Certificate Number: PP10185999

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

1 NAME OF THE MEDICINAL PRODUCT

Lynparza 100 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 100 mg olaparib.

Excipient with known effect:
This medicinal product contains 0.24 mg sodium per 100 mg tablet..

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Yellow to dark yellow, oval, bi-convex tablet, debossed with 'OP100' 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 (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a *BRCA1/2* mutation and/or genomic instability (see section 5.1).

Breast cancer
Lynparza is indicated as:

- monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline *BRCA1/2*-mutations who have HER2-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy (see sections 4.2 and 5.1).
- monotherapy for the treatment of adult patients with germline *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 *BRCA1/2*-mutations who have metastatic adenocarcinoma of the pancreas and have not progressed after a minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen.

Prostate cancer
Lynparza is indicated:

- as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) and *BRCA1/2*-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent.
- in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated (see section 5.1).

4.2 Posology and method of administration

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

Patient selection
First-line maintenance treatment of BRCA-mutated advanced ovarian cancer:
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.

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

First-line maintenance treatment of HRD positive advanced ovarian cancer in combination with bevacizumab:
Before Lynparza with bevacizumab treatment is initiated for the first-line maintenance treatment of EOC, FTC or PPC, patients must have confirmation of either deleterious or suspected deleterious *BRCA1/2* mutation and/or genomic instability determined using a validated test (see section 5.1).

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 g*BRCA1/2* mutation using a validated test (see section 5.1).
Monotherapy treatment of g*BRCA1/2-mutated HER2-negative metastatic breast cancer:*
For germline breast cancer susceptibility genes (g*BRCA1/2*) mutated human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer, patients must have confirmation of a deleterious or suspected deleterious g*BRCA1/2* mutation before Lynparza treatment is initiated. g*BRCA1/2* 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.

Certificate Number: PP10185999

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

First-line maintenance treatment of g*BRCA-mutated metastatic adenocarcinoma of the pancreas*:
For first-line maintenance treatment of germline *BRCA1/2*-mutated metastatic adenocarcinoma of the pancreas, patients must have confirmation of a deleterious or suspected deleterious g*BRCA1/2* mutation before Lynparza treatment is initiated. g*BRCA1/2* mutation status should be determined by an experienced laboratory using a validated test method. Data demonstrating clinical validation of tumour *BRCA1/2* tests in adenocarcinoma of the pancreas are not currently available.

Monotherapy treatment of BRCA1/2-mutated metastatic castration-resistant prostate cancer:
For *BRCA1/2*-mutated metastatic castration-resistant prostate cancer (mCRPC), patients must have confirmation of a deleterious or suspected deleterious *BRCA1/2* mutation (using either tumour or blood sample) before Lynparza treatment is initiated (see section 5.1). *BRCA1/2* mutation status should be determined by an experienced laboratory using a validated test method.

Treatment of mCRPC in combination with abiraterone and prednisone or prednisolone:
No genomic testing is required prior to using Lynparza in combination with abiraterone and prednisone or prednisolone for the treatment of patients with mCRPC.

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

Posology

Lynparza is available as 100 mg and 150 mg tablets.

The recommended dose of Lynparza in monotherapy or in combination with bevacizumab for ovarian cancer or in combination with abiraterone and prednisone or prednisolone for prostate cancer or endocrine therapy is 300 mg (two 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg. The 100 mg tablet is available for dose reduction.

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.

Lynparza in combination with abiraterone and prednisone or prednisolone
When Lynparza is used in combination with abiraterone for the treatment of patients with mCRPC, the dose of abiraterone is 1000 mg orally once daily (see section 5.1). Abiraterone should be given with

prednisone or prednisolone 5 mg orally twice daily. Please refer to the full product information for abiraterone.

Duration of treatment

First-line maintenance treatment of BRCA-mutated advanced 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.

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

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.

Monotherapy treatment of g*BRCA1/2-mutated HER2-negative metastatic breast cancer:*
It is recommended that treatment be continued until progression of the underlying disease or unacceptable toxicity.

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).

First-line maintenance treatment of g*BRCA-mutated metastatic adenocarcinoma of the pancreas*:
It is recommended that treatment be continued until progression of the underlying disease or unacceptable toxicity.

Monotherapy treatment of BRCA1/2-mutated metastatic castration-resistant prostate cancer:
It is recommended that treatment be continued until progression of the underlying disease or unacceptable toxicity. Medical castration with luteinising hormone releasing hormone (LHRH) analogue should be continued during treatment in patients not surgically castrated.

Treatment of mCRPC in combination with abiraterone and prednisone or prednisolone:

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

It is recommended that treatment be continued until progression of the underlying disease or unacceptable toxicity when Lynparza is used in combination with abiraterone and prednisone or prednisolone. Treatment with a gonadotropin-releasing hormone (GnRH) analogue should be continued during treatment in all patients, or patients should have had prior bilateral orchiectomy. Please refer to the product information for abiraterone.

There are no efficacy or safety data on retreatment with Lynparza in prostate cancer patients (see section 5.1).

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.

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

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 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 ≤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 *BRCA*m platinum-sensitive relapsed ovarian cancer who had received at least two prior lines of platinum chemotherapy and were followed up for 5 years (see section 4.8). The majority of events had a fatal outcome. The duration of therapy with olaparib in patients who developed MDS/AML varied from <6 months to >4 years.

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

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.

Venous Thromboembolic Events

Venous thromboembolic events, predominantly events of pulmonary embolism, have occurred in patients treated with Lynparza and had no consistent clinical pattern. A higher incidence was observed in patients with metastatic castration-resistant prostate cancer, who also received androgen deprivation therapy, compared with other approved indications (see section 4.8). Monitor patients for clinical signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate. Patients with a prior history of VTE may be more at risk of a further occurrence and should be monitored 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.

Hepatotoxicity

Cases of hepatotoxicity have been reported in patients treated with olaparib (see section 4.8). If clinical symptoms or signs suggestive of hepatotoxicity develop, prompt clinical evaluation of the patient and measurement of liver function tests should be performed. In case of suspected drug-induced liver injury (DILI), treatment should be interrupted. In case of severe DILI treatment discontinuation should be considered as clinically appropriate.

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 6 months 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).

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

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).

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per 100 mg or 150 mg tablet, that is to say essentially "sodium-free".

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, pimozide, 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 (IC50 = 76 μM), 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.

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

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 (≥ 10%) were nausea, fatigue/asthenia, anaemia, vomiting, diarrhoea, decreased appetite, headache, neutropenia, dysgeusia, cough, leukopenia, dizziness, dyspnoea and dyspepsia.

The Grade ≥ 3 adverse reactions occurring in > 2% of patients were anaemia (15%), neutropenia (5%), fatigue/asthenia (4%), leukopenia (3%) and thrombocytopenia (2%).

Adverse reactions that most commonly led to dose interruptions and/ or reductions in monotherapy were anaemia (16%), nausea (7%), fatigue/asthenia (6%), neutropenia (6%) and vomiting (6%). Adverse reactions that most commonly led to permanent discontinuation were anaemia (1.7%), nausea (0.9%), fatigue/asthenia (0.8%), thrombocytopenia (0.7%), neutropenia (0.6%) and vomiting (0.5%).

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

When Lynparza is used in combination with bevacizumab for ovarian cancer or in combination with abiraterone and prednisone or prednisolone for prostate cancer, the safety profile is generally consistent with that of the individual therapies.

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%).

Adverse events led to dose interruption and/or reduction of olaparib in 46.9% of patients when used in combination with abiraterone and led to permanent discontinuation of treatment with olaparib/abiraterone and placebo/abiraterone in 16.2% and 8.1% of patients, respectively. The adverse reactions that most commonly led to dose interruption and/or reduction were anaemia (15.6%), nausea (3%), fatigue/asthenia (2.6%) and neutropenia (2.1%). The adverse reaction that most commonly led to permanent discontinuation was anaemia (4.1%).

