

1. NAME OF THE MEDICINAL PRODUCT

Lynparza 100 mg film-coated tablets

Lynparza 150 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lynparza 100 mg film-coated tablets: Each film-coated tablet contains 100 mg olaparib.

Lynparza 150 mg film-coated tablets: Each film-coated tablet contains 150 mg olaparib.

Excipient with known effect:

This medicinal product contains 0.24 mg sodium per 100 mg tablet and 0.35 mg sodium per 150 mg tablet, i.e. essentially “sodium-free”.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Lynparza 100 mg film-coated tablets:

Yellow to dark yellow, oval, bi-convex tablet, debossed with ‘OP100’ on one side and plain on the other side.

Lynparza 150 mg film-coated tablets:

Green to green/grey, oval, bi-convex tablet, debossed with ‘OP150’ on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ovarian cancer

Lynparza is indicated as monotherapy for the:

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

Lynparza in combination with bevacizumab is indicated for the:

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

Breast cancer

Lynparza is indicated as monotherapy for the:

- 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).
- treatment of adult patients with germline *BRCA1/2*-mutations, who have HER2 negative locally advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments (see section 5.1).

Patients with hormone receptor (HR)-positive breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy.

Adenocarcinoma of the pancreas

Lynparza is indicated as monotherapy for the:

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

Prostate cancer

Lynparza is indicated as monotherapy for the:

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

4.2 Posology and method of administration

Treatment with Lynparza should be initiated and supervised by a 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

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

Before Lynparza treatment is initiated for adjuvant treatment of HER2 negative high risk early breast cancer, patients must have confirmation of deleterious or suspected deleterious *gBRCA1/2* mutation using a validated test (see section 5.1).

Detection of *BRCA1/2* mutations

Before Lynparza treatment is initiated for first-line maintenance treatment of high-grade epithelial ovarian cancer (EOC), fallopian tube cancer (FTC) or primary peritoneal cancer (PPC), patients must have confirmation of deleterious or suspected deleterious germline and/or somatic mutations in the breast cancer susceptibility genes (*BRCA*) 1 or 2 using a validated test.

There is no requirement for *BRCA1/2* testing prior to using Lynparza for the maintenance treatment of relapsed EOC, FTC or PPC who are in a complete or partial response to platinum-based therapy.

For germline breast cancer susceptibility genes (*gBRCA1/2*) mutated human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer, patients must have confirmation of a deleterious or suspected deleterious *gBRCA1/2* mutation before Lynparza treatment is initiated. *gBRCA1/2* mutation status should be determined by an experienced laboratory using a validated test method. Data demonstrating clinical validation of tumour *BRCA1/2* tests in breast cancer are not currently available.

Genetic counselling for patients tested for mutations in *BRCA1/2* genes should be performed according to local regulations.

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.

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

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

Posology

Lynparza is available as 100 mg and 150 mg tablets.

The recommended dose of Lynparza in monotherapy or in combination with bevacizumab 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.

Lynparza monotherapy

Patients with platinum-sensitive relapsed (PSR) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy should start treatment with Lynparza no later than 8 weeks after completion of their final dose of the platinum-containing regimen.

Lynparza in combination with bevacizumab

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

Lynparza in combination with endocrine therapy

Please refer to the full product information of the endocrine therapy combination partner(s) (aromatase inhibitor/anti-oestrogen agent and/or LHRH) for the recommended posology.

Duration of treatment

Monotherapy maintenance treatment of newly diagnosed advanced BRCA-mutated ovarian cancer:

Patients can continue treatment until radiological disease progression, unacceptable toxicity or for up to 2 years if there is no radiological evidence of disease after 2 years of treatment. Patients with evidence of disease at 2 years, who in the opinion of the treating physician can derive further benefit from continuous treatment, can be treated beyond 2 years.

Maintenance treatment of platinum sensitive relapsed ovarian cancer:

For patients with platinum sensitive relapsed high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer, it is recommended that treatment be continued until progression of the underlying disease or unacceptable toxicity.

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 Prescribing Information for bevacizumab for recommended dosing information (see section 5.1).

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

It is recommended that patients are treated for up to 1 year, or until disease recurrence, or unacceptable toxicity, whichever occurs first.

gBRCA1/2-mutated HER2-negative metastatic breast cancer:

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

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

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

HRR-gene mutated metastatic castration-resistant prostate cancer:

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

There are no efficacy or safety data on maintenance retreatment with Lynparza following first or subsequent relapse in ovarian cancer patients or on retreatment of breast cancer patients (see section 5.1).

Important differences in posology between Lynparza tablets and capsules

Lynparza tablets (100 mg and 150 mg) should not be substituted for Lynparza capsules (50 mg) on a milligram-to-milligram basis due to differences in the dosing and bioavailability of each formulation. Therefore, the specific dose recommendations for each formulation should be followed.

Missing dose

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

Dose adjustments for adverse reactions

Treatment may be interrupted to manage adverse reactions such as nausea, vomiting, diarrhoea, and anaemia and dose reduction can be considered (see section 4.8).

The recommended dose reduction is to 250 mg (one 150 mg tablet and one 100 mg tablet) twice daily (equivalent to a total daily dose of 500 mg).

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

Dose adjustments for 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 populations

Elderly

No adjustment in starting dose is required for elderly patients.

Renal impairment

For patients with moderate renal impairment (creatinine clearance 31 to 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) (see section 5.2).

Lynparza can be administered in patients with mild renal impairment (creatinine clearance 51 to 80 ml/min) with no dose adjustment.

Lynparza is not recommended for use in patients with severe renal impairment or end-stage renal disease (creatinine clearance \leq 30 ml/min), as safety and pharmacokinetics have not been studied in these patients. Lynparza may only be used in patients with severe renal impairment if the benefit outweighs the potential risk, and the patient should be carefully monitored for renal function and adverse events.

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).

Paediatric population

The safety and efficacy of Lynparza in children and adolescents have not been established. No data are available.

Method of administration

Lynparza is for oral use.

Lynparza tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Lynparza tablets may be taken without regard to meals.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Breast-feeding during treatment and for 1 month after the last dose (see section 4.6).

4.4 Special warnings and precautions for use

Haematological toxicity

Haematological toxicity has been reported in patients treated with Lynparza, including clinical diagnoses and/or laboratory findings of generally mild or moderate (CTCAE grade 1 or 2) anaemia, neutropenia, thrombocytopenia and lymphopenia. Patients should not start treatment with Lynparza until they have recovered from haematological toxicity caused by previous anticancer therapy (haemoglobin, platelet and neutrophil levels should be \leq 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 overall incidence of myelodysplastic syndrome/acute myeloid leukaemia (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 *BRC*A 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 olaparib in patients who developed MDS/AML varied from <6 months to >4 years.

If MDS/AML is suspected, the patient should be referred to a haematologist for further investigations, including bone marrow analysis and blood sampling for cytogenetics. If, following investigation for prolonged haematological toxicity, MDS/AML is confirmed, Lynparza should be discontinued and the patient treated appropriately.

Pneumonitis

Pneumonitis, including events with a fatal outcome, has been reported in <1.0% of patients treated with Lynparza in clinical studies. Reports of pneumonitis had no consistent clinical pattern and were confounded by a number of pre-disposing factors (cancer and/or metastases in lungs, underlying pulmonary disease, smoking history, and/or previous chemotherapy and radiotherapy). If patients present with new or worsening respiratory symptoms such as dyspnoea, cough and fever, or an abnormal chest radiologic finding is observed, Lynparza treatment should be interrupted and prompt investigation initiated. If pneumonitis is confirmed, Lynparza treatment should be discontinued and the patient treated appropriately.

Embryofoetal toxicity

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

Pregnancy/contraception

Lynparza should not be used during pregnancy. Women of childbearing potential must use two forms of reliable contraception before starting Lynparza treatment, during therapy and for 1 month after receiving the last dose of Lynparza. Two highly effective and complementary forms of contraception are recommended. Male patients and their female partners of childbearing potential should use reliable contraception during therapy and for 3 months after receiving the last dose of Lynparza (see section 4.6).

Interactions

Lynparza co-administration 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 sections 4.2 and 4.5).

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

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Clinical studies of olaparib in combination with other anticancer medicinal products, 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 medicinal products.

Combination of olaparib with vaccines or immunosuppressant agents has not been studied. Therefore, caution should be taken if these medicinal products are co-administered with Lynparza and patients should be closely monitored.

Pharmacokinetic interactions

Effect of other medicinal products on olaparib

CYP3A4/5 are the isozymes predominantly responsible for the metabolic clearance of olaparib.

A clinical study to evaluate the impact of itraconazole, a known CYP3A inhibitor, has shown that co-administration with olaparib increased mean olaparib C_{max} by 42% (90% CI: 33-52%) and mean AUC by 170% (90% CI: 144-197%). Therefore, known strong (e.g. itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, boceprevir, telaprevir) or moderate (e.g. erythromycin, diltiazem, fluconazole, verapamil) inhibitors of this isozyme are 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. The recommended Lynparza dose reduction is to 100 mg taken twice daily (equivalent to a total daily dose of 200 mg) with a strong CYP3A inhibitor or 150 mg taken twice daily (equivalent to a total daily dose of 300 mg) with a moderate CYP3A inhibitor (see sections 4.2 and 4.4). It is also not recommended to consume grapefruit juice while on Lynparza therapy as it is a CYP3A inhibitor.

A clinical study to evaluate the impact of rifampicin, a known CYP3A inducer, has shown that co-administration with olaparib decreased olaparib mean C_{max} by 71% (90% CI: 76-67%) and mean AUC by 87% (90% CI: 89-84%). Therefore, known strong inducers of this isozyme (e.g. phenytoin, rifampicin, rifapentine, carbamazepine, nevirapine, phenobarbital and St John's Wort) are not recommended with Lynparza, as it is possible that the efficacy of Lynparza could be substantially reduced. The magnitude of the effect of moderate to strong inducers (e.g. efavirenz, rifabutin) on olaparib exposure is not established, therefore the co-administration of Lynparza with these medicinal products is also not recommended (see section 4.4).

Effect of olaparib on other medicinal products

Olaparib inhibits CYP3A4 *in vitro* and is predicted to be a mild CYP3A inhibitor *in vivo*. Therefore, caution should be exercised when sensitive CYP3A substrates or substrates with a narrow therapeutic margin (e.g. simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozone, sirolimus, tacrolimus and quetiapine) are combined with olaparib. Appropriate clinical monitoring is recommended for patients receiving CYP3A substrates with a narrow therapeutic margin concomitantly with olaparib.

Induction of CYP1A2, 2B6 and 3A4 has been shown *in vitro* with CYP2B6 being most likely to be induced to a clinically relevant extent. The potential for olaparib to induce CYP2C9, CYP2C19 and P-gp can also not be excluded. Therefore, olaparib upon co-administration may reduce the exposure to substrates of these metabolic enzymes and transport protein. The efficacy of some hormonal contraceptives may be reduced if co-administered with olaparib (see sections 4.4 and 4.6).

In vitro, olaparib inhibits the efflux transporter P-gp ($IC_{50} = 76 \mu M$), therefore it cannot be excluded that olaparib may cause clinically relevant drug interactions with substrates of P-gp (e.g. simvastatin, pravastatin, dabigatran, digoxin and colchicine). Appropriate clinical monitoring is recommended for patients receiving this type of medicinal product concomitantly.

In vitro, olaparib has been shown to be an inhibitor of BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. It cannot be excluded that olaparib may increase the exposure to substrates of BCRP (e.g. methotrexate, rosuvastatin), OATP1B1 (e.g. bosentan, glibenclamide, repaglinide, statins and valsartan), OCT1 (e.g. metformin), OCT2 (e.g. serum creatinine), OAT3 (e.g. furosemide and methotrexate), MATE1 (e.g. metformin) and MATE2K (e.g. metformin). In particular, caution should be exercised if olaparib is administered in combination with any statin.

Combination with anastrozole, letrozole and tamoxifen

A clinical study has been performed to assess the combination of olaparib with anastrozole, letrozole or tamoxifen. No clinically relevant interactions were observed.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in females

Women of childbearing potential should not become pregnant while on Lynparza and not be pregnant at the beginning of treatment. A pregnancy test should be performed on all women of childbearing potential prior to treatment and considered regularly throughout treatment.

Women of childbearing potential must use two forms of reliable contraception before starting Lynparza therapy, during therapy and for 6 months after receiving the last dose of Lynparza, unless abstinence is the chosen method of contraception (see section 4.4). Two highly effective and complementary forms of contraception are recommended.

Since it cannot be excluded that olaparib may reduce exposure to substrates of CYP2C9 through enzyme induction, the efficacy of some hormonal contraceptives may be reduced if co-administered with olaparib. Therefore, an additional non-hormonal contraceptive method should be considered during treatment (see section 4.5). For women with hormone dependent cancer, two non-hormonal contraceptive methods should be considered.

Contraception in males

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 highly effective contraception if they are of childbearing potential (see section 4.4). Male patients should not donate sperm during therapy and for 3 months after receiving the last dose of Lynparza.

Pregnancy

Studies in animals have shown reproductive toxicity including serious teratogenic effects and effects on embryofoetal survival in the rat at maternal systemic exposures lower than those in humans at therapeutic doses (see section 5.3). There are no data from the use of olaparib in pregnant women, however, based on the mode of action of olaparib, Lynparza should not be used during pregnancy and in women of childbearing potential not using reliable contraception during therapy and for 6 months after receiving the last dose of Lynparza. (See previous paragraph: “Women of childbearing potential/contraception in females” for further information about birth control and pregnancy testing.)

Breast-feeding

There are no animal studies on the excretion of olaparib in breast milk. It is unknown whether olaparib or its metabolites are excreted in human milk. Lynparza is contraindicated during breast-feeding and for 1 month after receiving the last dose, given the pharmacologic property of the product (see section 4.3).

Fertility

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

4.7 Effects on ability to drive and use machines

Lynparza has moderate influence on the ability to drive and use machines. Patients who take Lynparza may experience fatigue, asthenia or dizziness. Patients who experience these symptoms should observe caution when driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

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

The Grade ≥ 3 adverse reactions occurring in $> 2\%$ of patients were anaemia (15%), neutropenia (5%), fatigue/asthenia (4.2%), leukopenia (2.5%) and thrombocytopenia (2.1%).

Adverse reactions that most commonly led to dose interruptions and/ or reductions in monotherapy were anaemia (16%), nausea (7%), vomiting (6%), fatigue/asthenia (6%) and neutropenia (6%). Adverse reactions that most commonly led to permanent discontinuation were anaemia (1.8%), nausea (1.0%), fatigue/asthenia (0.9%), thrombocytopenia (0.7%), neutropenia (0.6%) and vomiting (0.5%).

