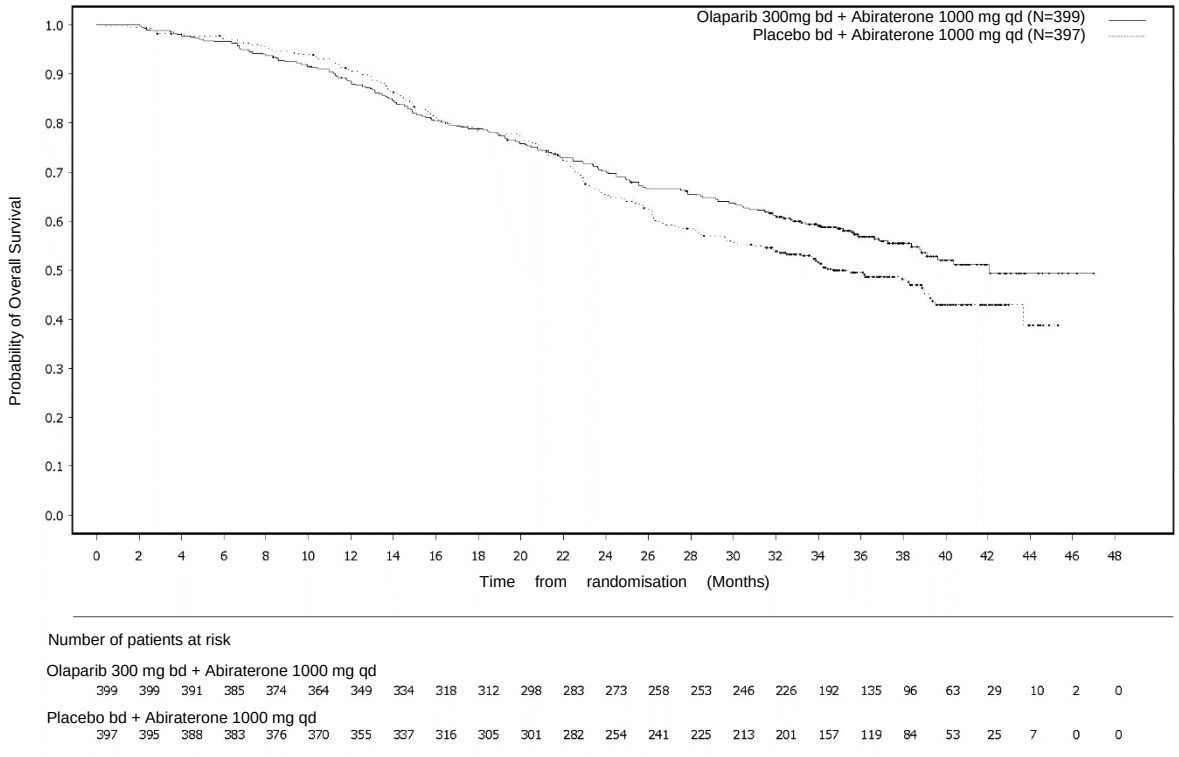


Figure 16 PROpel: Kaplan-Meier plot of OS



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.

Study 8 in patients who had received prior taxane in the mCRPC setting

Study 8 was a two part study. Part A was an open-label safety run-in study to assess the safety, tolerability and pharmacokinetics of olaparib when given in addition to abiraterone 1000 mg once daily. Part B was a Phase II, 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 and abiraterone in patients with mCRPC who had received up to two lines of prior chemotherapy including docetaxel but no prior exposure to NHA. Patients in both arms also received either prednisone or prednisolone 5 mg twice daily. Patients who discontinued docetaxel for toxicity reasons and without completing the full course were still eligible to enter this study provided they received at least 2 cycles of chemotherapy. All patients continued on a GnRH analogue or had bilateral orchiectomy. Of the 171 patients enrolled in Part B, 142 patients were randomised (1:1 randomisation; 71 olaparib/abiraterone:71 placebo/abiraterone). All of the randomised patients received at least one dose of study treatment.

The primary endpoint of the study (Part B) was rPFS determined by investigator using RECIST 1.1 (soft tissue) and PCWG-2 (bone). Secondary endpoints included PFS2, OS and TFST.

The study demonstrated a statistically significant and clinically meaningful improvement in the investigator-assessed rPFS olaparib/abiraterone arm compared to the placebo/abiraterone arm.

Subgroup analyses for subsets of patients based on demographic, baseline characteristics and pre-defined biomarker subgroups showed generally consistent reductions in the risk of radiological progression or death in olaparib/abiraterone-treated patients across the subgroups, in patients with or without HRRm.

The results from the secondary endpoints, including PFS2, TFST and OS also favoured olaparib/abiraterone arm.

Table 14 Summary of key efficacy findings in patients who had received prior taxane in the mCRPC setting in Study 8

	Olaparib/abiraterone N=71	**Placebo/abiraterone N=71**
rPFS (by investigator assessment)		
Number of events/total number of patients (%)	47/71 (65)	54/71 (76.1)
Median time (months)	14	8.2
HR (95% CI)	0.65 (0.44, 0.97)	
p-value (2-sided)	p=0.034	
OS (62% maturity)		
Number of events/total number of patients (%)	43/71 (60.6)	45/71 (63.4)
Median time (months)	23	21
HR (95% CI)	0.91 (0.60, 1.38)	
p-value (2-sided)	p=0.662	
PFS2		
Number of events/total number of patients (%)	37/71 (52.1)	45/71 (63.4)
Median time (months)	23.3	18.5
HR (95% CI)	0.79 (0.51, 1.22)	
p-value (2-sided)	p=0.280	
TFST		

	Olaparib/abiraterone N=71	**Placebo/abiraterone N=71**
Number of events/total number of patients (%)	57/71 (80.3)	58/71 (81.7)
Median time (months)	13.5	9.7
HR (95% CI)	0.78 (0.54, 1.13)	
p-value (2-sided)	p=0.189	

The mean change from baseline analyses of PRO measures (FACT-P total score, BPI-SF worst pain and worst bone pain scores) showed no detriment in the olaparib/abiraterone arm compared with the placebo/abiraterone arm.

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 .

Retreatment on relapse

There are no data to support retreatment with olaparib as maintenance following subsequent relapse.

5.2 PHARMACOKINETIC PROPERTIES

Pharmacokinetics

Olaparib displays high inter-patient variability in PK parameters, including C_{max}, AUC, Vd and CL/F.

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 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 fluorophenyl 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-opened 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} = 76µM), however, this is unlikely to be of clinical significance.

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

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, bodyweight, tumour location or race (including White and Japanese patients) were not significant covariates.

Effect on 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

Genotoxicity

Olaparib showed no mutagenic potential in bacterial cells, 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

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

4 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C

6.5 NATURE AND CONTENTS OF CONTAINER

Alu/Alu non-perforated blister containing 8 tablets. Cartons of 56 tablets (7 blisters).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Return unused and expired medicines to your local pharmacy for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

AstraZeneca Limited
PO Box 87453
Meadowbank
Auckland 1742.
Telephone: 0800 684 432

9 DATE OF FIRST APPROVAL

15 August 2019

10. DATE OF REVISION OF TEXT

7 March 2025

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4 & 4.8	Drug-induced liver injury is added.