Tabulated list of adverse reactions
The safety profile is based on pooled data from 4098 patients with solid tumours treated with Lynparza monotherapy 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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥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 reactions

	Adverse reactions	
MedDRA System Organ Class	**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

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

	Adverse reactions	
MedDRA System Organ Class	**Frequency of All CTCAE grades**	**Frequency of CTCAE grade 3 and above**
Blood and lymphatic system disorders[b]	**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]
Hepatobiliary disorders	**Common** Transaminases increased[a] **Not known** Drug-induced liver injury[*]	
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** Stomatitis[a], Diarrhoea **Rare** Dyspepsia, Upper abdominal pain

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

	Adverse reactions	
MedDRA System Organ Class	**Frequency of All CTCAE grades**	**Frequency of CTCAE grade 3 and above**
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)
Investigations[b]	**Common** Blood creatinine increased **Uncommon** Mean cell volume increased	**Rare** Blood creatinine increased
Vascular disorders	**Common** Venous thromboembolism[a]	**Common** Venous thromboembolism[a]

[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.
Transaminases increased includes PTs of alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, and hypertransaminasaemia
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 and dermatitis allergic.

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

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

[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 35.2% (CTCAE grade ≥3 14.8%) and the incidences of dose interruptions, reductions and discontinuations for anaemia were 16.4%, 11.1% and 2.1%, respectively; 15.6% of patients treated with olaparib needed one or more blood transfusions. An exposure-response relationship between olaparib and decreases in haemoglobin has been demonstrated. In clinical studies with Lynparza the incidence of CTCAE grade ≥ 2 shifts (decreases) from baseline in haemoglobin was 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 51%. Levels appeared to return to normal after treatment discontinuation and did not appear to have any clinical consequences.

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

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

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 (g*BRCA*1/2) mutation carriers. The incidence of MDS/AML cases was similar among g*BRCA1m* and g*BRCA2m* 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 *BRCA*m platinum-sensitive relapsed ovarian cancer who had received at least two prior lines of platinum chemotherapy and received study treatment until disease progression (SOLO2 study, with olaparib treatment ≥ 2 years in 45% of patients), the incidence of MDS/AML was 8% in patients receiving olaparib and 4% in patients receiving placebo at a follow-up of 5 years. In the olaparib arm, 9 out of 16 MDS/AML cases occurred after discontinuation of olaparib during the survival follow-up. The incidence of MDS/AML was observed in the context of extended overall survival in the olaparib arm and late onset of MDS/AML. The risk of MDS/AML remains < 1.5% at 5 year follow up in the first-line setting when olaparib maintenance treatment is given after one line of platinum chemotherapy for a duration of 2 years (1.2%) in SOLO1 study and 0.7% in PAOLA-1 study). For risk mitigation and management, see section 4.4.

Venous Thromboembolic Events
In men who received olaparib plus abiraterone as first line therapy for mCRPC (PROpel study), the incidence of venous thromboembolic events was 8% in the olaparib plus abiraterone arm, and 3.3% in the placebo plus abiraterone arm. The median time to onset in this study was 170 days (range: 12 to 906 days). The majority of patients recovered from the event and were able to continue olaparib with standard medical treatment.

Patients with significant cardiovascular disease were excluded. Please refer to the product information for abiraterone for cardiovascular exclusion criteria (section 4.4).

Other laboratory findings
In clinical studies with Lynparza 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 non-Caucasian patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Schemewebsite: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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: 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 or new hormonal agents (NHA).
PARPs are required for the efficient repair of DNA single strand breaks and an important aspect of PARP-induced repair requires that after chromatin modification, PARP auto-modifies itself and dissociates from the DNA to facilitate access for base excision repair (BER) enzymes. When olaparib is bound to the active site of DNA-associated PARP it prevents the dissociation of PARP and traps it on the

DNA, thus blocking repair. In replicating cells this also leads to the formation of DNA double-strand breaks (DSBs) when replication forks meet the PARP-DNA adducts. In normal cells, homologous recombination repair (HRR) pathway is effective at repairing these DNA DSBs. In cancer cells lacking critical functional components for efficient HRR such as BRCA1 or 2, DNA DSBs cannot be repaired accurately or effectively, leading to substantial homologous recombination deficiency (HRD). Instead, alternative and error-prone pathways are activated, such as the classical non-homologous end joining (NHEJ) pathway, leading to a high degree of genomic instability. After a number of rounds of replication, genomic instability can reach insupportable levels and result in cancer cell death, as cancer cells already have a high DNA damage load relative to normal cells. HRR pathway may be compromised by other mechanisms, although the causative aberrancy and penetrance are not fully elucidated. Absence of fully functional HRR pathway is one of the key determinants of platinum sensitivity in ovarian and possibly other cancers.

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

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

Detection of *BRCA1/2* mutations
Genetic testing should be conducted by an experienced laboratory using a validated test. Local or central testing of blood and/or tumour samples for germline and/or somatic *BRCA1/2* mutations have been used in different studies. DNA obtained from a tissue or blood sample has been tested in most of the studies, with testing of ctDNA being used for exploratory purposes. Depending on the test used and the international classification consensus, the *BRCA1/2* mutations have been classified as deleterious/suspected deleterious or pathogenic/likely pathogenic. Homologous recombination deficiency (HRD) positive status can be defined by detection of a BRCA1/2 mutation classified as deleterious/suspected deleterious or pathogenic/likely pathogenic. Detection of these mutations could be combined with positive HRD score (below) to determine HRD positive status.

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

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

Certificate Number: PP10185999

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

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 g*BRCAm* 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 g*BRCAwt* patients were confirmed to have s*BRCAm* 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.

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

Figure 1 **SOLO1: Kaplan-Meier plot of PFS in newly diagnosed patients with *BRCA1/2m* advanced ovarian cancer (51% maturity - investigator assessment)**

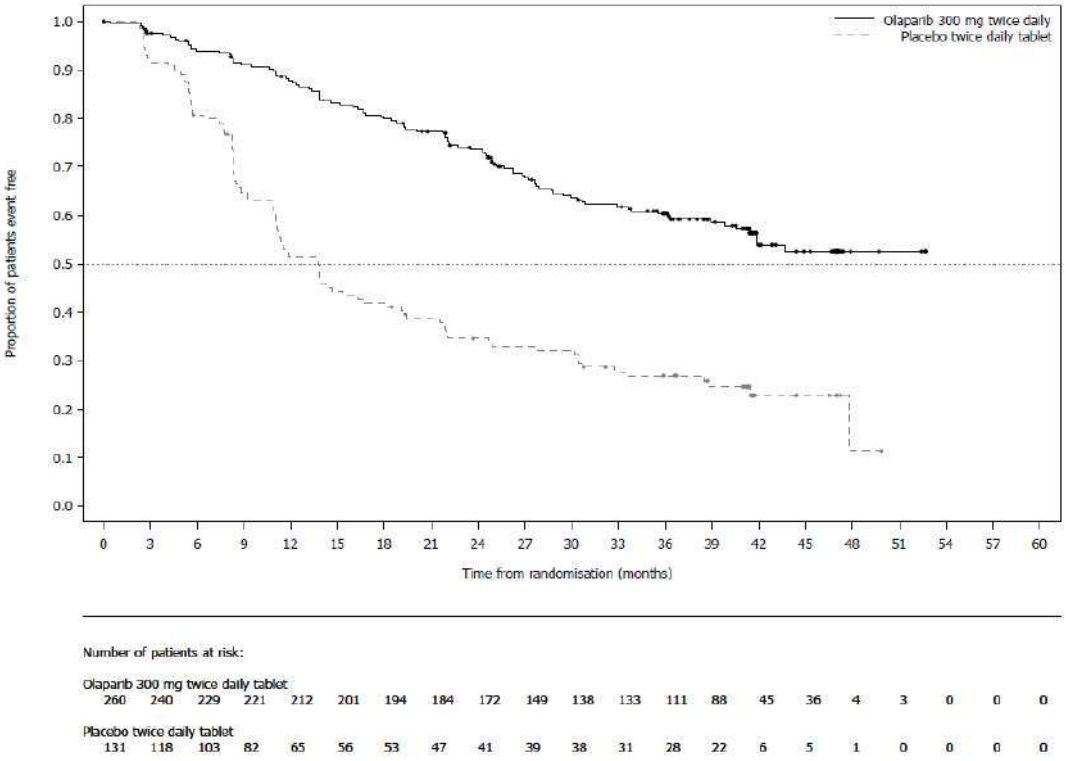
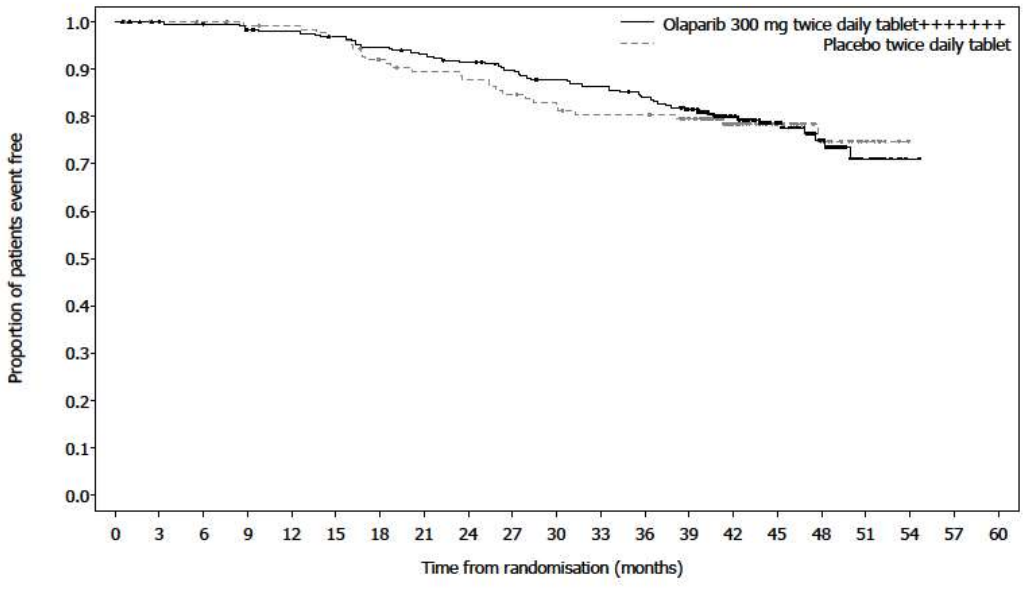