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

Adverse events led to dose interruption and/ or reduction of olaparib in 57% of patients when used in combination with bevacizumab and led to permanent discontinuation of treatment with olaparib/bevacizumab and placebo/bevacizumab in 20% and 6% of patients, respectively. The adverse reactions that most commonly led to dose interruption and/or reduction were anaemia (22%), nausea (10%) and fatigue/asthenia (5%). The adverse reactions that most commonly led to permanent discontinuation were anaemia (3.6%), nausea (3.4%) and fatigue/asthenia (1.5%).

Tabulated list of adverse drug reactions from clinical trials

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

The following adverse reactions have been identified in clinical trials with patients receiving Lynparza monotherapy where patient exposure is known. Adverse drug reactions are listed 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1000$); very rare ($< 1/10,000$); not known (cannot be estimated from available data).

Table 1: Tabulated list of adverse drug reactions reported in clinical trials with Lynparza monotherapy

MedDRA System Organ Class	Adverse reactions	
	Frequency of All CTCAE grades	Frequency of CTCAE grade 3 and above

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

Adverse reactions		
MedDRA System Organ Class	Frequency of All CTCAE grades	Frequency of CTCAE grade 3 and above
Investigations ^b	Common Blood creatinine increased Uncommon Mean cell volume increased	Rare Blood creatinine increased

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

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

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

Thrombocytopenia includes PTs of platelet count decreased and thrombocytopenia.

Leukopenia includes PTs of leukopenia and white blood cell count decreased

Lymphopenia includes PTs of lymphocyte count decreased and lymphopenia.

Hypersensitivity includes PTs of drug hypersensitivity and hypersensitivity.

Dysgeusia includes PTs of dysgeusia and taste disorder.

Cough includes PTs of cough and productive cough.

Dyspnoea includes PTs of dyspnoea and dyspnoea exertional.

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, dermatitis allergic.

^b Registered laboratory data are presented below under *Haematological toxicity* and *Other laboratory findings*.

* As observed in the post-marketing setting

Description of selected adverse reactions

Haematological toxicity

Anaemia and other haematological toxicities were generally low grade (CTCAE grade 1 or 2), however, there were reports of CTCAE grade 3 and higher events. Anaemia was the most common CTCAE grade ≥ 3 adverse reaction reported in clinical studies. Median time to first onset of anaemia was approximately 4 weeks (approximately 7 weeks for CTCAE grade ≥ 3 events). Anaemia was managed with dose interruptions and dose reductions (see section 4.2), and where appropriate with blood transfusions. In clinical studies with the tablet formulation, the incidence of anaemia adverse reactions was 35% (CTCAE grade ≥ 3 15%) and the incidences of dose interruptions, reductions and discontinuations for anaemia were 16%, 11 % and 2.1%, respectively; 17% of patients treated with olaparib needed one or more blood transfusions. An exposure-response relationship between olaparib and decreases in haemoglobin has been demonstrated. In clinical studies with Lynparza monotherapy the incidence of CTCAE grade ≥ 2 shifts (decreases) from baseline in haemoglobin was 21%, absolute neutrophils 17%, platelets 5%, lymphocytes 26% and leucocytes 19% (all % approximate).

The incidence of elevations in mean corpuscular volume from low or normal at baseline to above the ULN was approximately 68%. 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).

Myelodysplastic syndrome/Acute myeloid leukaemia

MDS/AML are serious adverse reactions that occurred uncommonly in monotherapy clinical studies at the therapeutic dose, across all indications (0.8%). The incidence was 0.5% including events reported during the long term safety follow up (rate calculated based on overall safety population of 17923

patients exposed to at least one dose of oral olaparib in clinical studies). 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 agents and radiotherapy. The majority of reports were in germline breast cancer susceptibility gene 1 or 2 (*gBRCA1/2*) mutation carriers. The incidence of MDS/AML cases was similar among *gBRCA1m* and *gBRCA2m* patients (1.6% and 1.2%, respectively). Some of the patients had a history of previous cancer or of bone marrow dysplasia.

In patients with *BRCAm* 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 (1.2% in SOLO1 study and 0.7% in PAOLA-1 study). For risk mitigation and management, see section 4.4.

Other laboratory findings

In clinical studies with Lynparza monotherapy the incidence of CTCAE grade ≥ 2 shifts (elevations) from baseline in blood creatinine was approximately 11%. Data from a double-blind placebo-controlled study showed median increase up to 23% from baseline remaining consistent over time and returning to baseline after treatment discontinuation, with no apparent clinical sequelae. 90% of patients had creatinine values of CTCAE grade 0 at baseline and 10% were CTCAE grade 1 at baseline.

Gastrointestinal toxicities

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 and can be managed by dose interruption, dose reduction and/or antiemetic therapy. Antiemetic prophylaxis is not required.

In first-line ovarian cancer maintenance treatment, patients experienced nausea events (77% on olaparib, 38% on placebo), vomiting (40% on olaparib, 15% on placebo), diarrhoea (34% on olaparib, 25% on placebo) and dyspepsia (17% on olaparib, 12% on placebo). Nausea events led to discontinuation in 2.3% of olaparib-treated patients (CTCAE Grade 2) and 0.8% of placebo-treated patients (CTCAE Grade 1); 0.8% and 0.4% of olaparib-treated patients discontinued treatment due to low grade (CTCAE Grade 2) vomiting and dyspepsia, respectively. No olaparib or placebo-treated patients discontinued due to diarrhoea. No placebo-treated patients discontinued due to vomiting or dyspepsia. Nausea events led to dose interruption and dose reductions in 14% and 4%, respectively, of olaparib-treated patients. Vomiting events led to interruption in 10% of olaparib-treated patients; no olaparib-treated patients experienced a vomiting event leading to dose reduction.

Paediatric population

No studies have been conducted in paediatric patients.

Other special populations

Limited safety data are available in elderly (age ≥ 75 years) and non-Caucasian patients.

4.9 Overdose

There is limited experience of overdose with olaparib. No unexpected adverse reactions were reported in a small number of patients who took a daily dose of up to 900 mg of olaparib tablets over two days. Symptoms of overdose are not established and there is no specific treatment in the event of Lynparza

overdose. In the event of an overdose, physicians should follow general supportive measures and should treat the patient symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action and pharmacodynamic effects

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

PARPs are required for the efficient repair of DNA single strand breaks and an important aspect of PARP-induced repair requires that after chromatin modification, PARP auto-modifies itself and dissociates from the DNA to facilitate access for base excision repair (BER) enzymes. When olaparib is bound to the active site of DNA-associated PARP it prevents the dissociation of PARP and traps it on the DNA, thus blocking repair. In replicating cells this also leads to the formation of DNA double-strand breaks (DSBs) when replication forks meet the PARP-DNA adducts. In normal cells, homologous recombination repair (HRR) pathway is effective at repairing these DNA DSBs. In HR-deficient cancer cells, the repair of these DNA DSBs is impaired. Cancer cells can become HR deficient due to inactivation of genes with a direct or indirect role in HRR, such as *BRCA1/2*, *ATM*, *CDK12* and others. Instead, alternative and error-prone pathways are activated, such as the classical 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 *BRCA1/2*-deficient *in vivo* models, olaparib given after platinum treatment resulted in a delay in tumour progression and an increase in overall survival compared to platinum treatment alone that correlated with the period of olaparib maintenance treatment.

Detection of *BRCA1/2* mutations

Local or central testing of blood and/or tumour samples for *BRCA1/2* mutations have been used in different studies. Depending on the test used and the international classification consensus, the *BRCA1/2* mutations have been classified as deleterious/suspected deleterious or pathogenic/likely pathogenic. Genetic testing should be conducted by an experienced laboratory using a validated test.

Clinical efficacy and safety

First-line maintenance treatment of BRCA-mutated advanced ovarian cancer: SOLO1 Study

The safety and efficacy of olaparib as maintenance therapy were studied in patients with newly diagnosed advanced (FIGO Stage III-IV) high-grade serous or endometrioid *BRCA1/2* mutated (*BRCA1/2m*) ovarian cancer following completion of first-line platinum-based chemotherapy in a Phase III randomised, double-blind, placebo-controlled, multicentre trial. In this study 391 patients were randomised 2:1 to receive either Lynparza (300 mg [2 x 150 mg tablets] twice daily) or placebo. Patients were stratified by response to first-line platinum chemotherapy; complete response (CR) or

partial response (PR). Treatment was continued until radiological progression of the underlying disease, unacceptable toxicity or for up to 2 years. 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 germline or somatic *BRCA1/2* mutations were identified prospectively either from germline testing in blood via a local test (n=208) or central test (n=181) or from testing a tumour sample using a local test (n=2). By central germline testing, deleterious or suspected deleterious mutations were identified in 95.3% (365/383) and 4.7% (18/383) of patients, respectively. Large rearrangements in the *BRCA1/2* genes were detected in 5.5% (21/383) of the randomised patients. The *gBRCAm* status of patients enrolled via local testing was confirmed retrospectively by central testing. Retrospective testing of patients with available tumour samples was performed using central testing and generated successful results in 341 patients, of which 95% had an eligible mutation (known [n=47] or likely pathogenic [n=277]) and 2 *gBRCAwt* patients were confirmed to have *sBRCAm* only. There were 389 patients who were germline *BRCA1/2m* and 2 who were somatic *BRCA1/2m* 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%), there are no data in patients with performance status 2 to 4. Sixty-three percent (63%) of the patients had upfront debulking surgery and of these the majority (75%) had no macroscopic residual disease. Interval debulking surgery was performed in 35% of the patients and of these 82% had no macroscopic residual disease reported. Seven patients, all stage IV, had no cytoreductive surgery. All patients had received first-line platinum-based therapy. There was no evidence of disease at study entry (CR), defined by the investigator as no radiological evidence of disease and cancer antigen 125 (CA-125) within normal range, in 73% and 77% of patients in the olaparib and placebo arms, respectively. PR, defined as the presence of any measurable or non-measurable lesions at baseline or elevated CA-125, was reported in 27% and 23% of patients in the olaparib and placebo arms, respectively. Ninety three percent (93%) of patients were randomised within 8 weeks of their last dose of platinum-based chemotherapy. Patients who had been treated with bevacizumab were excluded from the study, therefore there are no safety and efficacy data on olaparib patients who had previously received bevacizumab. There are very limited data in patients with a somatic *BRCA* mutation.

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 discontinuation of treatment or death (TDT), 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 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. The investigator assessment of PFS was supported with a blinded independent central radiological (BICR) review of PFS. At the time of PFS analysis, interim OS data were immature (21%), with HR 0.95 (95% CI 0.60, 1.53; p-value=0.9). Efficacy results are presented in Table 2 and Figures 1 and 2.

Table 2: Efficacy results for newly diagnosed patients with *BRCA1/2m* advanced ovarian cancer in SOLO1

	Olaparib 300 mg bd	Placebo^c
PFS (51% maturity)^a		
Number of events: Total number of patients (%)	102:260 (39)	96:131 (73)
Median time (months)	NR	13.8
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) ^c	0.50 (0.35-0.72)	
P value (2-sided)	p=0.0002	
TFST (49% maturity)		
Number of events: Total number of patients (%)	99:260 (38)	94:131 (72)
Median time (months)	51.8	15.1
HR (95% CI) ^c	0.30 (0.22-0.40)	
P value* (2-sided)	p<0.0001	

^a Based on Kaplan-Meier estimates, the proportion of patients that were progression free at 24 and 36 months were 74% and 60% for olaparib versus 35% and 27% for placebo; the median follow-up time was 41 months for both the olaparib and placebo arms.

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

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

* Not controlled for multiplicity.

bd Twice daily; NR Not reached; CI Confidence interval; 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 in newly diagnosed patients with *BRCA1/2m* advanced ovarian cancer (51% maturity - investigator assessment)

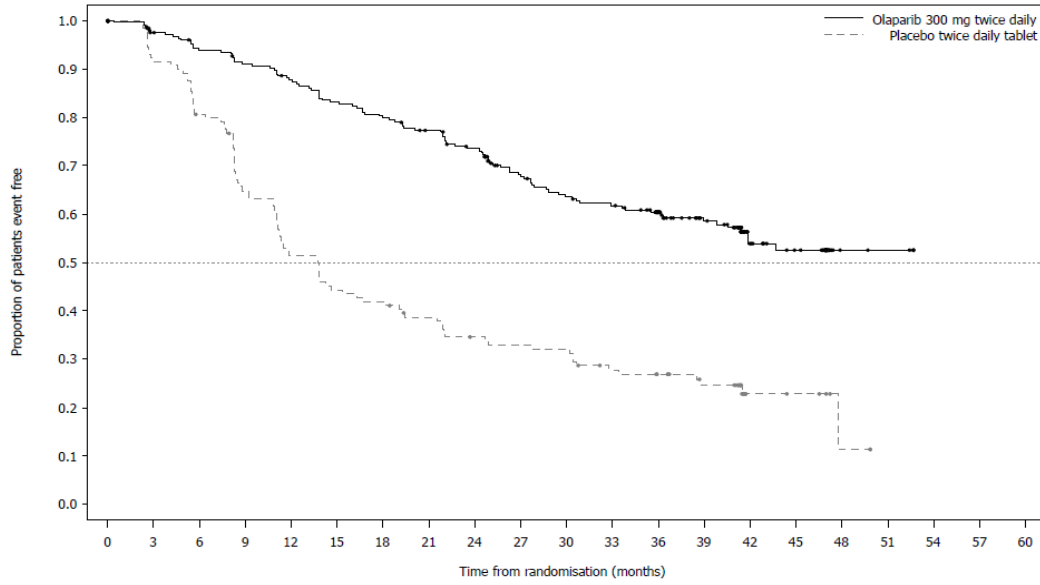
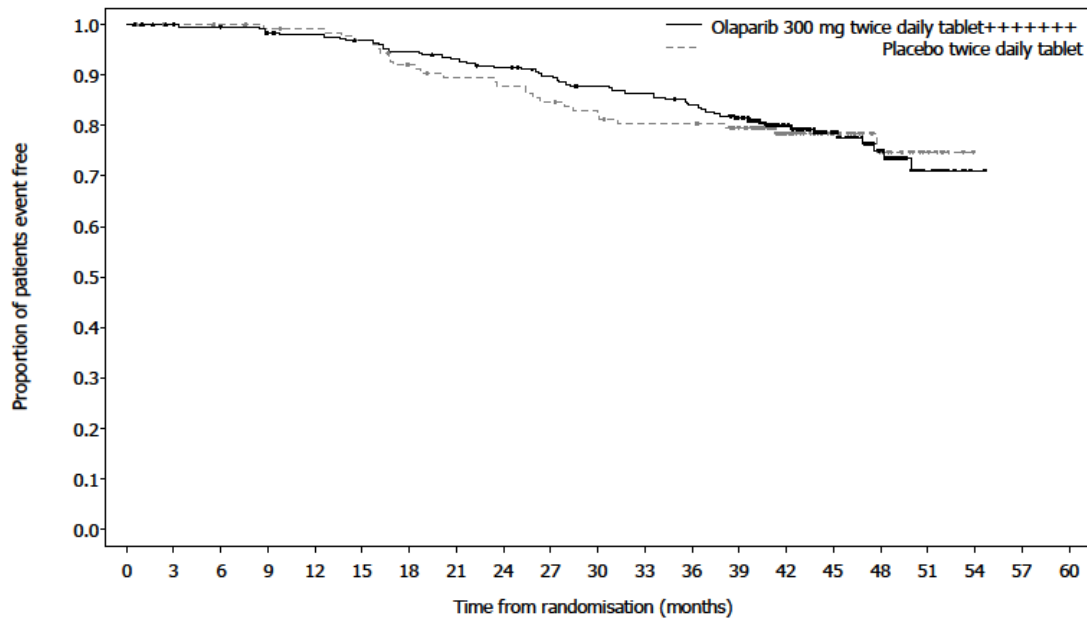


Figure 2: SOLO1: Kaplan-Meier plot of OS in newly diagnosed patients with BRCA1/2m advanced ovarian cancer (21% maturity)



Consistent results were observed in the subgroups of patients by evidence of the disease at study entry. Patients with CR defined by the investigator had HR 0.34 (95% CI 0.24–0.47); median PFS not reached on olaparib vs 15.3 months on placebo. At 24 and 36 months, respectively, 68% and 45% patients remained in CR in the olaparib arm, and 34% and 22% of patients in the placebo arm. Patients with PR at study entry had PFS HR 0.31 (95% CI 0.18, 0.52; median PFS 30.9 months on olaparib vs 8.4 months on placebo). Patients with PR at study entry either achieved CR (15% in olaparib arm and 4% in the placebo arm at 24 months, remained in CR at 36 months) or had further PR/stable disease (43% in olaparib arm and 15% in the placebo arm at 24 months; 17% in olaparib arm and 15% in placebo arm at 36 months). The proportion of patients who progressed within 6 months of the last dose of platinum-based chemotherapy was 3.5% for olaparib and 8.4% for placebo.