Figure 2 **SOLO1: Kaplan-Meier plot of OS in newly diagnosed patients with *BRCA1/2m* advanced ovarian cancer (21% maturity)**



SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

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 g*BRCA1/2m* 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 g*BRCA1/2m* PSR ovarian cancer in SOLO2 is presented in Table 3 and Figure 3.

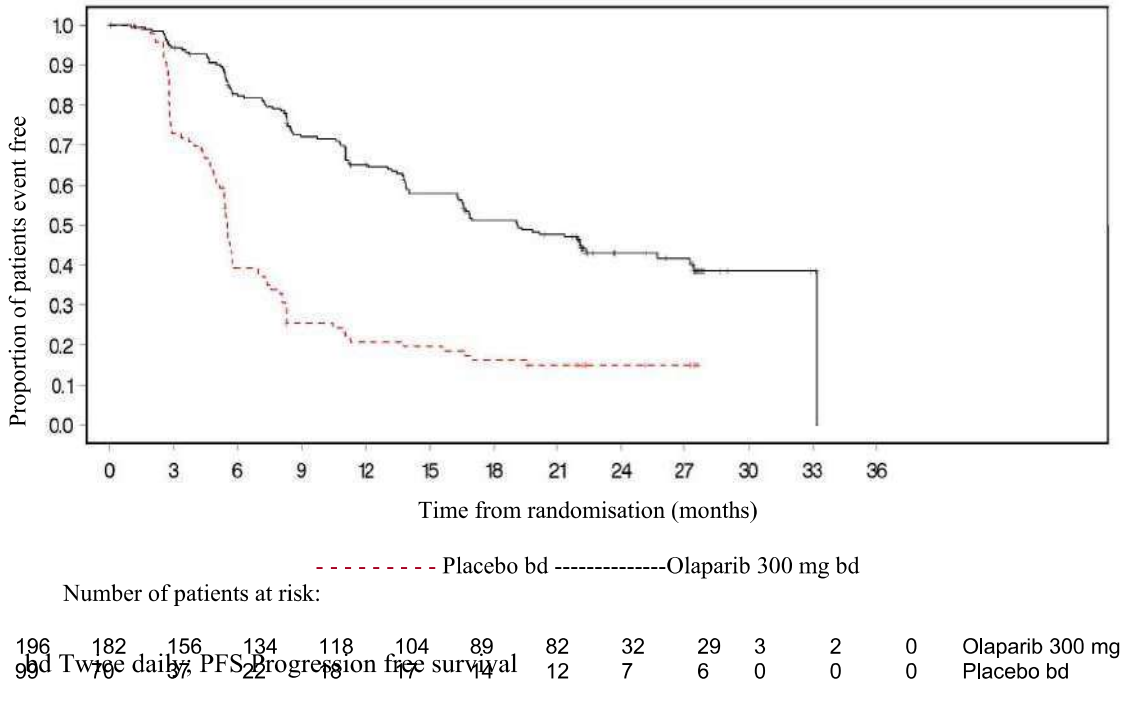
Table 3 Summary of primary objective outcome for patients with g*BRCA1/2m* PSR ovarian cancer in SOLO2

	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 g*BRCA1/2m* PSR ovarian cancer (63% maturity - investigator assessment)



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 g*BRCA1/2m* 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	
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.

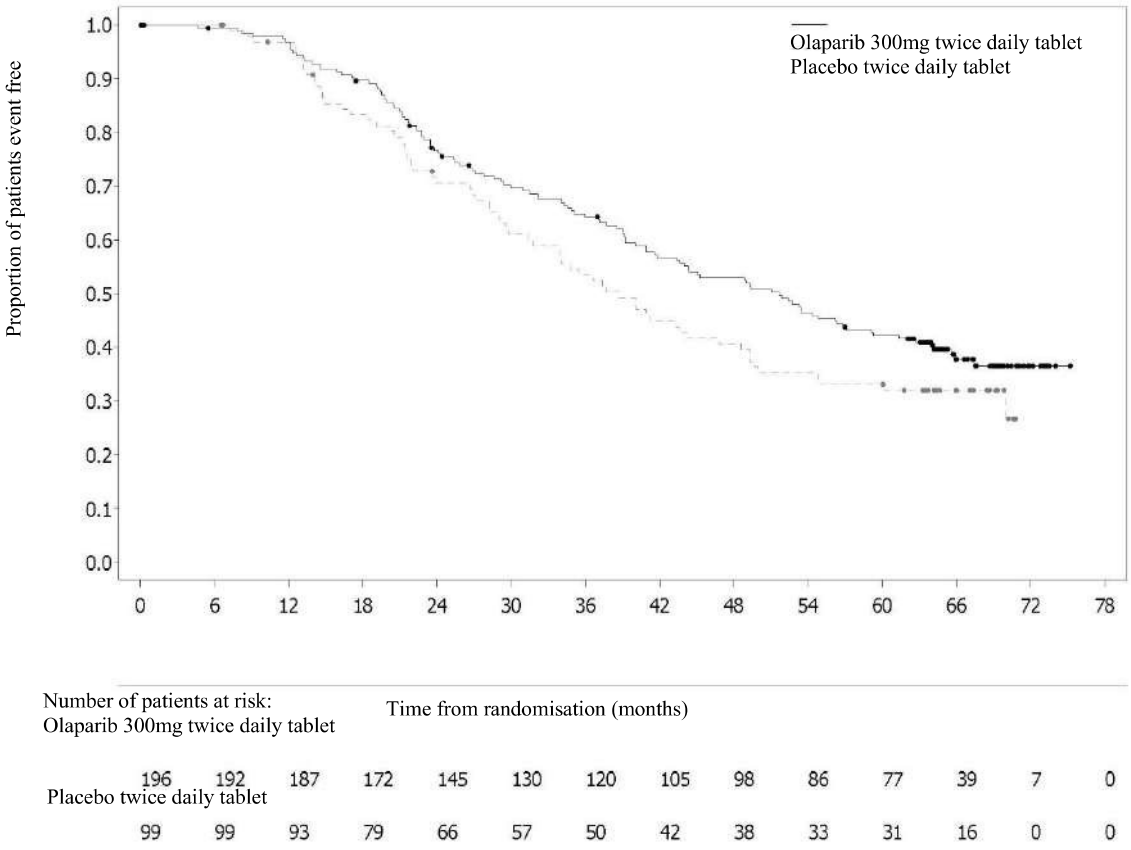
[a] HR= Hazard Ratio. A value <1 favours olaparib. The analysis was performed using a Cox proportional hazard model including response to previous platinum chemotherapy (CR or PR), and time to disease progression (>6-12 months and >12 months) in the penultimate platinum-based chemotherapy as covariates.

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.

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

Figure 4 **SOLO2: Kaplan-Meier plot of OS in patients with g*BRCA1/2m* PSR ovarian cancer (61% maturity)**



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.

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

Study 19 (D0810C00019)

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 maintenance treatment 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 5 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]		***BRCA1/2*-mutated**		***BRCA1/2 wt*/VUS**	
	Olaparib	**Placebo**	**Olaparib**	**Placebo**	**Olaparib**	**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).

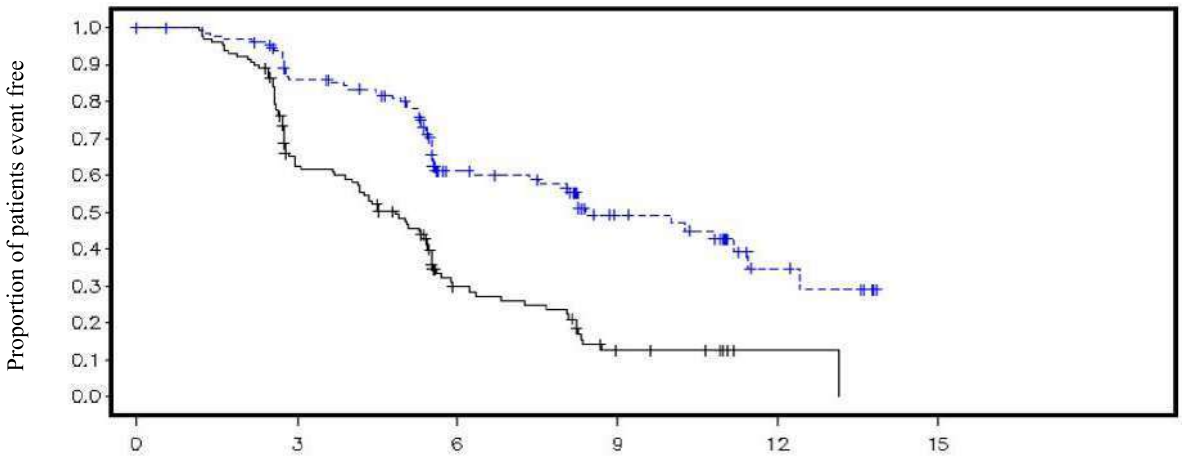
[b] HR= Hazard Ratio. A value <1 favours olaparib. The analysis was performed using a Cox proportional hazards model with factors for treatment, ethnic descent, platinum sensitivity and response to final platinum therapy.

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

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

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



Time from randomisation (months)

----------Placebo - - - - - - - - Olaparib

136	106	53	24	7	0	Olaparib
129	72	24	7	1	0	Placebo

Number of patients at risk:

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.

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

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]		***BRCA1/2*-mutated**		***BRCA1/2 wt*/VUS**	
	Olaparib	**Placebo**	**Olaparib**	**Placebo**	**Olaparib**	**Placebo**
OS - DCO 09 May 2016						
Number of events: Total number of patients (%)	98:136 (72)	112:129 (87)	49:74 (66)	50:62 (81) [c]	45:57 (79)	57:61 (93)
Median time (months) (95% CI)	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)
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 number of patients (%)	106:136 (78)	124:128 (97)	55:74 (74)	59:62 (95)	47:57 (83)	60:61 (98)
Median time (months) (95% CI)	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)
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.

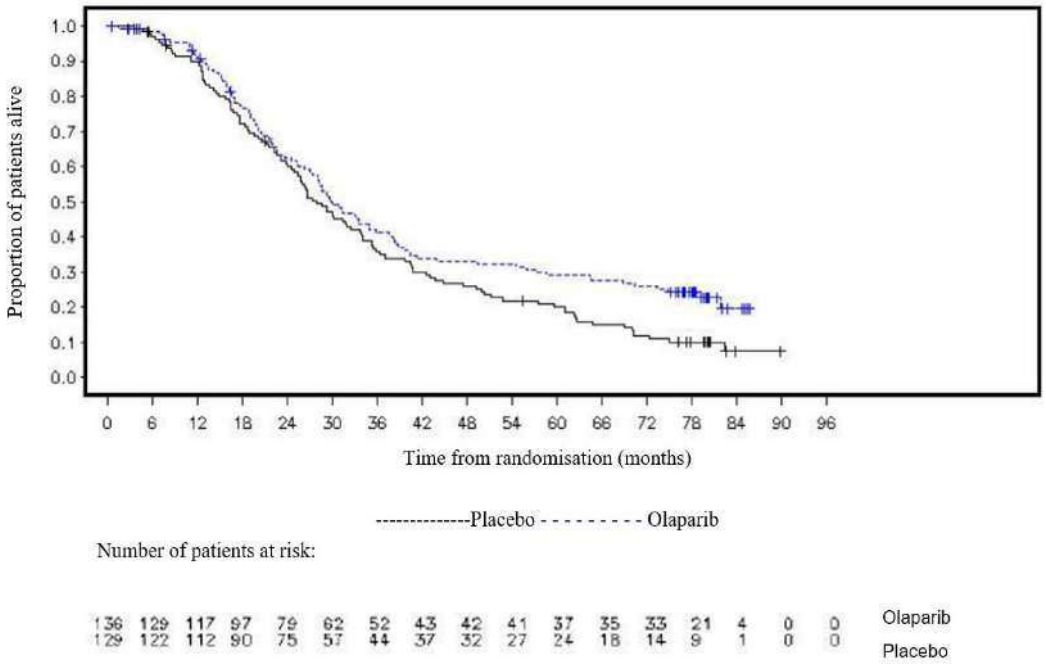
[c] Approximately a quarter of placebo-treated patients in the *BRCA*-mutated subgroup (14/62; 22.6%) received a subsequent PARP inhibitor.

OS Overall survival; DCO data cut off; CI confidence interval; TFST time from randomisation to start of first subsequent therapy or death.

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

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



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 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 g*BRCA* mutation. Patients whose disease was in response (CR or PR) following completion of platinum-based chemotherapy were enrolled. A total of 279 patients were enrolled and received olaparib treatment in this study until disease progression or unacceptable toxicity. Based on central testing 90.7% were confirmed with a non g*BRCA*m status, in addition 9.7% were identified as s*BRCA*m.

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

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

Olaparib, when used as maintenance therapy, demonstrated clinical activity in patients with non-g*BRCA*m PSR ovarian cancer. At the time of primary PFS analysis, the OS data were 30% mature.

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

Table 7 Summary of progression-free survival: non-g*BRCA*m 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 HRD positive 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 t*BRCAm* status, determined by prospective local testing. Patients continued bevacizumab in the maintenance setting and started treatment with Lynparza after a minimum of 3 weeks and up to a maximum of 9 weeks following completion of their last dose of chemotherapy. Treatment with Lynparza was continued 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 t*BRCA*m (prospectively and retrospectively defined), GIS and HRD status (defined in this study by a combination of both biomarkers). The median age of patients was 61

years overall. Most patients in both arms were ECOG performance status 0 (70%). Ovarian cancer was the primary tumour in 86% of the patients. The most common histological type was serous (96%) and endometrioid histology was reported in 2% of the patients. Most patients were diagnosed in FIGO stage IIIC (63%). All patients had received first-line platinum-based therapy and bevacizumab. Patients were not restricted by the surgical outcome with 63% having complete cytoreduction at initial or interval debulking surgery and 37% having residual macroscopic disease. Thirty percent (30%) of patients in both arms were t*BRCA*m at screening. Demographic and baseline characteristics in the biomarker sub-groups were consistent with those in the ITT population. In the HRD-positive subgroup, 65% of patients had complete cytoreduction and 35% of patients had residual macroscopic disease. In the overall patient population enrolled, 30% of patients in both arms were t*BRCA*m (deleterious/pathogenic mutation) at screening by local testing and for 4% of patients the *BRCA*m status was unknown. Retrospective analysis of available clinical samples was conducted in 97% of patients to confirm t*BRCA*m status and investigate genomic instability score as described above. Among non-t*BRCA*m patients, 29% (19% of the overall population) had positive GIS pre-defined in this study as composite score ≥42. When t*BRCA*m status and positive GIS were combined, patients with HRD-positive, HRD-negative and HRD unknown status in their tumours represented 48%, 34% and 18% of the overall patient population.