Maintenance treatment of platinum-sensitive relapsed (PSR) ovarian cancer **SOLO2 Study**

The safety and efficacy of olaparib as maintenance therapy were studied in a Phase III randomised, double-blind, placebo-controlled trial in patients with germline *BRCA1/2*-mutated PSR ovarian, fallopian tube or primary peritoneal cancer. The study compared the efficacy of Lynparza maintenance treatment (300 mg [2 x 150 mg tablets] twice daily) taken until 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.

Patients who have received two or more platinum-containing regimens 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.

All patients had evidence of *gBRCA1/2m* at baseline. Patients with *BRCA1/2* mutations were identified either from germline testing in blood via a local test or by central testing at Myriad or from testing a tumour sample using a local test. Large rearrangements in the *BRCA1/2* genes were detected in 4.7% (14/295) of the randomised patients.

Demographic and baseline characteristics were generally well balanced between the olaparib and placebo arms. Median age was 56 years in both arms. Ovarian cancer was the primary tumour in >80% of the patients. The most common histological type was serous (> 90%), endometrioid histology was reported in 6% of the patients. In the olaparib arm 55% of the patients had only 2 prior lines of treatment with 45% receiving 3 or more prior lines of treatment. In the placebo arm 61% of patients had received only 2 prior lines with 39% receiving 3 or more prior lines of treatment. Most patients were ECOG performance status 0 (81%), there are no data in patients with performance status 2 to 4. Platinum free interval was >12 months in 60% and >6-12 months in 40% of the patients. Response to prior platinum chemotherapy was complete in 47% and partial in 53% of the patients. In the olaparib and placebo arms, 17% and 20% of patients had prior bevacizumab, respectively.

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 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 olaparib vs 5.5 months 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 and 5.5 months placebo). At 2 years, 43% olaparib-treated patients remained progression free compared with only 15% placebo-treated patients.

A summary of the primary objective outcome for patients with *gBRCA1/2m* PSR ovarian cancer in SOLO2 is presented in Table 3 and Figure 3.

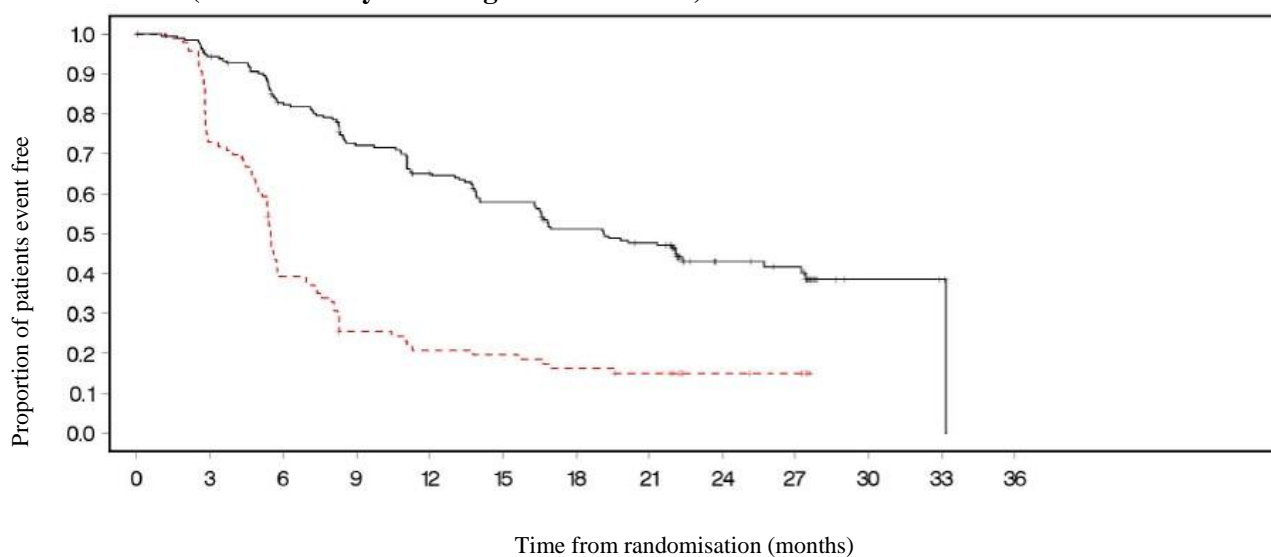
Table 3: Summary of primary objective outcome for patients with gBRCA1/2m PSR ovarian cancer in SOLO2

	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) (95% CI)	19.1 (16.3-25.7)	5.5 (5.2-5.8)
HR (95% CI) ^a	0.30 (0.22-0.41)	
P value (2-sided)	p<0.0001	

^a HR= Hazard Ratio. 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.

bd Twice daily; PFS progression-free survival; CI confidence interval

Figure 3: SOLO2: Kaplan-Meier plot of PFS in patients with gBRCA1/2m PSR ovarian cancer (63% maturity - investigator assessment)



Number of patients at risk:

196	182	156	134	118	104	89	82	32	29	3	2	0	Olaparib 300 mg bd
99	70	37	22	18	17	14	12	7	6	0	0	0	Placebo bd

bd Twice daily; PFS Progression free survival

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. The secondary endpoints TFST and PFS2 demonstrated a persistent and statistically significant improvement for olaparib compared with placebo. Results for OS, TFST and PFS2 are presented in Table 4 and Figure 4.

Table 4: Summary of key secondary objective outcomes for patients with gBRCA1/2m PSR ovarian cancer in SOLO2

	Olaparib 300 mg tablet bd	Placebo
OS (61% maturity)		
Number of events: Total number of patients (%)	116:196 (59)	65:99 (66)
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	

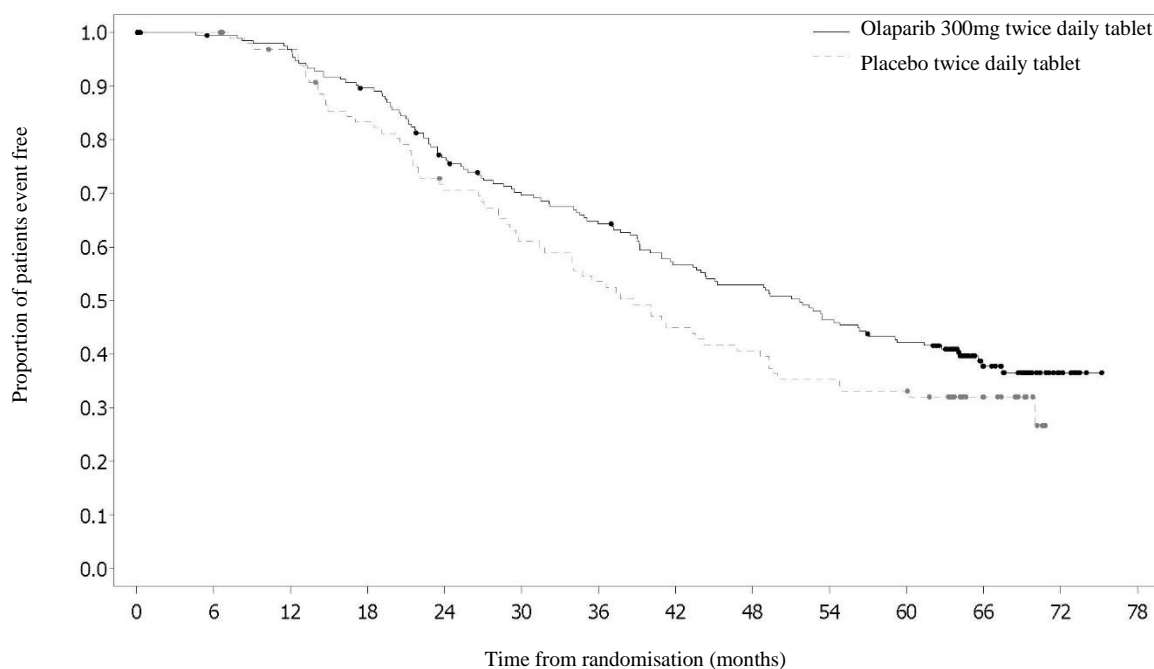
	Olaparib 300 mg tablet bd	Placebo
TFST (71% maturity)		
Number of events: Total number of patients (%)	139:196 (71)	86:99 (87)
Median time (months) (95% CI)	27.4 (22.6-31.1)	7.2 (6.3-8.5)
HR (95% CI) ^a	0.37 (0.28-0.48)	
P value* (2-sided)	p<0.0001	
PFS2 (40% maturity)		
Number of events: Total number of patients (%)	70:196 (36)	49:99 (50)
Median time (months) (95% CI)	NR (24.1-NR)	18.4 (15.4-22.8)
HR (95% CI) ^a	0.50 (0.34-0.72)	
P value (2-sided)	p=0.0002	

* Not controlled for multiplicity.

^a HR= Hazard Ratio. 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.

bd Twice daily; NR not reached; CI confidence interval; PFS2 time from randomisation to second progression or death; TFST Time from randomisation to start of first subsequent therapy or death.

Figure 4 SOLO2: Kaplan-Meier plot of OS in patients with gBRCA1/2m PSR ovarian cancer (61% maturity)



Number of patients at risk:

Olaparib 300mg twice daily tablet

196 192 187 172 145 130 120 105 98 86 77 39 7 0

Placebo twice daily tablet

99 99 93 79 66 57 50 42 38 33 31 16 0 0

Among the patients entering the trial with measurable disease (target lesions at baseline), an objective response rate of 41% was achieved in the Lynparza arm versus 17% on placebo. Of patients treated with Lynparza, who entered the study with evidence of disease (target or non-target lesions at baseline), 15.0% experienced complete response compared with 9.1% of patients on placebo.

At the time of the analysis of PFS the median duration of treatment was 19.4 months for olaparib and 5.6 months for placebo. The majority of patients remained on the 300 mg bd starting dose of olaparib. The incidence of dose interruptions, reductions, discontinuations due to an adverse event was 45.1%, 25.1% and 10.8%, respectively. Dose interruptions occurred most frequently in the first 3 months and dose reductions in the first 3-6 months of treatment. The most frequent adverse reactions leading to dose interruption or dose reduction were anaemia, nausea and vomiting.

Patient-reported outcome (PRO) data indicate no difference for the olaparib-treated patients as compared to placebo as assessed by the change from baseline in the TOI of the FACT-O.

Study 19

The safety and efficacy of olaparib as a maintenance therapy in the treatment of PSR ovarian, including fallopian tube or primary peritoneal cancer patients, following treatment with two or more platinum-containing regimens, were studied in a large Phase II randomised, double-blind, placebo-controlled trial (Study 19). The study compared the efficacy of Lynparza capsule maintenance treatment (400 mg [8 x 50 mg capsules] twice daily) taken until progression with placebo treatment in 265 (136 olaparib and 129 placebo) PSR high grade serous ovarian cancer patients who were in response (CR or PR) following completion of platinum-containing chemotherapy. The primary endpoint was PFS based on investigator assessment using RECIST 1.0. Secondary efficacy endpoints included OS, disease control rate (DCR) defined as confirmed CR/PR + SD (stable disease), HRQoL and disease related symptoms. Exploratory analyses of TFST and TSST were also performed.

Patients whose disease had recurred >6 months after completion of penultimate platinum-based chemotherapy were enrolled. Enrolment did not require evidence of *BRCA1/2* mutation (*BRCA* mutation status for some patients was determined retrospectively). 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. Retreatment with olaparib was not permitted following progression on olaparib.

Patients with *BRCA1/2* mutations were identified either from germline testing in blood via a local test or by central testing at Myriad or from testing a tumour sample using a test performed by Foundation Medicine. Large rearrangements in the *BRCA1/2* genes were detected in 7.4% (10/136) of the randomised patients.

Demographic and baseline characteristics were generally well balanced between the olaparib and placebo arms. Median age was 59 years in both arms. Ovarian cancer was the primary tumour in 86% of the patients. In the olaparib arm 44% of the patients had only 2 prior lines of treatment with 56% receiving 3 or more prior lines of treatment. In the placebo arm 49% of patients had received only 2 prior lines with 51% receiving 3 or more prior lines of treatment. Most patients were ECOG performance status 0 (77%), there are no data in patients with performance status 2 to 4. Platinum free interval was > 12 months in 60% and 6-12 months in 40% of the patients. Response to prior platinum chemotherapy was complete in 45% and partial in 55% of the patients. In the olaparib and placebo arms, 6% and 5% of patients had prior bevacizumab, respectively.