The primary endpoint was progression-free survival (PFS), defined as time from randomisation to progression determined by investigator assessment using modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, or death. Secondary efficacy endpoints included time from randomisation to second progression or death (PFS2), overall survival (OS), time from randomisation to first subsequent anti-cancer therapy or death (TFST) and health related quality of life (HRQoL). Patients had RECIST 1.1 tumour assessments at baseline and every 24 weeks (CT/MRI at 12 weeks if clinical or CA 125 progression) for up to 42 months or until objective radiological disease progression.

The study met its primary endpoint in the ITT population demonstrating a statistically significant improvement in investigator assessed PFS for olaparib/bevacizumab compared to placebo/bevacizumab (HR 0.59, 95% CI 0.49-0.72, p<0.0001 with a median of 22.1 months for olaparib/bevacizumab vs 16.6 months for placebo/bevacizumab). This was consistent with a BICR analysis of PFS. However, patients defined as biomarker-positive (t*BRCA*m, GIS, HRD status positive defined as t*BRCA*m and/or GIS positive) derived most of the benefit.

Final analysis of PFS2 (DCO 22 March 2020, 53% maturity) in the overall population was statistically significant (HR 0.78, 95% CI 0.64-0.95, p=0.0125 with a median of 36.5 months for olaparib/ bevacizumab vs 32.6 months for placebo/bevacizumab). 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.

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

In the t*BRCA*m as randomised subgroup (241/806 patients) median PFS for the olaparib/bevacizumab arm was 37.2 months vs 22.0 months for the placebo/bevacizumab arm (HR=0.34, 95% CI 0.23, 0.51) 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 t*BRCA*m and/or GIS in advanced ovarian cancer patients in PAOLA-1**

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

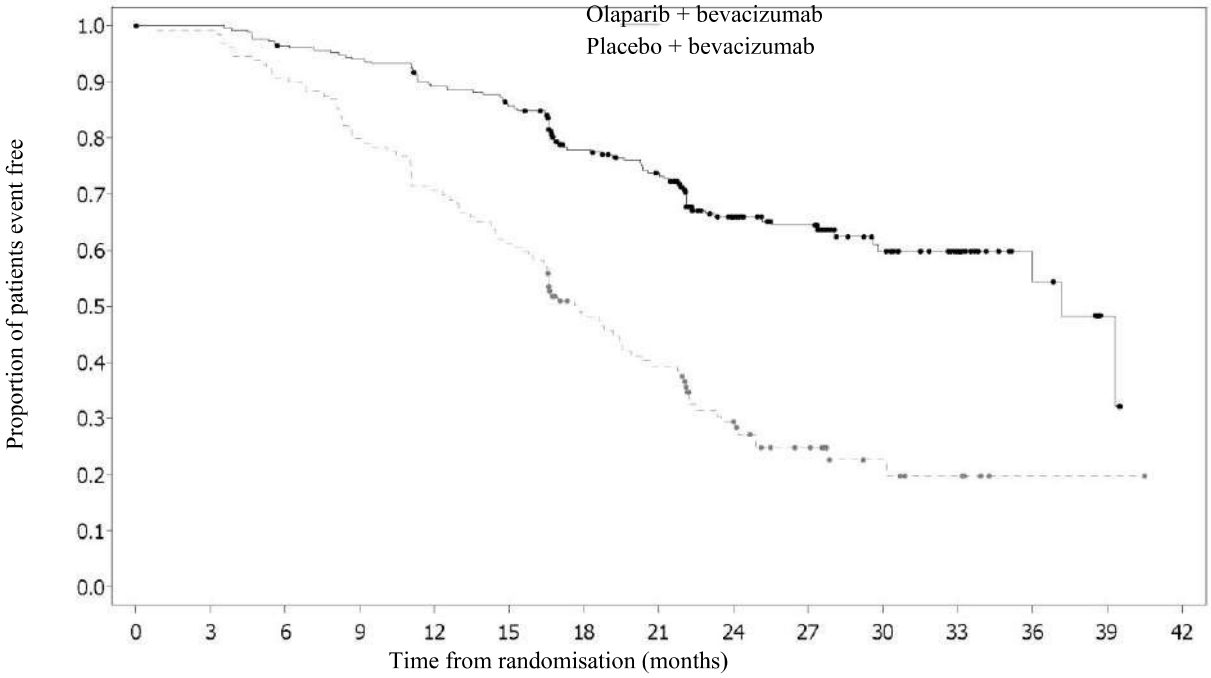
SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

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 t*BRCA* status.
[c] t*BRCA*m status by Myriad
[d] Genomic instability score (GIS) by Myriad ≥42 (pre-specified cut-off)
CI Confidence interval; HR Hazard ratio; NR not reached

Figure 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

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
	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 tumour; 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 endpoint 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 randomisation until evidence of first distant recurrence of breast cancer), the incidence of new primary contralateral breast cancers (invasive and non-invasive), new primary ovarian cancer, new primary fallopian tube cancer and new primary peritoneal cancer, and patient reported outcomes (PRO) using the FACIT-Fatigue and EORTC QLQ-C30 questionnaires.

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

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

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 endpoint 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[c]	90 (87, 92)	86 (84, 89)

[a] Based on the stratified Cox's proportional hazards model, <1 indicates a lower risk with olaparib compared with placebo arm.

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

[c] Percentages are calculated using KM estimates.