The study met its primary objective demonstrating a statistically significant improvement in PFS for olaparib compared with placebo in the overall population with a HR of 0.35 (95% CI 0.25-0.49; $p < 0.00001$; median 8.4 months olaparib vs 4.8 months placebo). At the final OS analysis (data cut off [DCO] 9 May 2016) at 79% maturity, the hazard ratio 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). In the olaparib-treated group, 23.5% ($n = 32/136$) of patients remained on treatment for ≥ 2 years as compared with 3.9% ($n = 5/128$) of the patients on placebo. Although patient numbers were limited, 13.2% ($n = 18/136$) of the patients in the olaparib-treated group remained on treatment for ≥ 5 years as compared with 0.8% ($n = 1/128$) in the placebo group.

Preplanned subgroup analysis identified patients with *BRCA1/2*-mutated ovarian cancer (n=136, 51.3%; including 20 patients identified with a somatic tumour *BRCA1/2* mutation) as the subgroup that derived the greatest clinical benefit from olaparib maintenance monotherapy. A benefit was also observed in patients with *BRCA1/2* wild-type/variants of uncertain significance (*BRCA1/2 wt/VUS*), although of a lesser magnitude. There was no strategy for multiple testing in place for the sub-group analyses.

A summary of the primary objective outcome for patients with *BRCA1/2*-mutated and *BRCA1/2 wt/VUS* PSR ovarian cancer in Study 19 is presented in Table 4 and for all patients in Study 19 in Table 5 and Figure 5.

Table 5: Summary of primary objective outcome for all patients and patients with *BRCA1/2*-mutated and *BRCA1/2 wt/VUS* PSR ovarian cancer in Study 19

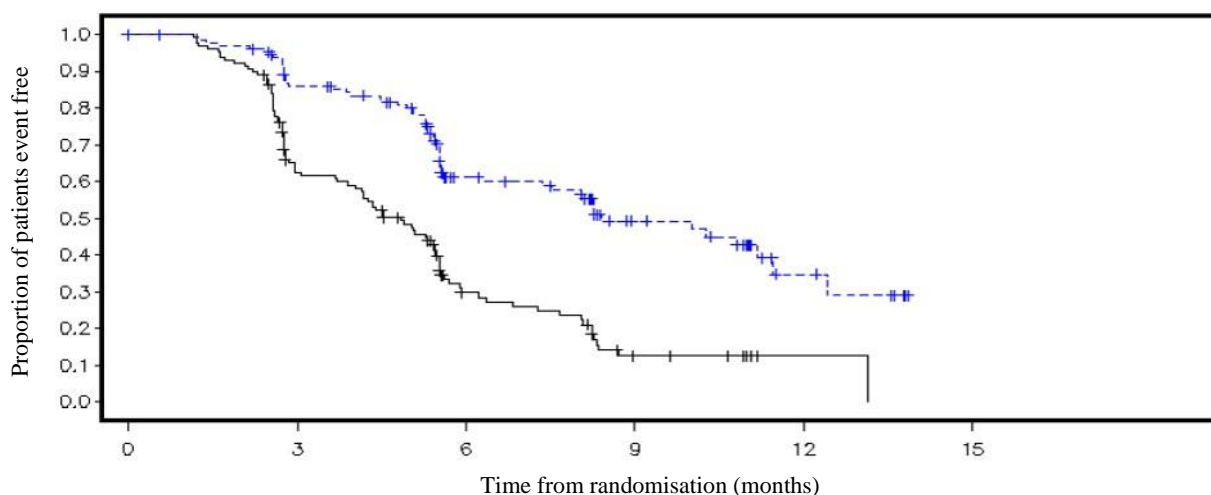
	All patients ^a		<i>BRCA1/2</i> -mutated		<i>BRCA1/2 wt/VUS</i>	
	Olaparib 400 mg capsule bd	Placebo	Olaparib 400 mg capsule bd	Placebo	Olaparib 400 mg capsule bd	Placebo
PFS – DCO 30 June 2010						
Number of events: Total number of patients (%)	60:136 (44)	94:129 (73)	26:74 (35)	46:62 (74)	32:57 (56)	44:61 (72)
Median time (months) (95% CI)	8.4 (7.4-11.5)	4.8 (4.0-5.5)	11.2 (8.3-NR)	4.3 (3.0-5.4)	7.4 (5.5-10.3)	5.5 (3.7-5.6)
HR (95% CI) ^b	0.35 (0.25-0.49)		0.18 (0.10–0.31)		0.54 (0.34-0.85)	
P value (2-sided)	p<0.00001		p<0.00001		p=0.00745	

^a All patients comprises of the following subgroups: *BRCA1/2*-mutated, *BRCA1/2 wt/VUS* and *BRCA1/2* status unknown (11 patients with status unknown, not shown as a separate subgroup in table).

^b 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.

bd Twice daily; PFS progression-free survival; DCO data cut off; CI confidence interval; NR not reached.

Figure 5: Study 19: Kaplan-Meier plot of PFS in the FAS (58% maturity - investigator assessment) DCO 30 June 2010



Number of patients at risk:						
136	106	53	24	7	0	Olaparib 400 mg bd
129	72	24	7	1	0	Placebo

bd Twice daily; DCO Data cut-off; FAS Full analysis set; PFS progression-free survival

A summary of key secondary objective outcomes for patients with *BRCA1/2*-mutated and *BRCA1/2 wt/VUS* PSR ovarian cancer in Study 19 is presented in Table 6 and for all patients in Study 19 in Table 6 and Figure 6.

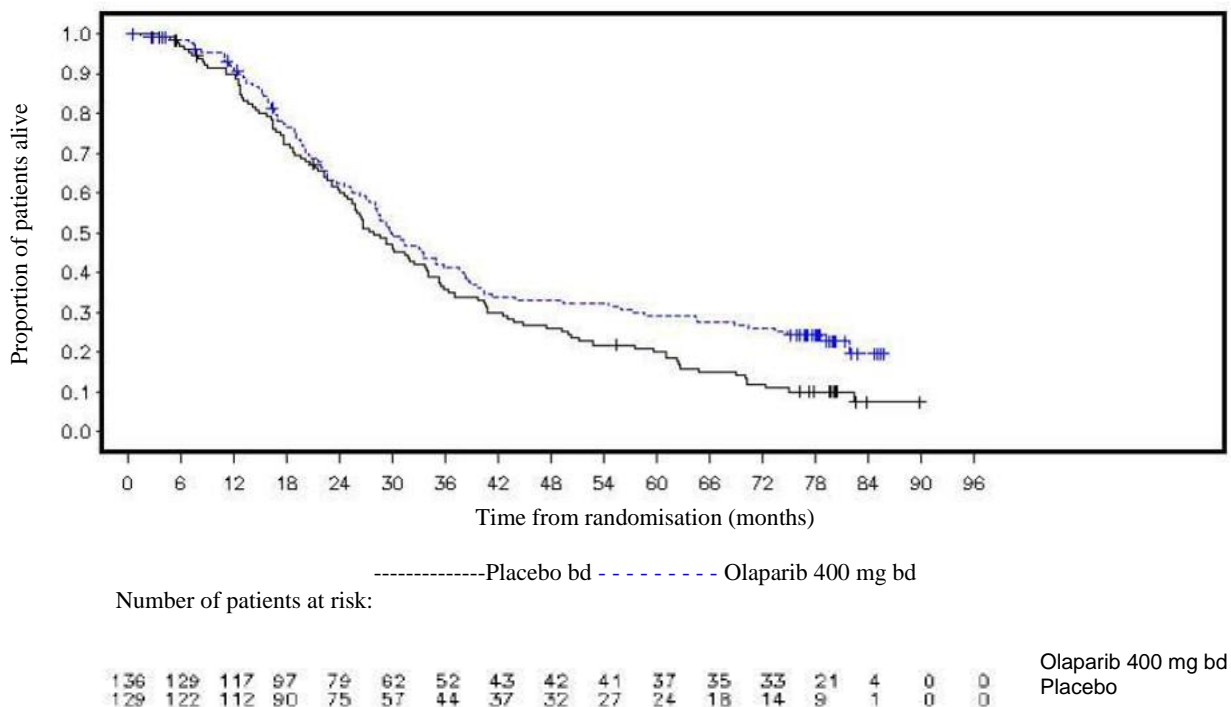
Table 6: Summary of key secondary objective outcomes for all patients and patients with *BRCA1/2*-mutated and *BRCA1/2 wt/VUS* PSR ovarian cancer in Study 19

	All patients ^a		<i>BRCA1/2</i> -mutated		<i>BRCA1/2 wt/VUS</i>	
	Olaparib 400 mg capsule bd	Placebo	Olaparib 400 mg capsule bd	Placebo	Olaparib 400 mg capsule bd	Placebo
OS - DCO 09 May 2016						
Number of events: Total	98:136 (72)	112:129 (87)	49:74 (66)	50:62 (81) ^c	45:57 (79)	57:61 (93)
number of patients (%)						
Median time (months)	29.8 (26.9-35.7)	27.8 (24.9-33.7)	34.9 (29.2-54.6)	30.2 (23.1-40.7)	24.5 (19.8-35.0)	26.6 (23.1-32.5)
(95% CI)						
HR (95% CI) ^b	0.73 (0.55–0.95)		0.62 (0.42–0.93)		0.84 (0.57-1.25)	
P value* (2-sided)	p=0.02138		p=0.02140		p=0.39749	
TFST – DCO 09 May 2016						
Number of events: Total	106:136 (78)	124:128 (97)	55:74 (74)	59:62 (95)	47:57 (83)	60:61 (98)
number of patients (%)						
Median time (months)	13.3 (11.3-15.7)	6.7 (5.7-8.2)	15.6 (11.9-28.2)	6.2 (5.3-9.2)	12.9 (7.8-15.3)	6.9 (5.7-9.3)
(95% CI)						
HR (95% CI) ^b	0.39 (0.30–0.52)		0.33 (0.22-0.49)		0.45 (0.30-0.66)	
P value* (2-sided)	p<0.00001		p<0.00001		p=0.00006	

* There was no strategy for multiple testing in place for the sub-group analyses or for the all patients TFST.
^a All patients comprises of the following subgroups: *BRCA1/2*-mutated, *BRCA1/2 wt/VUS* and *BRCA1/2* status unknown (11 patients with status unknown, not shown as a separate subgroup in table).

- ^b 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.
- ^c 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; DCO data cut off; CI confidence interval; TFST time from randomisation to start of first subsequent therapy or death.

Figure 6: Study 19: Kaplan Meier plot of OS in the FAS (79% maturity) DCO 09 May 2016



bd Twice daily; DCO Data cut off; FAS Full analysis set; OS Overall survival

At the time of the analysis of PFS the median duration of treatment was 8 months for olaparib and 4 months for placebo. The majority of patients remained on the 400 mg bd starting dose of olaparib. The incidence of dose interruptions, reductions and discontinuations due to an adverse event was 34.6%, 25.7% and 5.9%, respectively. Dose interruptions and reductions occurred most frequently in the first 3 months of treatment. The most frequent adverse reactions leading to dose interruption or dose reduction were nausea, anaemia, vomiting, neutropenia and fatigue. The incidence of anaemia adverse reactions was 22.8% (CTCAE grade ≥ 3 7.4%).

Patient-reported outcome (PRO) data indicate no difference for the olaparib-treated patients as compared to placebo as measured by improvement and worsening rates in the TOI and FACT-O total.

OPINION Study

OPINION, a Phase IIIb single arm, multicentre study, investigated olaparib as a maintenance treatment in patients with PSR ovarian, fallopian tube or primary peritoneal cancer following 2 or more lines of platinum based chemotherapy and who did not have a known deleterious or suspected deleterious *gBRCA* mutation. Patients whose disease was in response (CR or PR) following completion of platinum-based chemotherapy were enrolled. A total of 279 patients were enrolled and received olaparib treatment in this study until disease progression or unacceptable toxicity. Based on central testing 90.7% were confirmed with a non *gBRCAm* status, in addition 9.7% were identified as *sBRCAm*.

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-*gBRCAm* PSR ovarian cancer. At the time of primary PFS analysis, the OS data were 30% mature. A

summary of the primary objective outcome for patients with non-*gBRCAm* PSR ovarian cancer in OPINION is presented in Table 7.

Table 7 Summary of progression-free survival: non-*gBRCAm* patients with PSR ovarian cancer in OPINION

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

^a Calculated using the Kaplan-Meier technique.

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

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

First-line maintenance treatment of advanced ovarian cancer

PAOLA-1 Study

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 *tBRCAm* 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 balanced between both arms in the ITT population and in the biomarker-defined sub-groups by *tBRCAm* (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 *tBRCAm* 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 *tBRCAm*

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

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 (*tBRCAM*, GIS, HRD status positive defined as *tBRCAM* 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). Overall survival data were immature in the overall population and biomarker subgroups. Sixty percent (60%) of patients in the olaparib/bevacizumab arm and 74% in the placebo/bevacizumab arm received subsequent therapy and of these patients, 20% and 47% in the olaparib/bevacizumab and placebo/bevacizumab arms, respectively, received a PARP inhibitor.

In the *tBRCAM* as randomised subgroup (241/806 patients) median PFS for the olaparib/bevacizumab arm was 37.2 months vs 22.0 months for the placebo/bevacizumab arm (HR=0.34, 95% CI 0.23, 0.51) and for OS (DCO 22 March 2020) the HR was 0.68 (95% CI 0.40, 1.19).

Efficacy results in other biomarkers subgroup analyses based on retrospectively analysed tumour samples are presented in Table 8

Table 8 **Summary of key efficacy findings for patients with homologous recombination deficiency (HRD) positive status defined by either *tBRCAM* and/or GIS in advanced ovarian cancer patients in PAOLA-1**

	tBRCAm^{*,c} (n=235)		GIS positive^{*,d} (n=152)		HRD positive[*] (n=387)	
	Olaparib/ bevacizumab	Placebo/ bevacizumab	Olaparib/ bevacizumab	Placebo/ bevacizumab	Olaparib/ bevacizumab	Placebo/ bevacizumab
PFS, investigator assessment (46% maturity) DCO 22 March 2019^a						
Number of events: Total number of patients (%)	44/158 (28)	52/77 (68)	43/97 (44)	40/55 (73)	87/255 (34)	92/132 (70)
Median time (months)	37.2	18.8	28.1	16.6	37.2	17.7
HR (95%) CI ^b	0.28 (0.19, 0.42)		0.43 (0.28, 0.66)		0.33 (0.25, 0.45)	
PFS2, investigator assessment (40% maturity) DCO 22 March 2020						
Number of events: Total number of patients (%)	44/158 (28)	37/77 (48)	41/97 (42)	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)	
Interim OS (27% maturity) DCO 22 March 2020						
Number of events: Total number of patients (%)	31/158 (20)	23/77 (30)	30/97 (31)	19/55 (35)	61/255 (24)	42/132 (32)
Median time (months)	NR	NR	NR	45.8	NR	NR
HR (95%) CI ^b	0.61 (0.36, 1.06)		0.84 (0.48, 1.52)		0.70 (0.47, 1.04)	

* 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.

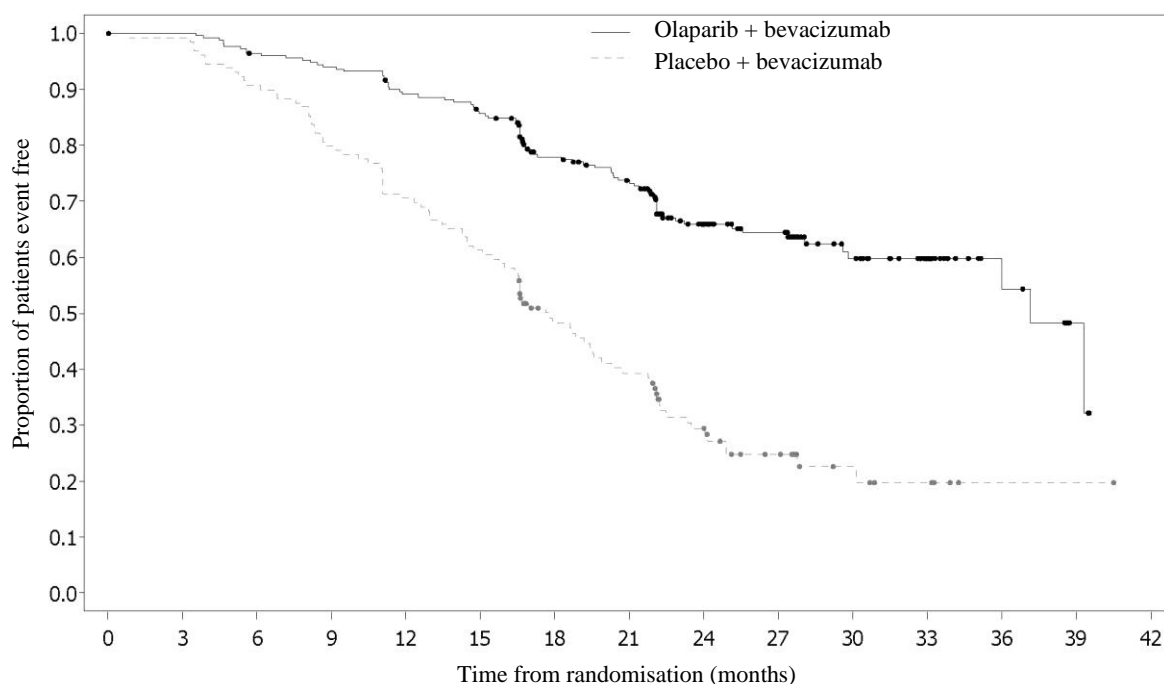
^b A value <1 favours olaparib. The analysis was performed using a Cox proportional hazards model stratified by first line treatment outcome at screening and screening laboratory tBRCA status.

^c tBRCAm status by Myriad

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

CI Confidence interval; HR Hazard ratio; NR not reached

Figure 7 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

**Adjuvant treatment of germline BRCA-mutated high risk early breast cancer
OlympiA study**

The safety and efficacy of olaparib 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 was studied in a Phase III randomised, double-blind, parallel group, placebo-controlled, multicentre study (OlympiA). 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 CPS&EG 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 9

Table 9 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

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

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

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

Patients were randomised (1:1) to either olaparib 300 mg (2 x 150 mg tablets) twice daily (n=921) or placebo (n=915). Randomisation was stratified by hormone receptor status (HR positive/ HER2 negative versus TNBC), by prior neoadjuvant versus adjuvant chemotherapy, and by prior platinum use for current breast cancer (yes versus no). Treatment was continued for up to 1 year, or until disease recurrence, or unacceptable toxicity. Patients with HR positive tumours also received endocrine therapy.

The primary end-point was invasive disease free survival (IDFS), defined as the time from randomisation to date of first recurrence, where recurrence is defined as invasive 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 randomization 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 (PRO) using the FACITFatigue and EORTC QLQ-C30 questionnaires.

Central testing at Myriad or local *gBRCA* testing, if available, was used to establish study eligibility. Patients enrolled based on local *gBRCA* test results provided a sample for retrospective confirmatory testing. Out of 1836 patients enrolled into OlympiA, 1623 were confirmed as *gBRCAm* by central testing, either prospectively or retrospectively.

Demographic and baseline characteristics were well balanced between the two treatment 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 HR positive disease. 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 percent (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. Overall, 89.5% of patients with HR positive disease received an endocrine therapy, which included letrozole (23.7%), tamoxifen (40.9%), anastrozole (17.2%), or exemestane (14.8%).

The study met its primary end-point demonstrating a statistically significant improvement in IDFS in the olaparib arm compared with the placebo arm. Two hundred and eighty-four (284) patients had IDFS events, this represented 12% of patients in the olaparib arm (distant 8%, local/regional 1.4%, contralateral invasive breast cancer 0.9%, non-breast second primary malignancies 1.2%, death 0.2%) and 20% of patients in the placebo arm (distant 13%, local/regional 2.7%, contralateral invasive breast

cancer 1.3%, non-breast second primary malignancies 2.3%, death 0%). A statistically significant improvement in DDFS in the olaparib arm compared with the placebo arm was also observed. At the next planned OS analysis, a statistically significant improvement in OS was observed in the Olaparib arm compared with the placebo arm. Efficacy results in the FAS are presented in Table 10 and Figures 8 and 9.

Table 10 Efficacy results for adjuvant treatment of patients with germline *BRCA*-mutated early breast cancer 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 (95% CI) 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 (98.5% CI) ^a	0.68 (0.47, 0.97)	
p-value (2-sided) ^b	0.0091	
Percentage (95% CI) of patients alive at 3 years ^c	93 (91, 94)	89 (87, 91)
Percentage (95% CI) of patients alive at 4 years	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.

^a P-value from a stratified log-rank test.

^b 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 8 Kaplan-Meier plot of IDFS for adjuvant treatment of patients with germline *BRCA*-mutated high risk early breast cancer in OlympiA

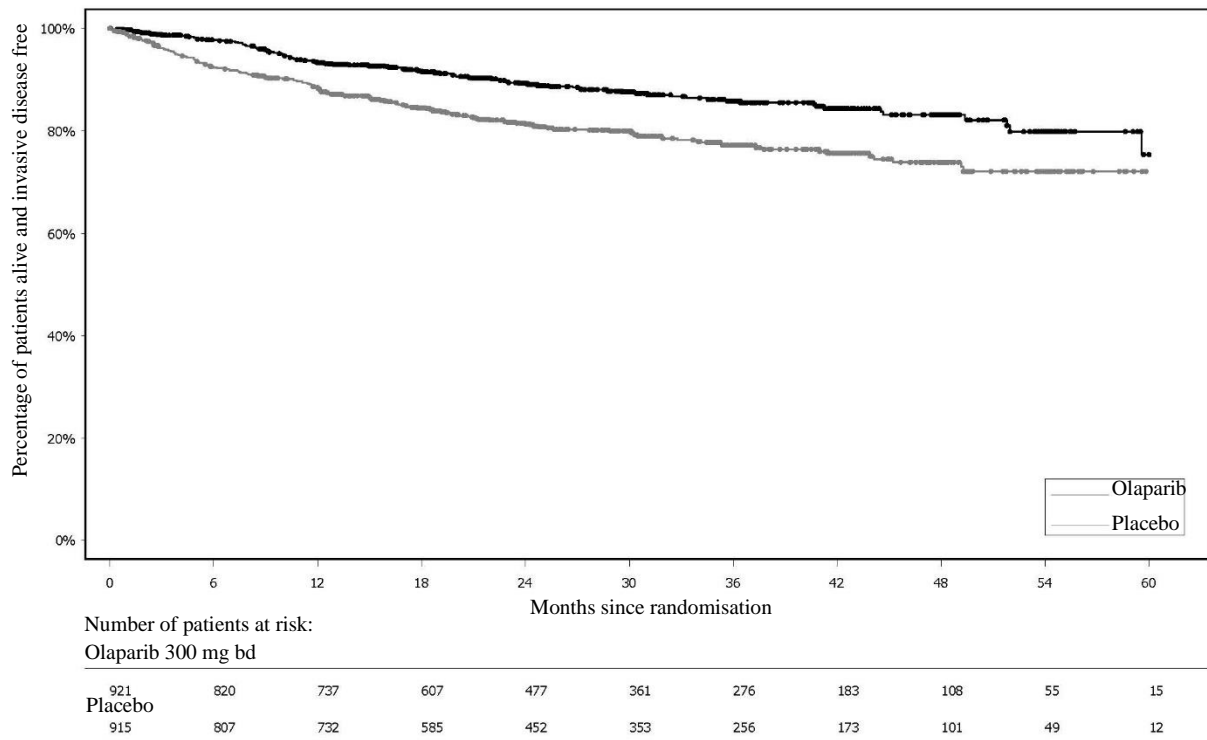
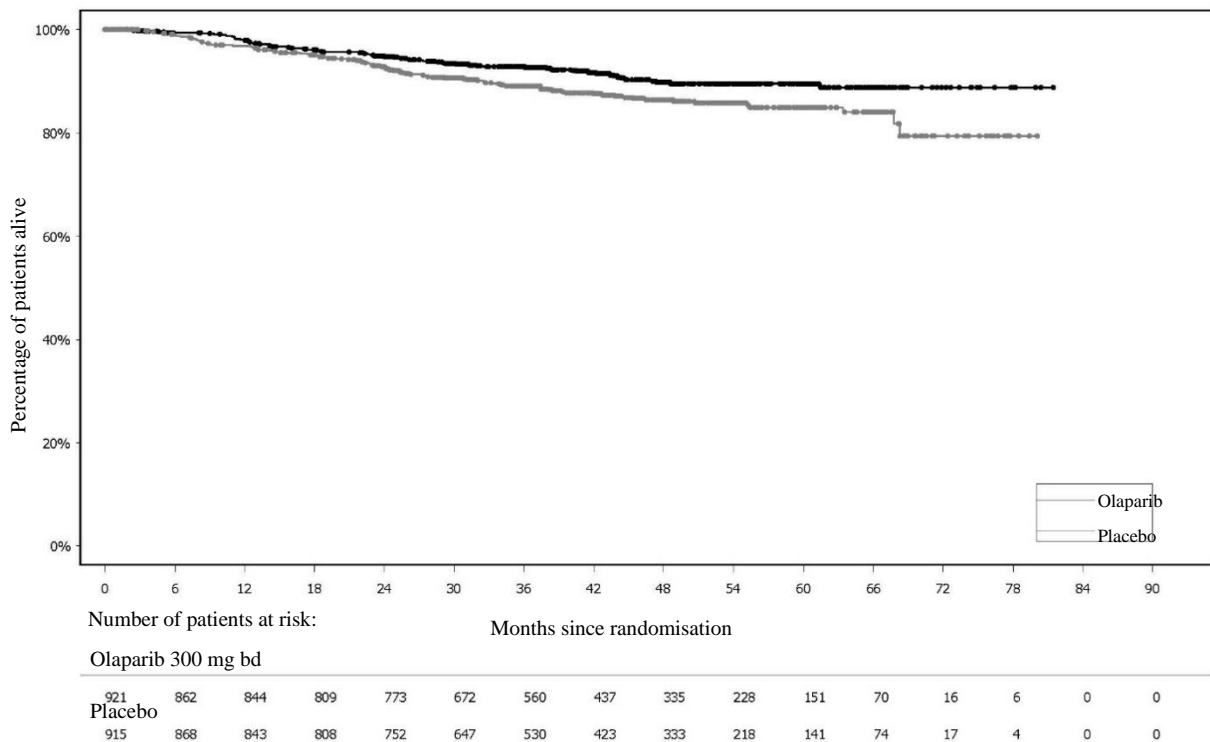


Figure 9 Kaplan-Meier plot of OS for adjuvant treatment of patients with germline *BRCA*-mutated high risk early breast cancer in OlympiA



gBRCA1/2-mutated HER2-negative metastatic breast cancer
OlympiAD study

The safety and efficacy of olaparib in patients with *gBRCA1/2*-mutations who had HER2-negative metastatic breast cancer were studied in a Phase III randomised, open-label, controlled trial (OlympiAD). In this study 302 patients with a documented deleterious or suspected deleterious

gBRCA mutation were randomised 2:1 to receive either Lynparza (300 mg [2 x 150 mg tablets] twice daily) or physician's choice of chemotherapy (capecitabine 42%, eribulin 35%, or vinorelbine 17%) until progression or unacceptable toxicity. Patients with *BRCA1/2* mutations were identified from germline testing in blood via a local test or by central testing at Myriad. Patients were stratified based on: receipt of prior chemotherapy regimens for metastatic breast cancer (yes/no), hormone receptor (HR) positive vs triple negative (TNBC), prior platinum treatment for breast cancer (yes/no). The primary endpoint was PFS assessed by blinded independent central review (BICR) using RECIST 1.1. Secondary endpoints included PFS2, OS, objective response rate (ORR) and HRQoL.

Patients must have received treatment with an anthracycline unless contraindicated and a taxane in either a (neo)adjuvant or metastatic setting. Patients with HR+ (ER and/or PgR positive) tumours 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. Prior therapy with platinum was allowed in the metastatic setting provided there had been no evidence of disease progression during platinum treatment and in the (neo)adjuvant setting provided the last dose was received at least 12 months prior to randomisation. No previous treatment with a PARP inhibitor, including olaparib, was permitted.

Demographic and baseline characteristics were generally well balanced between the olaparib and comparator arms (see Table 11).