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

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

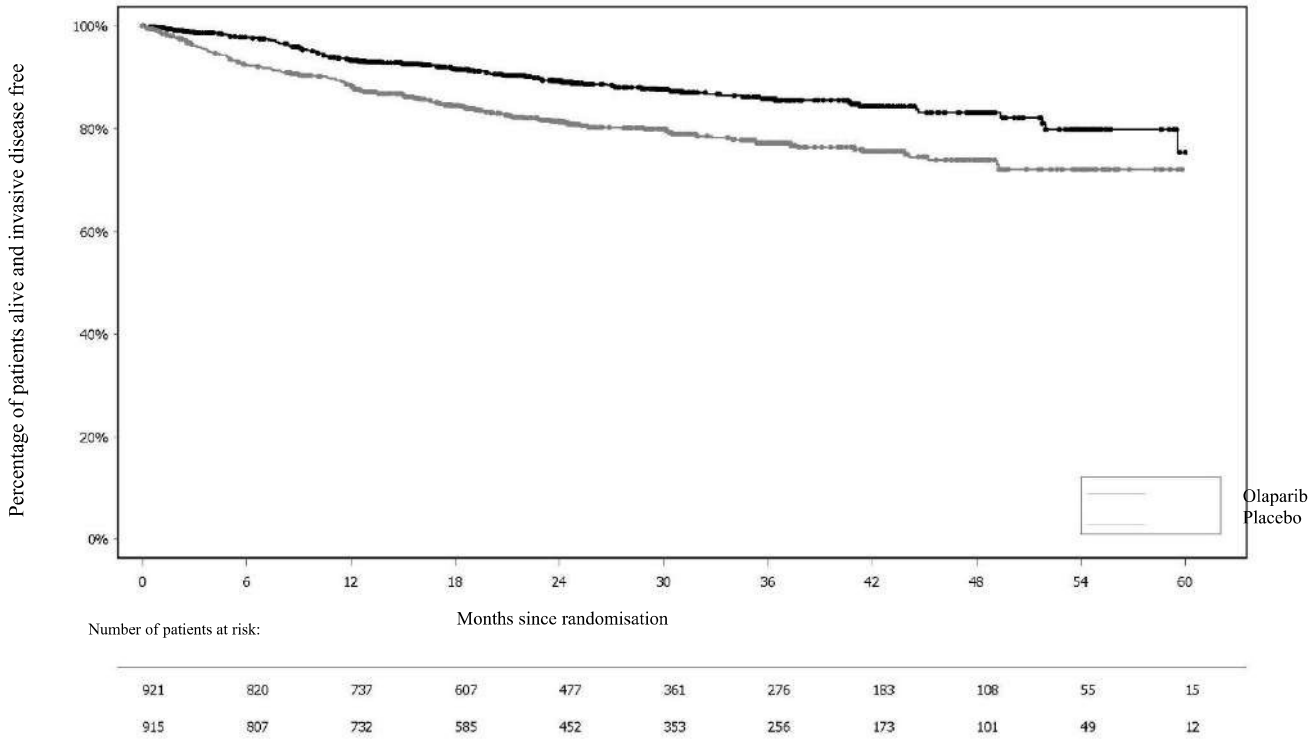
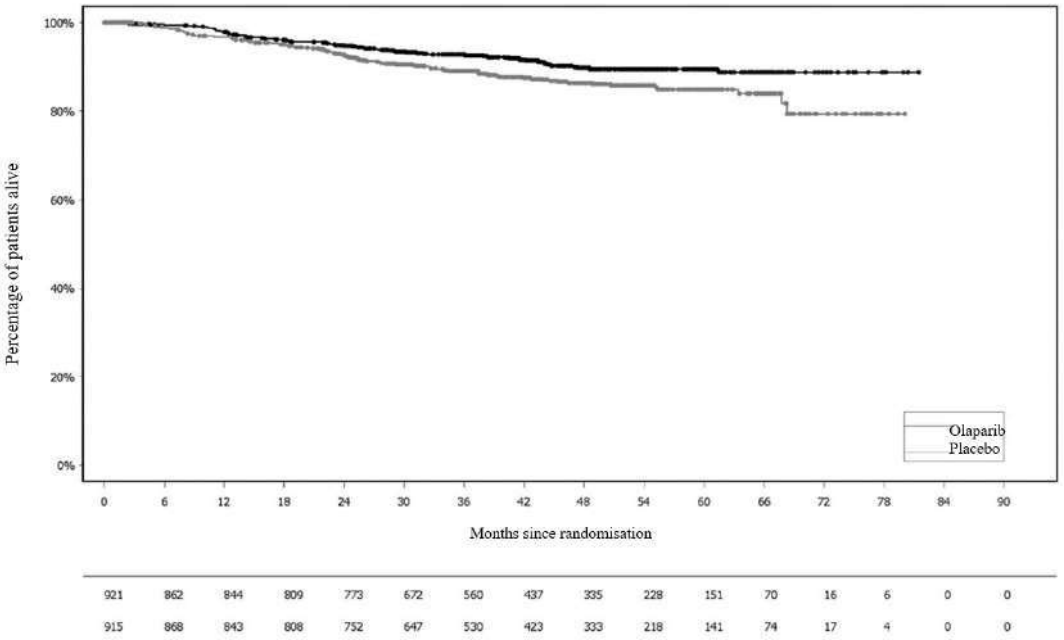


Figure 9 **Kaplan-Meier plot of OS for adjuvant treatment of patients with germline *BRCA*-mutated high risk early breast cancer in OlympiA**



g*BRCA1/2-mutated HER2-negative metastatic breast cancer*
OlympiAD (Study D0819C00003)

The safety and efficacy of olaparib in patients with g*BRCA1/2*-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 g*BRCA* 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 (32)	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)
g*BRCA* mutation type (%)		
g*BRCA1*	117 (57)	51 (53)
g*BRCA2*	84 (41)	46 (47)
g*BRCA1* and g*BRCA2*	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 by BICR (%)	167 (81)	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 (%)	55 (27)	21 (22)
in (neo)adjuvant setting only	12 (6)	6 (6)
metastatic setting only	40 (20)	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.

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

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 g*BRCA1/2*-mutated HER2-negative metastatic breast cancer in OlympiAD

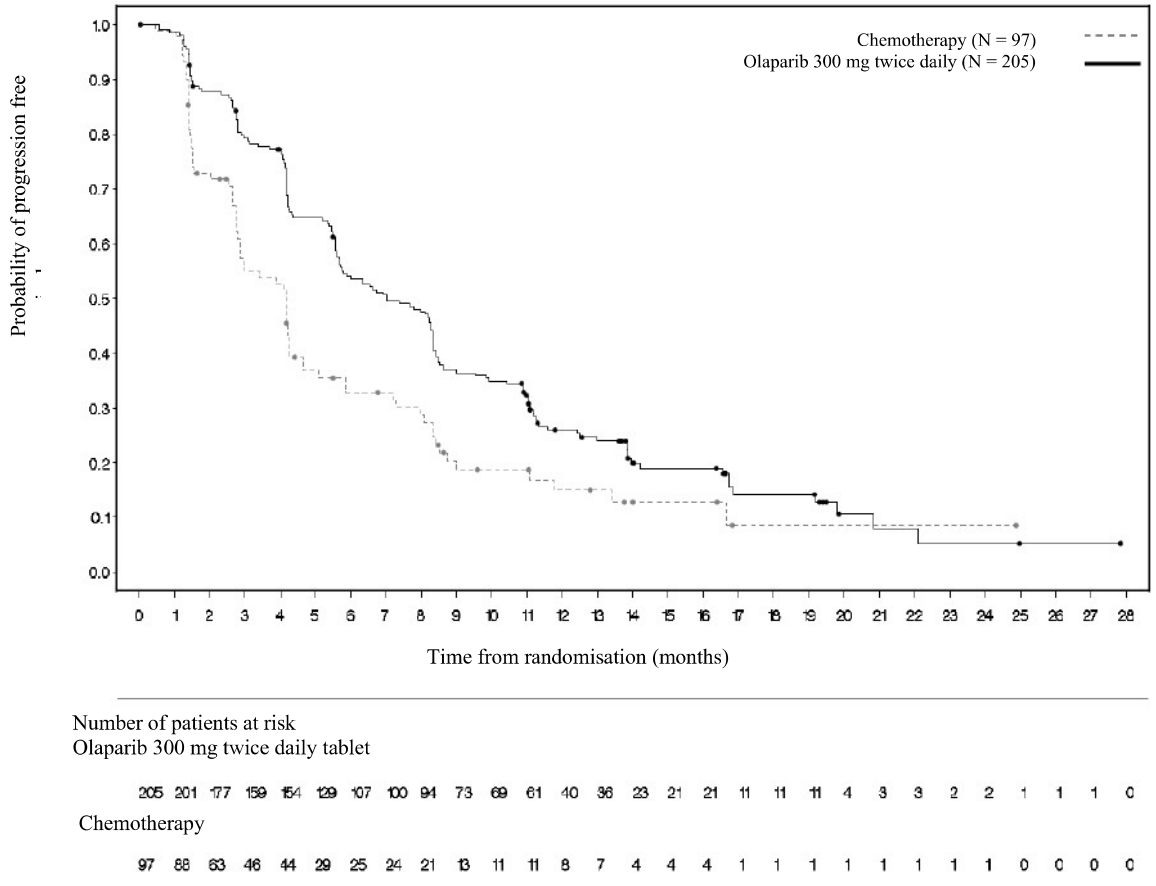
	Olaparib 300 mg bd	Chemotherapy
PFS (77% maturity) – DCO 09 December 2016		
Number of events: Total number of patients (%)	163:205 (80)	71:97 (73)
Median time (months) (95% CI)	7.0 (5.7-8.3)	4.2 (2.8-4.3)
HR (95% CI)	0.58 (0.43-0.80)	
P value (2-sided)[a]	p=0.0009	
PFS2 (65% maturity) - DCO 25 September 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	13.3-35.7
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 g*BRCA1/2*-mutated HER2-negative metastatic breast cancer (77% maturity) DCO 09 December 2016