Table 11: Patient demographic and baseline characteristics in OlympiAD

	Olaparib 300 mg bd n=205	Chemotherapy n=97
Age - year (median)	44	45
Gender (%)		
Female	200 (98)	95 (98)
Male	5 (2)	2 (2)
Race (%)		
White	134 (65)	63 (65)
Asian	66 (33)	28 (29)
Other	5 (2)	6 (6)
ECOG performance status (%)		
0	148 (72)	62 (64)
1	57 (28)	35 (36)
Overall disease classification		
Metastatic	205 (100)	97 (100)
Locally advanced	0	0
New metastatic breast cancer (%)	26 (13)	12 (12)
Hormone receptor status (%)		
HR+	103 (50)	49 (51)
TNBC	102 (50)	48 (49)
<i>gBRCA</i> mutation type (%)		
<i>gBRCA1</i>	117 (57)	51 (53)
<i>gBRCA2</i>	84 (41)	46 (47)
<i>gBRCA1</i> and <i>gBRCA2</i>	4 (2)	0
≥2 Metastatic sites (%)	159 (78)	72 (74)
Location of the metastasis (%)		
Bone only	16 (8)	6 (6)
Other	189 (92)	91 (94)
Measurable disease (%)	167 (82)	66 (68)
Progressive disease at time of randomization (%)	159 (78)	73 (75)
Tumour grade at diagnosis		
Well differentiated (G1)	5 (2)	2 (2)
Moderately differentiated (G2)	52 (25)	23 (24)
Poorly differentiated (G3)	108 (53)	55 (57)
Undifferentiated (G4)	4 (2)	0
Unassessable (GX)	27 (13)	15 (16)
Missing	9 (4)	2 (2)

Number of prior lines of chemotherapy for metastatic breast cancer (%)		
0	68 (33)	31 (32)
1	80 (39)	42 (43)
2	57 (28)	24 (25)
Previous platinum-based therapy (%)	60 (29)	26 (27)
in (neo)adjuvant setting	15 (7)	7 (7)
metastatic setting	43 (21)	14 (14)
in (neo)adjuvant and metastatic setting	3 (1)	1 (1)
Previous anthracycline treatment		
in (neo) adjuvant setting	169 (82)	76 (78)
metastatic setting	41 (20)	16 (17)
Previous taxane treatment		
in (neo)adjuvant setting	146 (71)	66 (68)
metastatic setting	107 (52)	41 (42)
Previous anthracycline and taxane treatment	204 (99.5)	96 (99)

As subsequent therapy, 0.5% and 8% of patients received a PARP inhibitor in the treatment and comparator arms, respectively; 29% and 42% of patients, respectively, received subsequent platinum therapy.

A statistically significant improvement in PFS, the primary efficacy outcome, was demonstrated for olaparib-treated patients compared with those in the comparator arm (see Table 12 and Figure 10).

Table 12: Summary of key efficacy findings for patients with gBRCA1/2-mutated HER2-negative metastatic breast cancer in OlympiAD

	Olaparib 300 mg bd	Chemotherapy
PFS (77% maturity) – DCO 09 December 2016		
Number of events: Total number of patients (%)	163:205 (80)	71:97 (73)
Median time (months) (95% CI)	7.0 (5.7-8.3)	4.2 (2.8-4.3)
HR (95% CI)	0.58 (0.43-0.80)	
P value (2-sided) ^a	p=0.0009	
PFS2 (65% maturity) - DCO 25 September 2017^b		
Number of events: Total number of patients (%)	130:205 (63)	65:97 (67)
Median time (months) (95% CI)	12.8 (10.9-14.3)	9.4 (7.4-10.3)
HR (95% CI)	0.55 (0.39-0.77)	
P value (2-sided) ^a	p=0.0005	
OS (64% maturity) – DCO 25 September 2017		
Number of events: Total number of patients (%)	130:205 (63)	62:97 (64)
Median time (months) (95% CI)	19.3 (17.2-21.6) ^c	17.1 (13.9-21.9)
HR (95% CI)	0.90 (0.66-1.23)	
P value (2-sided) ^a	p=0.5131	
Confirmed ORR – DCO 09 December 2016		
Number of objective responders: Total number of patients with measurable disease (%)	87: 167 (52) ^d	15:66 (23)
95% CI	44.2-59.9	13.3-34.7
DOR – DCO 09 December 2016		
Median, months (95% CI)	6.9 (4.2, 10.2)	7.9 (4.5, 12.2)

^a Based on stratified log-rank test.

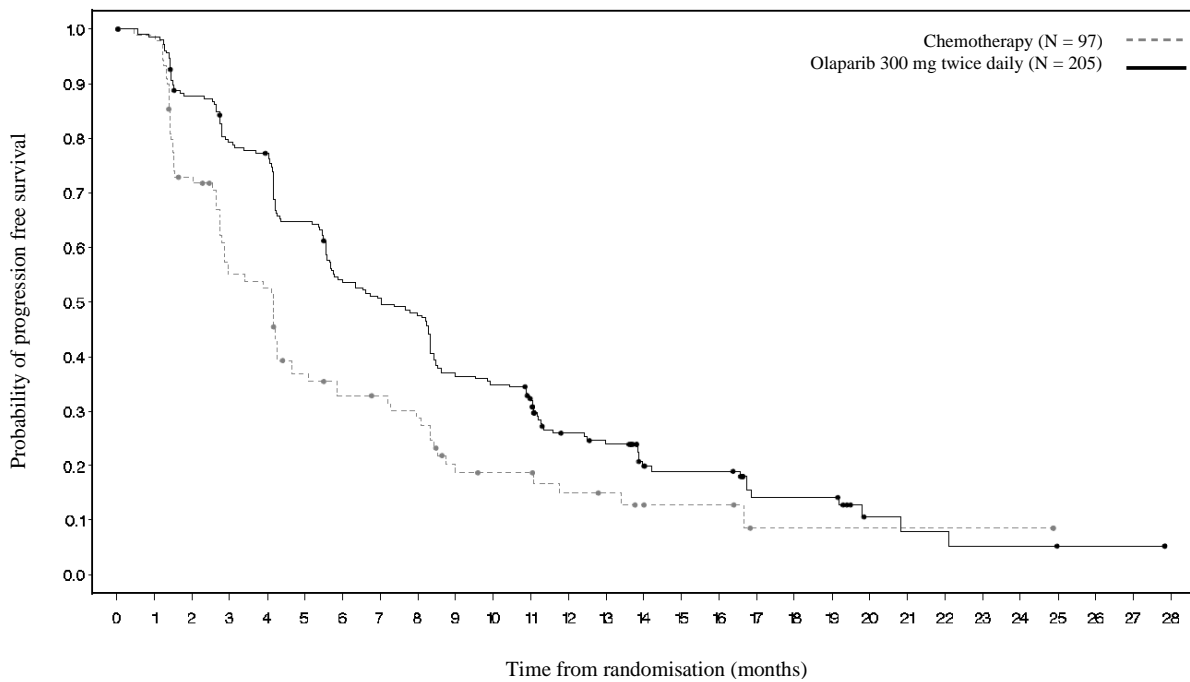
^b Post-hoc analysis.

^c The median follow-up time in censored patients was 25.3 months for olaparib versus 26.3 months for comparator.

^d Confirmed responses (by BICR) were defined as a recorded response of either CR/PR, confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed. In the olaparib arm 8% with measurable disease had a complete response versus 1.5% of patients in the comparator arm; 74/167 (44%) of patients in the olaparib arm had a partial response versus 14/66 (21%) of patients in the chemotherapy arm. In the TNBC patient subgroup the confirmed ORR was 48% (41/86) in the olaparib arm and 12% (4/33) in the comparator arm. In the HR+ patient subgroup the confirmed ORR was 57% (46/81) in the olaparib arm and 33% (11/33) in the comparator arm.

bd Twice daily; CI Confidence interval; DOR Duration of response; DCO Data cut off; HR Hazard ratio; HR+ Hormone receptor positive, ORR Objective response rate; OS overall survival; PFS progression-free survival; PFS2 Time to second progression or death, TNBC triple negative breast cancer.

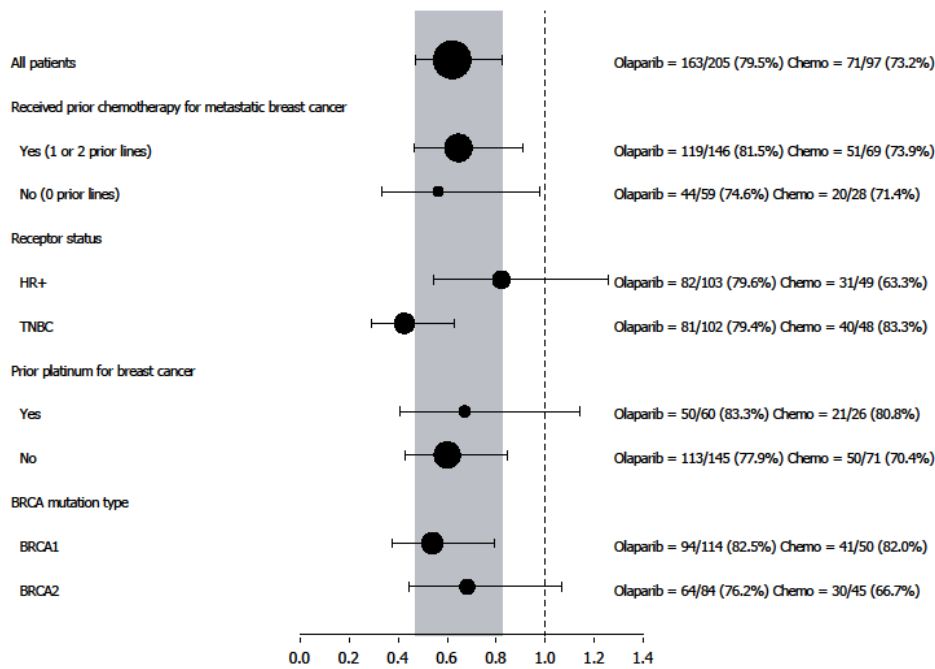
Figure 10: OlympiAD: Kaplan-Meier plot of BICR PFS in patients with gBRCA1/2-mutated HER2-negative metastatic breast cancer (77% maturity) DCO 09 December 2016



Number of patients at risk																													
Olaparib 300 mg twice daily tablet																													
205	201	177	159	154	129	107	100	94	73	69	61	40	36	23	21	21	11	11	11	4	3	3	2	2	1	1	1	0	
Chemotherapy																													
97	88	63	46	44	29	25	24	21	13	11	11	8	7	4	4	4	1	1	1	1	1	1	1	1	1	0	0	0	0

Consistent results were observed in all predefined patient subgroups (see Figure 12). Subgroup analysis indicated PFS benefit of olaparib versus comparator in TNBC (HR 0.43; 95% CI: 0.29-0.63, n=152) and HR+ (HR 0.82; 95% CI: 0.55-1.26, n=150) patient subgroups.

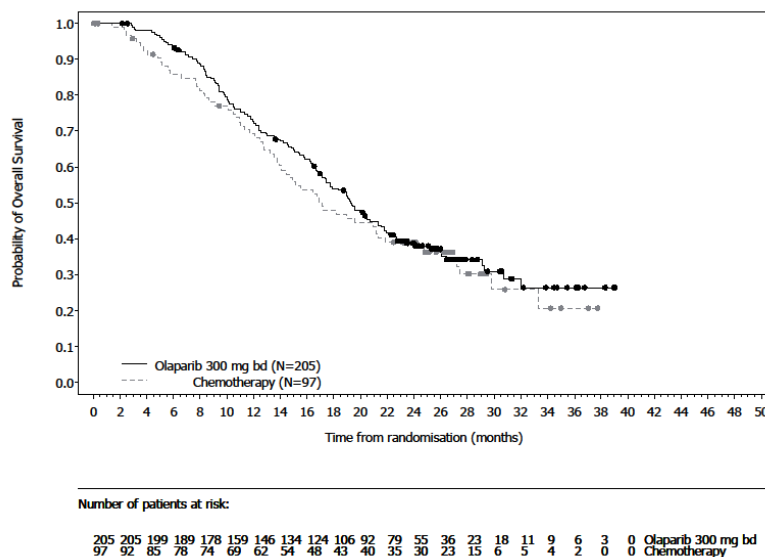
Figure 11: PFS (BICR), Forest plot, by prespecified subgroup



In a post-hoc analysis of the subgroup of patients that had not progressed on chemotherapy other than platinum, the median PFS in the olaparib arm (n=22) was 8.3 months (95% CI 3.1-16.7) and 2.8 months (95% CI 1.4-4.2) in the chemotherapy arm (n=16) with a HR of 0.54 (95% CI 0.24-1.23). However, the number of patients is too limited to make meaningful conclusions on the efficacy in this subgroup.

Seven male patients were randomised (5 olaparib and 2 comparator). At the time of the PFS analysis, 1 patient had a confirmed partial response with a duration of response of 9.7 months in the olaparib arm. There were no confirmed responses in the comparator arm.

Figure 12: OlympiAD: Kaplan-Meier plot of OS in patients with gBRCA1/2-mutated HER2-negative metastatic breast cancer (64% maturity) DCO 25 September 2017



OS analysis in patients with no prior chemotherapy for metastatic breast cancer indicated benefit in these patients with a HR of 0.45 (95% CI 0.27-0.77), while for further lines of therapy HR exceeded 1.

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

POLO Study

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 gBRCA-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 \geq 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 BRCAAnalysis® or Myriad BRCAAnalysis CDx® test. The BRCAm status of all patients identified using prior local testing results was confirmed, where sent, using the Myriad BRCAAnalysis® or Myriad BRCAAnalysis 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 \geq 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 13: Summary of key efficacy findings for patients with *gBRCAm* metastatic adenocarcinoma of the pancreas in POLO

	Olaparib 300 mg bd	Placebo
PFS (68% maturity)		
Number of events: Total number of patients (%)	60:92 (65)	44:62 (71)
Median time (months)	7.4	3.8
HR (95% CI) ^{a,b}	0.53 (0.35-0.82)	
P value (2-sided)	p=0.0038	
OS (70% maturity)		
Number of events: Total number of patients (%)	61:92 (66)	47:62 (76) ^c
Median time (months)	19.0	19.2
HR (95% CI) ^{b,c}	0.83 (0.56-1.22)	
P value (2-sided)	p=0.3487	
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 13: POLO: Kaplan-Meier plot of PFS for patients with *gBRCAm* metastatic adenocarcinoma of the pancreas (68% maturity – BICR)