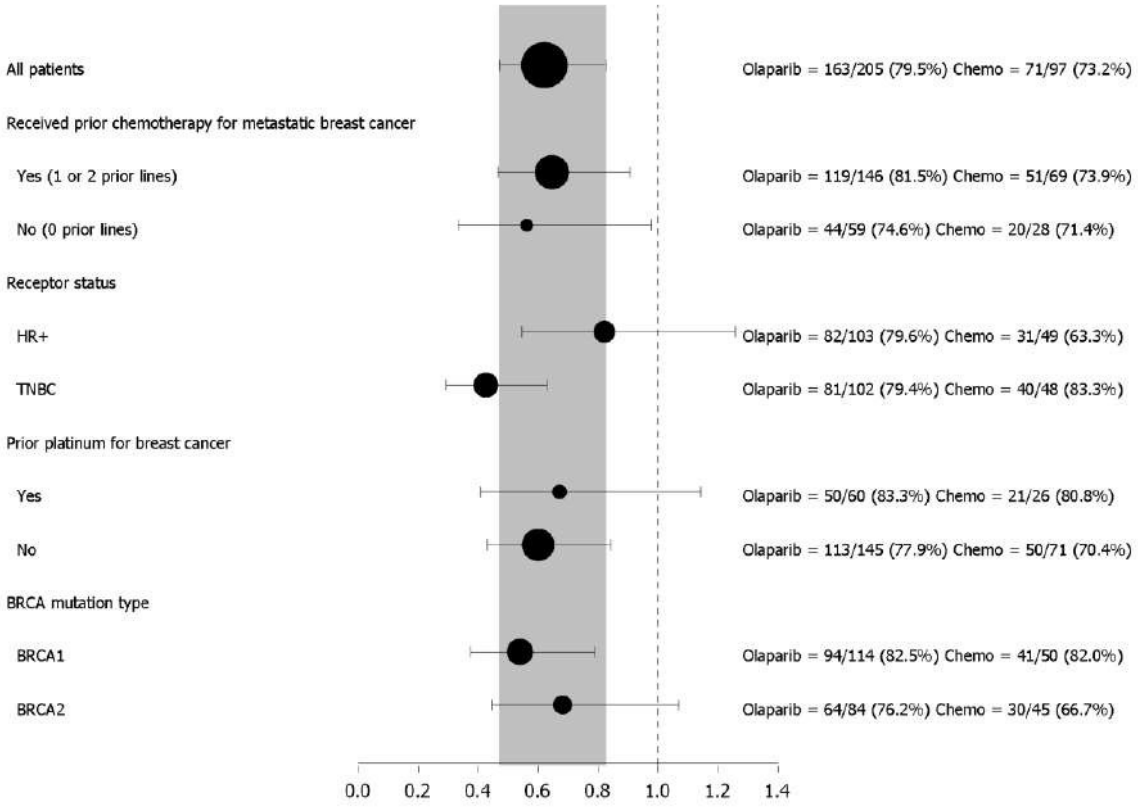


Consistent results were observed in all predefined patient subgroups (see Figure 11). Subgroup analysis indicated PFS benefit of olaparib versus comparator in TNBC (HR 0.43; 95% CI: 0.29-0.63, n=152) and HR+ (HR 0.82; 95% CI: 0.55-1.26, n=150) patient subgroups.

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

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



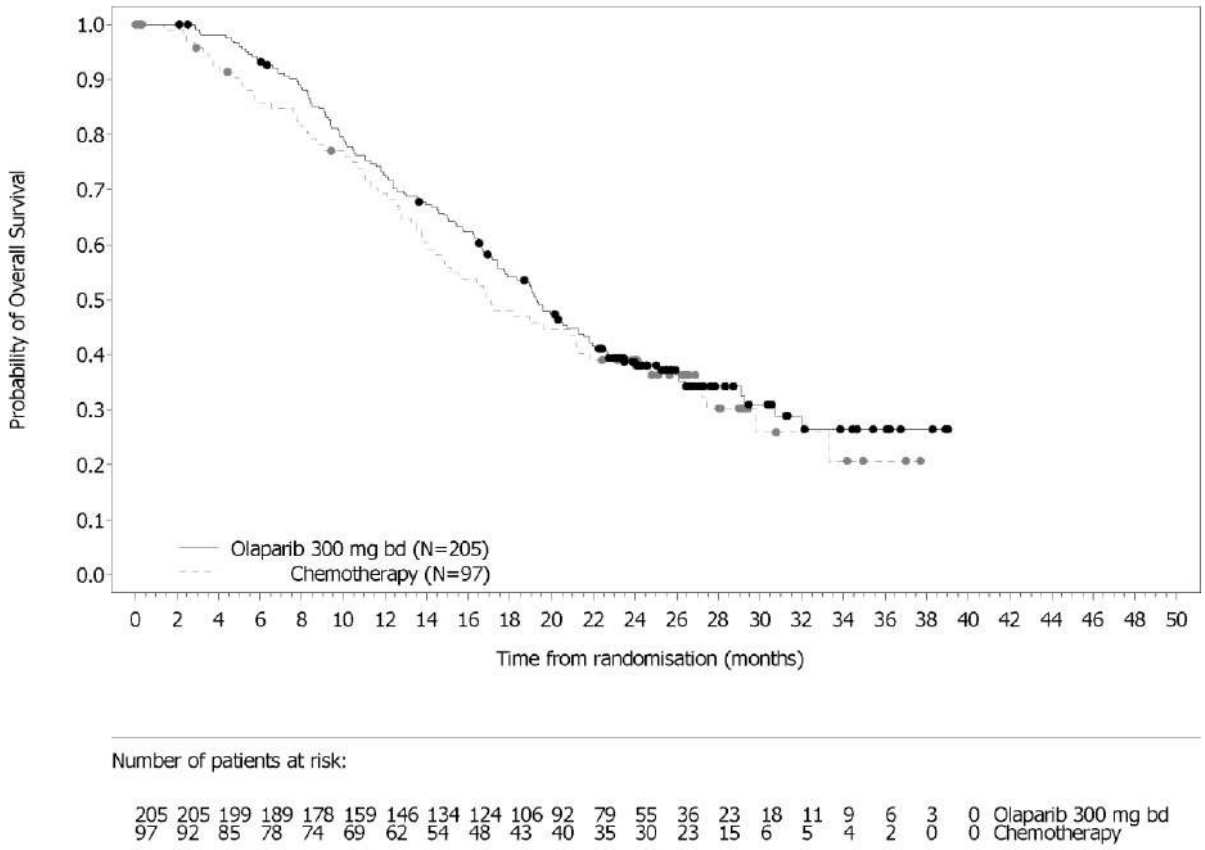
In a post-hoc analysis of the subgroup of patients that had not progressed on chemotherapy other than platinum, the median PFS in the olaparib arm (n=22) was 8.3 months (95% CI 3.1-16.7) and 2.8 months (95% CI 1.4-4.2) in the chemotherapy arm (n=16) with a HR of 0.54 (95% CI 0.24-1.23). However, the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

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

Figure 12 **OlympiAD: Kaplan-Meier plot of OS in patients with g*BRCA1/2*-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

The safety and efficacy of olaparib as maintenance therapy were studied in a randomised (3:2), double-blind, placebo-controlled, multicentre trial in 154 patients with germline *BRCA1/2* mutations who had metastatic adenocarcinoma of the pancreas. Patients received either Lynparza 300 mg (2 x 150 mg tablets) twice daily (n=92) or placebo (n=62) until radiological disease progression or unacceptable toxicity. Patients should have not progressed during first-line platinum-based chemotherapy and should have received a minimum of 16 weeks of continuous platinum treatment, which could be discontinued at any time thereafter for unacceptable toxicity while the remaining agents continued according to the planned regimen or unacceptable toxicity for other component(s). Patients who could tolerate complete platinum-containing chemotherapy regimen until progression have not been considered for this study. The maintenance therapy was started 4 to 8 weeks after the last dose of first-line chemotherapy

component(s) in the absence of progression and if all toxicities from previous anti-cancer therapy had been resolved to CTCAE grade 1, except for alopecia, grade 3 peripheral neuropathy and Hgb ≥ 9 g/dL.