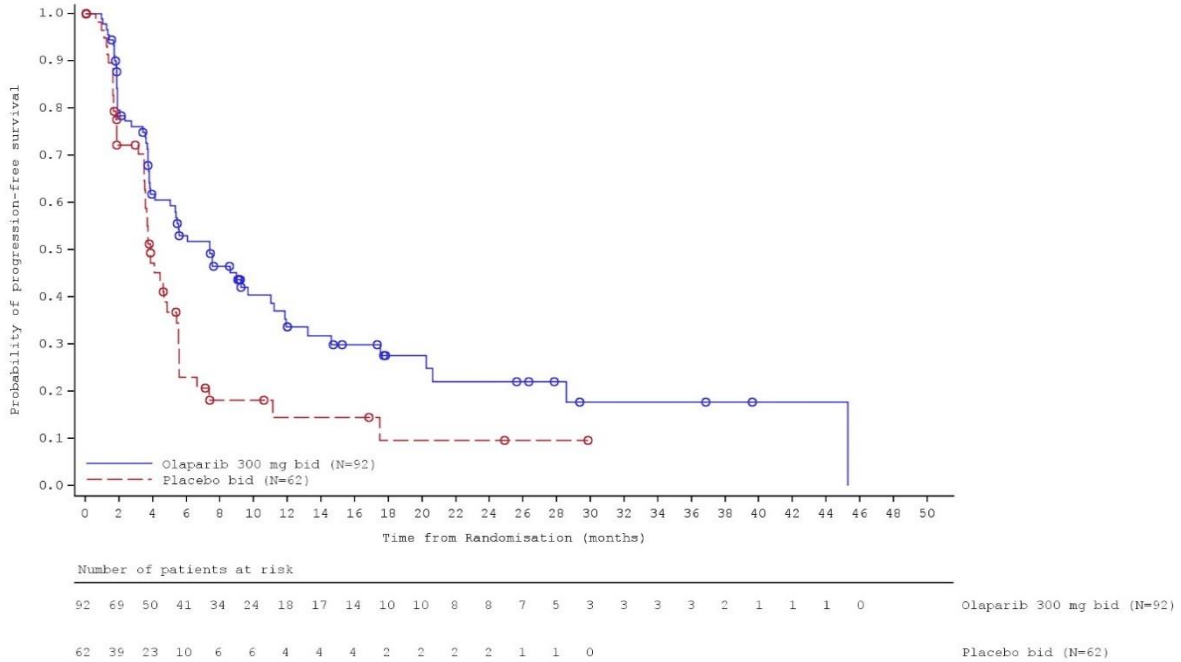
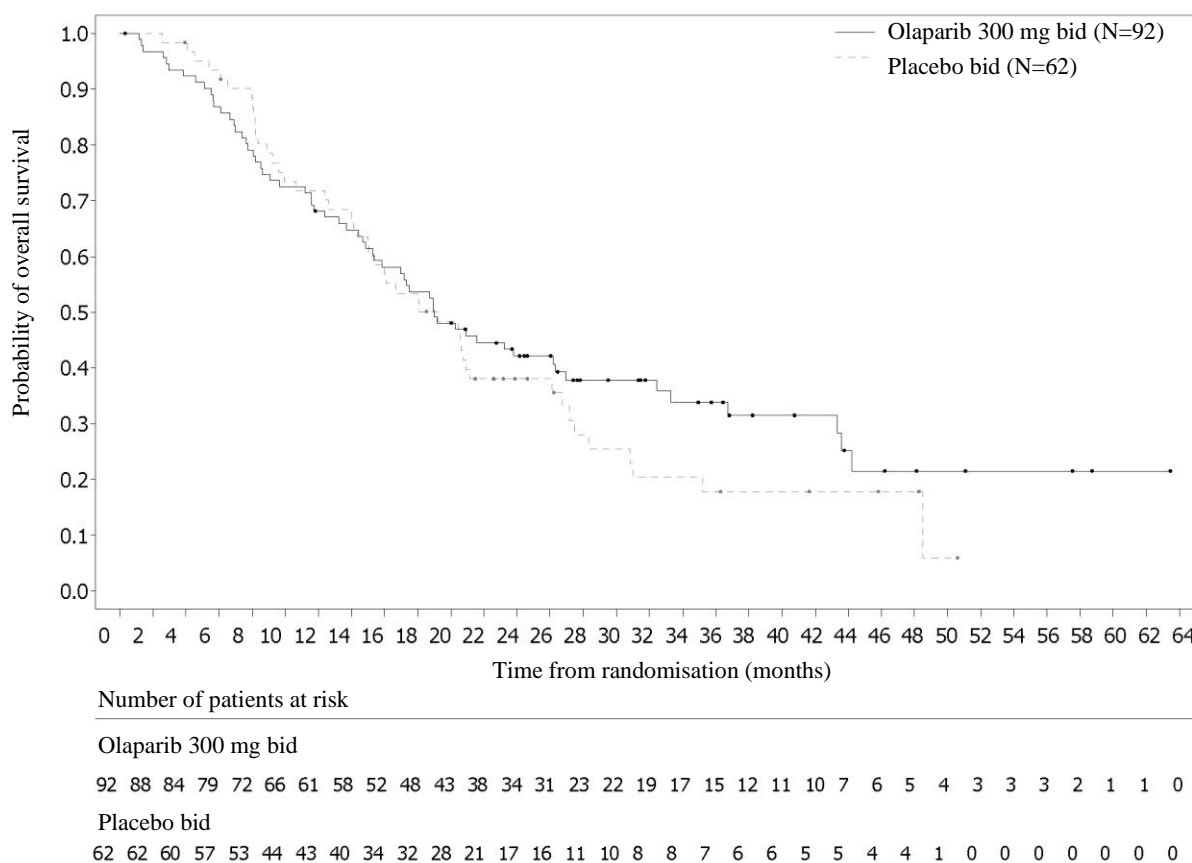


Figure 14 POLO: Kaplan-Meier plot of OS for patients with *gBRCAm* metastatic adenocarcinoma of the pancreas (70% maturity)



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

Homologous recombination repair gene mutated metastatic castration-resistant prostate cancer PROfound Study

PROfound was a Phase III randomised, open-label, multicentre trial that evaluated the efficacy of Lynparza (300 mg [2 x 150 mg tablets] twice daily) versus a comparator arm of investigator's choice of NHA ([new hormonal agent] enzalutamide or abiraterone acetate) in men with metastatic castration-resistant prostate cancer (mCRPC). Patients needed to have progressed on prior NHA for the treatment of metastatic prostate cancer and/or CRPC and have a tumour mutation in one of 15 genes involved in the homologous recombination repair (HRR) pathway.

Patients were divided into two cohorts based on HRR gene mutation status. Patients with mutations in either *BRCA1*, *BRCA2* or *ATM* were randomised in Cohort A; patients with mutations among 12 other genes involved in the HRR pathway (*BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D* or *RAD54L*) were randomised in Cohort B. Patients with co-mutations (*BRCA1*, *BRCA2* or *ATM* plus a Cohort B gene) were randomised in Cohort A. Although

patients with *PPP2R2A* gene mutations were enrolled in the trial, Lynparza is not indicated for the treatment of patients with this gene mutation due to unfavourable benefit-risk.

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

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

Demographics and baseline characteristics were generally well balanced between the olaparib and comparator arms in Cohort A+B. Median age was 69 years in both arms. Prior therapy in the olaparib arm was 66% taxane, 40% enzalutamide, 38% abiraterone acetate and 20% both enzalutamide and abiraterone acetate. Prior therapy in the comparator arm was 63% taxane, 41% enzalutamide, 41% abiraterone acetate and 18% both enzalutamide and abiraterone acetate. Fifty-eight percent (58%) of patients in the olaparib arm and 55% in the comparator arm had measurable disease at study entry. The proportion of patients with bone, distant lymph node, locoregional lymph node, liver and respiratory metastases was 85%, 39%, 21%, 10% and 17%, respectively in the olaparib arm and 86%, 39%, 24%, 14% and 12%, respectively in the comparator arm. Most patients in both treatment arms had an ECOG of 0 or 1 (95%). Baseline pain scores (BPI-SF worst pain) were 0- $<$ 2 (48%), 2-3 (12%) or $>$ 3 (36%) in the olaparib arm and 0- $<$ 2 (44%), 2-3 (10%) or $>$ 3 (43%) in the comparator arm. Median baseline PSA was 68.22 μ g/L in the olaparib arm and 106.49 μ g/L in the comparator arm.

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

Other secondary endpoints in Cohort A and Cohort A+B included time to first symptomatic skeletal-related event (SSRE), duration of response (DoR), time to opiate use for cancer-related pain, confirmed soft tissue ORR, prostate specific antigen (PSA₅₀) response, circulating tumour cells (CTC) conversion rate, time to second progression or death (PFS2) and disease-related symptoms and health related quality of life ([HRQoL], pain progression, pain severity progression, pain interference and pain palliation). Other secondary end-points in Cohort B included rPFS by BICR. In addition, other secondary end-points in Cohort B and Cohort A+B included confirmed ORR by BICR, OS and time to pain progression.

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

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

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

Table 14 Summary of key efficacy findings in Cohort A and Cohort A + B in PROfound

	Cohort A Olaparib 300 mg bd (N=162)	Cohort A Investigators choice of NHA (N=83)	Cohort A+B Olaparib 300 mg bd (N=256)	Cohort A+B Investigators choice of NHA (N=131)
rPFS by BICR^{a,b}				
Number of events/total number of patients (%)	106/162 (65) ^c	68/83 (82) ^c	180/256 (70) ^c	99/131 (76) ^c
Median rPFS (95% CI) [months]	7.4 (6.2, 9.3)	3.6 (1.9, 3.7)	5.8 (5.5, 7.4)	3.5 (2.2, 3.7)
HR (95% CI) ^d	0.34 (0.25, 0.47)		0.49 (0.38, 0.63)	
P value (2-sided) ^e	<0.0001		<0.0001	
Confirmed ORR by BICR				
Number of objective responders/total number of patients with measurable disease at baseline (%)	28/84 (33)	1/43 (2)	30/138 (22)	3/67 (5)
Odds ratio (95% CI)	20.86 (4.18, 379.18)		5.93 (2.01, 25.40)	
P-value (2-sided)	<0.0001		0.0006	
DoR (patients with confirmed objective response)^f				
N	28	1	30	3
Median (95% CI) [months]	5.9 (5.5, 9.0)	7.4 (NR, NR)	5.9 (5.5, 9.0)	7.4 (3.6, 7.4)
OS				
Number of events/total number of patients (%)	91/162 (56)	57/83 (69)	160/256 (63)	88/131 (67)
Median OS (95% CI) [months]	19.1 (17.2, 23.4)	14.7 (11.9, 18.8)	17.3 (15.5, 18.6)	14.0 (11.5, 17.1)
HR (95% CI)	0.69 (0.50, 0.97)		0.79 (0.61, 1.03)	
P-value (2-sided) [nominal]	0.0175		.f	
PFS2 (by investigator)^f				
Number of events/total number of patients (%)	61/162 (38)	44/83 (53)	113/256 (44)	69/131 (53)
Median PFS2 (95% CI) [months]	17.2 (12.7, 18.3)	10.6 (9.1, 11.2)	13.0 (11.4, 15.8)	9.7 (8.2, 11.0)
HR (95% CI)	0.53 (0.36, 0.79)		0.61 (0.45, 0.83)	
P-value (2-sided) [nominal]	p=0.0003		p=0.0003	
Time to first SSRE^f				
Number of events/total number of patients (%)	25/162 (15)	19/83 (23)	41/256 (16)	25/131 (19)
Median (95% CI) [months]	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)
HR (95% CI)	0.37 (0.20, 0.70)		0.49 (0.29, 0.82)	
P-value (2-sided) [nominal]	0.0013		0.0050	
Time to pain progression^g				
Number of events/total number of patients (%)	21/162 (13)	14/83 (17)	32/256 (13)	16/131 (12)
Median (95% CI) [months]	NR (NR, NR)	9.9 (5.4, NR)	NR (NR, NR)	NR (NR, NR)
HR (95% CI)	0.44 (0.22, 0.91)		0.64 (0.35, 1.21)	
P-value (2-sided)	0.0192		0.1490	
Time to opiate use for cancer-related pain^f				
Number of events/total number of patients (%)	42/113 (37)	29/58 (50)	65/175 (37)	44/92 (48)
Median (95% CI) [months]	18.0 (12.7, NR)	7.5 (3.2, NR)	18.0 (11.6, NR)	9.0 (5.4, NR)
Opiate-free use at 6 months (%)	75.6	56.7	74.8	61.0
Opiate-free use at 12 months (%)	61.5	45.6	58.8	47.7
HR (95% CI)	0.61 (0.38, 0.99)		0.67 (0.46, 0.99)	
P-value (2-sided) [nominal]	0.0443		0.0229	
PSA₅₀ response^f				
Number of patients with single visit response (n)	69	9	78	17
Single visit response (%) [95% CI]	42.6 (34.87, 50.59)	10.8 (5.08, 19.59)	30.5 (24.89, 36.51)	13.0 (7.74, 19.96)
Number of patients with confirmed response (n)	66	6	73	12
Confirmed response (%) [95% CI]	40.7 (33.10, 48.73)	7.2 (2.70, 15.07)	28.5 (23.07, 34.47)	9.2 (4.82, 15.45)

CTC conversion rate ^{f,h}				
Number of patients with CTC conversion (n)	29	5	41	7
CTC conversion (%) [95% CI]	17.9 (12.33, 24.69)	6.0 (1.98, 13.50)	16.0 (11.74, 21.09)	5.3 (2.18, 10.70)

- ^a rPFS (Cohort A), rPFS (Cohort A+B), ORR (Cohort A), TTPP (Cohort A) and OS (Cohort A) were tested for multiplicity. The multiplicity strategy for primary endpoint and key secondary endpoints was that upon achieving statistical significance on the primary endpoint rPFS in Cohort A, testing of each of the secondary endpoints, ORR (Cohort A), rPFS (Cohort A + B), TTPP (Cohort A) and OS (Cohort A) were performed sequentially.
- ^b Cohort A - the sensitivity analysis of rPFS by investigator assessment (HR=0.24, 95% CI 0.17, 0.34, p<0.0001 [nominal]; median rPFS 9.8 months vs 3.6 months for olaparib vs investigators choice of NHA, respectively) was consistent with the rPFS analysis by BICR assessment. Cohort A+B - the sensitivity analysis of rPFS by investigator assessment (HR=0.36, 95% CI 0.27, 0.47, p<0.0001 [nominal]; median rPFS 7.5 months vs 3.5 months for olaparib vs investigators choice of NHA, respectively) was consistent with the rPFS analysis by BICR.
- ^c rPFS 71% maturity (Cohort A), 72% maturity (Cohort A+B)
- ^d The HR and CI were calculated using a Cox proportional hazards model adjusted for prior taxane use and measurable disease. The Efron approach was used for handling ties. HR <1 favours olaparib
- ^e The analysis was performed using the log-rank test stratified by prior taxane use and measurable disease using the Breslow method for handling ties
- ^f Not controlled for multiplicity
- ^g Time to pain progression was defined as the time from randomisation to the first date of a clinically meaningful worsening (≥2 points increase from baseline on a scale of 0-10) in average BPI-SF worst pain [Item 3] score and/or an increase in or initiation of opioid analgesic use.
- ^h Circulating tumour cell conversion was defined as the proportion of patients achieving a decline in the number of CTCs from ≥5 cells/7.5 mL at baseline to <5 cells/7.5 mL at any visit post baseline
- bd Twice daily; BICR Blinded independent central review; CI Confidence interval; CTC Circulating tumour cells; DoR Duration of response; HR Hazard ratio; NHA New hormonal agent; ORR Objective response rate; OS Overall survival; PFS2 Time from randomisation to second progression or death; PSA Prostate specific antigen; rPFS Radiological progression-free survival; SSRE Symptomatic skeletal-related event; TTPP Time to pain progression.

Figure 15 Cohort A: Kaplan-Meier plot of rPFS (by BICR)

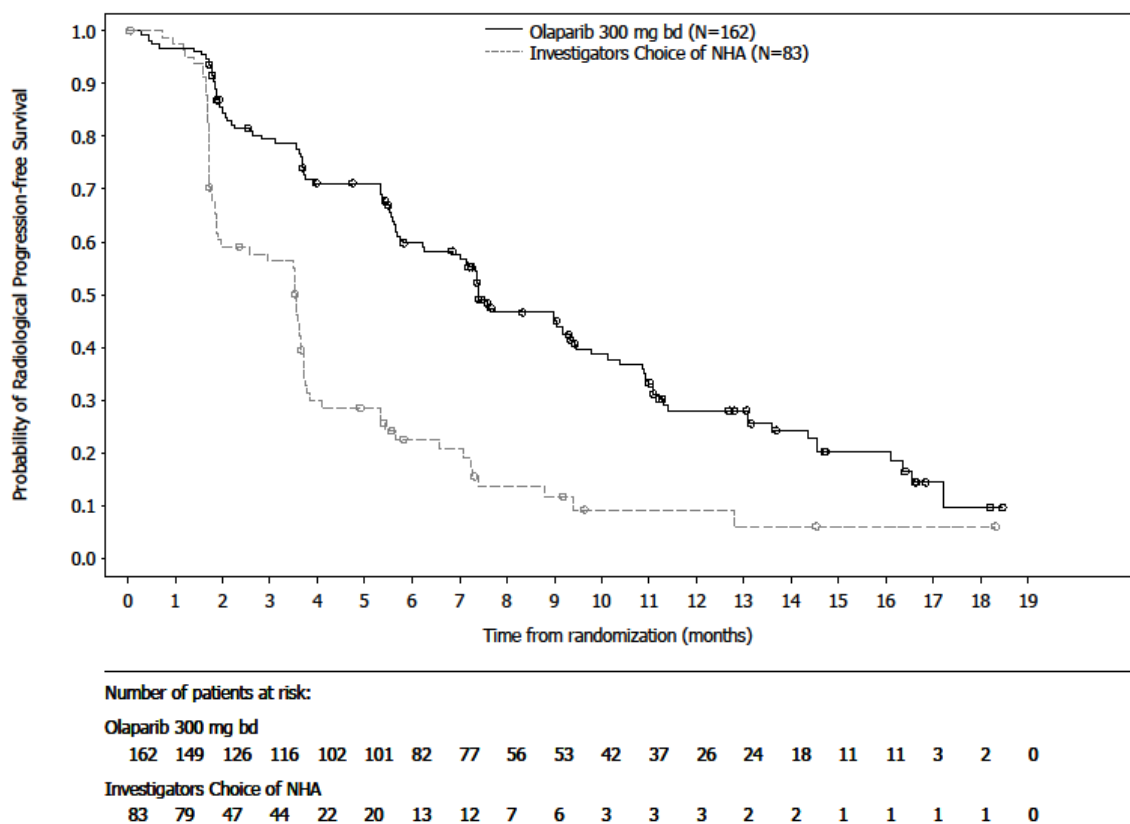
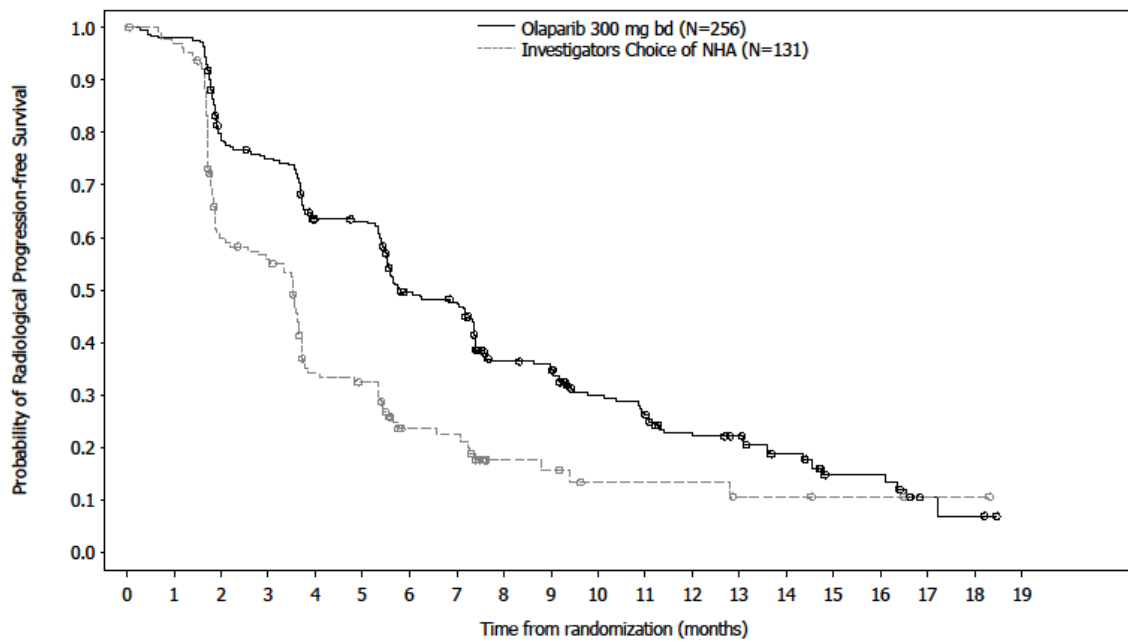


Figure 16 Cohort A+B: Kaplan-Meier plot of rPFS (by BICR)



Number of patients at risk:

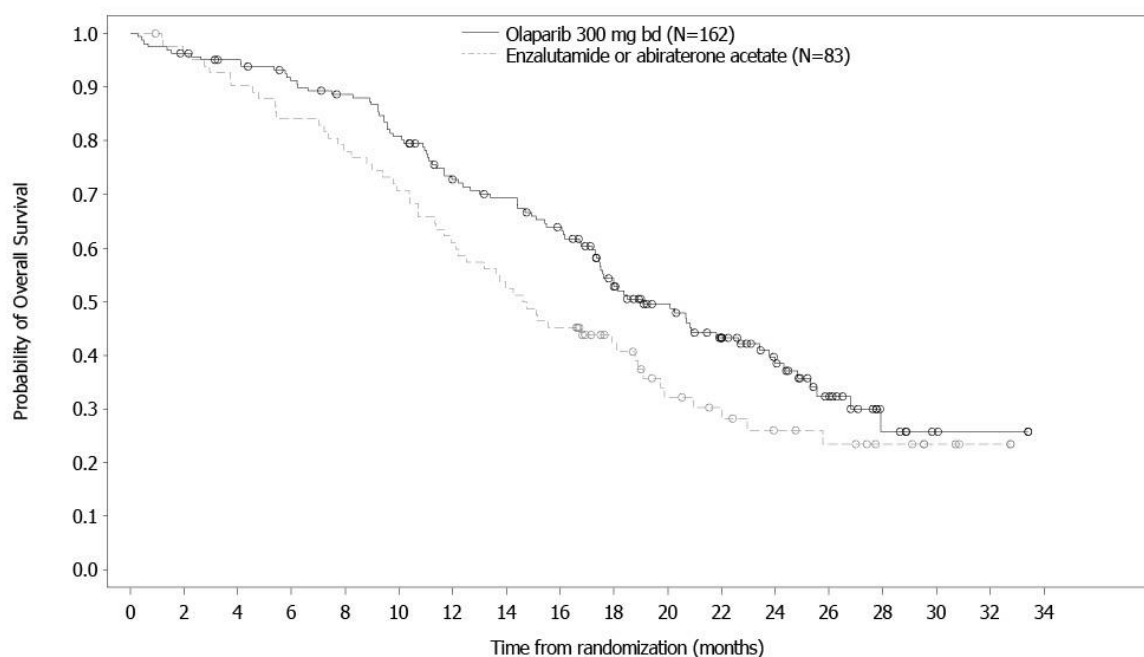
Olaparib 300 mg bd

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

Investigators Choice of NHA

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

Figure 17 Cohort A: Kaplan-Meier plot of OS



Number of patients at risk:

Olaparib 300 mg bd	162	155	150	142	136	124	107	101	91	71	56	44	30	18	6	2	1	0
Enzalutamide or abiraterone acetate	83	79	74	69	64	58	50	43	37	27	18	15	11	9	6	3	1	0

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

In Cohort B, the median rPFS was 4.8 months for olaparib vs 3.3 months for comparator with a HR of 0.88 (95% CI 0.58, 1.36; $p=0.3976$ [nominal]). Two patients (3.7%) in the olaparib arm and 2 patients (8.3%) in the comparator arm with measurable disease at baseline had a confirmed radiological objective response. The odds ratio (OR) and 95% CIs were not calculated due to the small number of responders. In the olaparib arm, the 2 patients had *CDK12* mutations and achieved a partial response. In the comparator arm, the 2 patients had co-occurring mutations (one with *PALB2+PPP2R2A* and one with *CDK12+PALB2*) and achieved a partial response. Stable disease was observed in 57.4% of patients in the olaparib arm and 29.2% of patients in the comparator arm. The final OS analysis had events in 100/142 patients. Median OS was 14.1 months for olaparib vs 11.5 months for comparator with a HR of 0.96 (95% CI 0.63, 1.49; $p=0.7921$, nominal). The HR indicates no detriment in OS for olaparib-treated patients.

With regards to the rPFS subgroup analysis by Cohort B gene, there was a trend for benefit of olaparib over comparator for patients with a single *CDK12* mutation. For *CHEK2*, *RAD54L* and *PPP2R2A*, results should be interpreted with caution due to the small number of events. Hazard ratios were not calculable for some of the Cohort B genes (*BARD1*, *BRIP1*, *CHEK1*, *PALB2*, *RAD51B*, and *RAD51D*) due to the small number of events in these subgroups. In Cohort B a subgroup analysis of confirmed ORR for each individual gene in patients with single HRR gene mutations only, 2/34 *CDK12m* patients (5.9%) in the olaparib arm and no patients in the comparator arm (N=12) had a response. The OR and 95% CIs were not calculable.

Table 15 Summary of rPFS in PROfound for Cohort B genes

		Number of events/total number of patients (%)			Median (95% CI) [months]	
	Patients n=142	Olaparib 300 mg bd n=94	Investigators choice of NHA n=48	HR (95% CI)	Olaparib 300 mg bd	Investigators choice of NHA
rPFS (BICR)						
Overall Cohort B		74/94 (78.7)	31/48 (64.6)	0.88 (0.58, 1.36)	4.8 (3.7, 5.5)	3.3 (1.9, 5.4)
<i>CDK12</i>	89	47/61 (77.0)	18/28 (64.3)	0.74 (0.44, 1.31)	5.1 (3.6, 5.5)	2.2 (1.7, 4.8)
<i>PALB2</i>	4	1/3 (33.3)	0/1 (0)	NC (NC, NC)	NC (NC, NC)	NC (NC, NC)
<i>RAD51B</i>	5	3/4 (75.0)	1/1 (100)	NC (NC, NC)	10.9 (1.6, 14.8)	1.77 (NC, NC)
<i>RAD51D</i>	1	1/1 (100)	0/0	NC (NC, NC)	1.9 (NC, NC)	NC (NC, NC)
<i>CHEK1</i>	2	1/1 (100)	1/1 (100)	NC (NC, NC)	1.8 (NC, NC)	3.7 (NC, NC)
<i>CHEK2</i>	12	6/7 (85.7)	3/5 (60.0)	0.87 (0.23, 4.13)	5.6 (1.6, 12.0)	3.4 (1.4, NC)
<i>RAD54L</i>	5	3/3 (100)	2/2 (100)	0.33 (0.05, 2.54)	7.2 (3.7, 7.4)	2.4 (1.8, 3.0)
<i>PPP2R2A</i>	10	5/6 (83.3)	2/4 (50.0)	6.61 (1.41, 46.41)	2.7 (1.8, 3.9)	NC (NC, NC)
<i>BRIP1</i>	3	2/2 (100)	1/1 (100)	NC (NC, NC)	3.6 (1.7, 5.4)	1.7 (NC, NC)
<i>BARD1</i>	1	0/0	1/1 (100)	NC (NC, NC)	NC (NC, NC)	5.8 (NC, NC)

Seven patients in Cohort B had a co-occurring mutation. Gene by gene analysis is presented for single mutations only. No patients in Cohort B had *FANCL* or *RAD51C* mutations.

Sensitivity analysis of rPFS by investigator assessment (HR=0.60, 95% CI 0.39, 0.93, p=0.0178 [nominal]; median rPFS 5.6 months vs 3.4 months for olaparib vs investigators choice of NHA.

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

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

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Lynparza in all subsets of the paediatric population, in ovarian carcinoma (excluding rhabdomyosarcoma and germ cell tumours) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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

Absorption

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

Co-administration with food slowed the rate (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 increased 8%). Consequently, Lynparza may be taken 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.

Biotransformation

In vitro, CYP3A4/5 were shown to be the enzymes primarily responsible for the metabolism of olaparib (see section 4.5).

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. The majority of the metabolism was attributable to oxidation reactions with a number of the components produced undergoing subsequent glucuronide or sulfate 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 UGT2B7, or CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 or 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. *In vitro*, olaparib is a substrate of the efflux transporter P-gp, however, this is unlikely to be of clinical significance (see section 4.5).

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

Elimination

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. Majority of the material was excreted as metabolites.

Special populations

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

Renal impairment

In 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.

In 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).

There are no data in patients with severe renal impairment or end-stage renal disease (creatinine clearance <30 ml/min).

Hepatic impairment

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

Paediatric population

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

5.3 Preclinical safety data

Genotoxicity

Olaparib showed no mutagenic potential, but was clastogenic in mammalian cells *in vitro*. When dosed orally to rats, olaparib induced micronuclei in bone marrow. This clastogenicity is consistent with the known 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 changes were reversible within 4 weeks of cessation of dosing. In rats, minimal degenerative effects on gastrointestinal tract were also noted. These findings occurred at exposures below those seen clinically. 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

In a female fertility study where rats were dosed until implantation, although extended oestrus was observed in some animals, mating performance and pregnancy rate was not affected. However, there was a slight reduction in embryofoetal survival.

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

Carcinogenicity

Carcinogenicity studies have not been conducted with olaparib.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Copovidone
Silica, colloidal anhydrous
Mannitol
Sodium stearyl fumarate

Tablet coating

Hypromellose
Macrogol 400
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide black (E172) (150 mg tablets only)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer to expiry date on the blister strip or outer carton

6.4 Special precautions for storage

Store below 30°C in the original package in order to protect from moisture.

This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Alu/Alu non-perforated blister containing 8 film-coated tablets.

A box of 56 film-coated tablets (7 blisters).

6.6 Instructions for use, handling and disposal

No specific requirements.

7. MARKETING AUTHORISATION HOLDER

AstraZeneca (Thailand) Ltd., Bangkok, Thailand.

8. DATE OF REVISION OF THE TEXT

January 2023