Thirty-one percent (31%) of patients with germline *BRCA1/2* mutations were identified from prior local testing results and 69% of patients by central testing. In the olaparib arm, 32% of patients carried a germline *BRCA1* mutation, 64% a germline *BRCA2* mutation and 1% carried both germline *BRCA1* and germline *BRCA2* mutations. In the placebo arm, 26% of patients carried a germline *BRCA1* mutation, 73% a germline *BRCA2* mutation and no patients carried both germline *BRCA1* and germline *BRCA2* mutations. The *BRCAm* status of all patients identified using prior local testing results was confirmed, where sent, by central testing. Ninety-eight percent (98%) of patients carried a deleterious mutation and 2% carried a suspected deleterious mutation. Large rearrangements in the *BRCA1/2* genes were detected in 5.2 % (8/154) of the randomised patients.

Demographic and baseline characteristics were generally well balanced between the olaparib and placebo arms. Median age was 57 years in both arms; 30% of patients in the olaparib arm were ≥ 65 years compared to 20% in the placebo arm. Fifty-eight per-cent (58%) of patients in the olaparib arm and 50% of patients in the placebo arm were male. In the olaparib arm 89% of patients were White and 11% were non-White; in the placebo arm 95% of patients were White and 5% were non-White. Most patients were ECOG performance status 0 (71% in the olaparib arm and 61% in the placebo arm). Overall, the sites of metastasis prior to chemotherapy were liver 72%, lung 10% and other sites 50%. The median time from original diagnosis to randomisation across both arms was 6.9 months (range 3.6 to 38.4 months).

Overall, 75% of patients received FOLFIRINOX with a median of 9 cycles (range 4-61), 8% received FOLFOX or XELOX, 4% received GEMOX, and 3% received gemcitabine plus cisplatin; the remaining 10% of patients received other chemotherapy regimens. Duration of the first-line chemotherapy for metastatic disease was 4 to 6 months, >6 to <12 months and ≥12 months, respectively, in 77%, 19% and 4% of patients in the olaparib arm and in 80%, 17% and 3% in the placebo arm, with around 1 month from the last dose of the first-line chemotherapy component(s) to the start of study treatment in both arms. As best response on first-line chemotherapy, 7% of olaparib patients and 5% of placebo patients had a complete response, 44% of olaparib patients and 44% of placebo patients had a partial response and 49% of olaparib and 50% of placebo patients had stable disease. At randomisation, measurable disease was reported in 85% and 84% of patients in the olaparib or placebo arms, respectively. The median time from initiation of the first-line platinum-based chemotherapy to randomisation was 5.7 months (range 3.4 to 33.4 months).

At the time of PFS analysis, 33% of patients in the olaparib arm and 13% on the placebo arm remained on study treatment. Forty-nine percent of patients (49%) in the olaparib arm and 74% in the placebo arm received subsequent therapy. Forty-two percent (42%) of patients in the olaparib arm and 55% in the placebo arm received platinum as subsequent therapy. One percent (1%) of patients in the olaparib arm and 15% in the placebo arm received PARP inhibitor as subsequent therapy. Of the 33 (36%) and 28 (45%) of patients who received a first subsequent platinum-containing therapy, in the olaparib and placebo arms, stable disease was reported in 8 vs 6 patients, whereas 1 vs 2 patients had responses, respectively.

The primary endpoint was progression-free survival (PFS), defined as time from randomisation to progression determined by BICR using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 modified to assess patients with no evidence of disease, 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), objective response rate (ORR), duration of response (DoR), response rate, time to response and health related quality of life (HRQoL).

The study demonstrated a statistically significant improvement in PFS for olaparib compared to placebo (Table 13). The BICR assessment of PFS was consistent with an investigator assessment.

At final analysis of OS, the percentage of patients that were alive and in follow-up was 28% in the olaparib arm and 18% in the placebo arm.

Table 13 Efficacy results for patients with g*BRCAm* metastatic adenocarcinoma of the pancreas in POLO

	Olaparib 300 mg bd	**Placebo**
PFS (68% maturity)[a,b] (BICR, DCO 15 January 2019)		
Number of events: Total number of patients (%)	60:92 (65)	44:62 (71)
Median time, months (95% CI)	7.4 (4.14-11.01)	3.8 (3.52-4.86)
HR (95% CI)[c,d]	0.53 (0.35-0.82)	
P value (2-sided)	p=0.0038	
OS (70% maturity)[e] (DCO 21 July 2020)		
Number of events: Total number of patients (%)	61:92 (66)	47:62 (76)
Median time (months) (95% CI)	19.0 (15.28-26.32)	19.2 (14.32-26.12)
HR (95% CI)[d]	0.83 (0.56-1.22)	
P value (2-sided)	p=0.3487	

[a] Based on Kaplan–Meier estimates, the proportion of patients that were alive and progression-free at 12 and 24 months were 34% and 22% for olaparib vs 15% and 10% for placebo.

[b] 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.

[c] A value <1 favours olaparib.

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

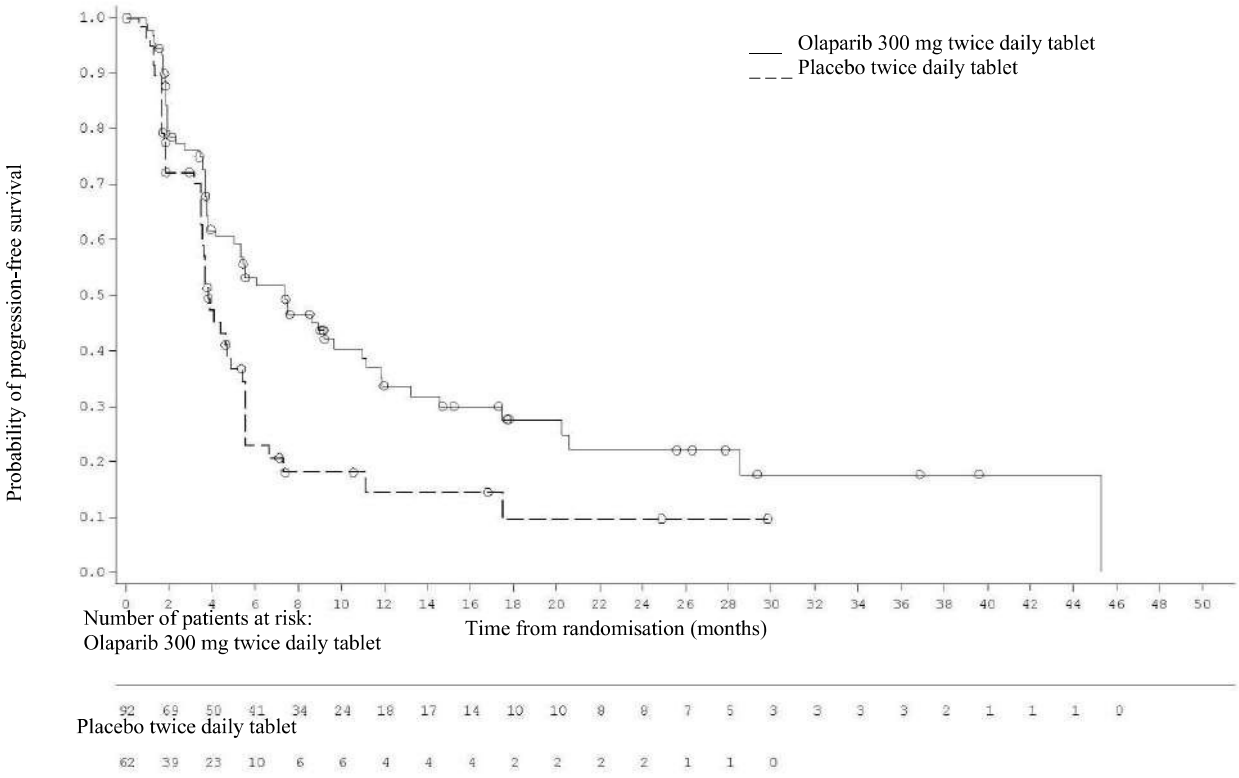
[e] For OS, the median follow-up time for censored patients was 31.3 months in the olaparib arm and 23.9 months in the placebo arm.

[bd] Twice daily; CI Confidence interval; HR Hazard Ratio; OS Overall Survival; PFS Progression-free survival.

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

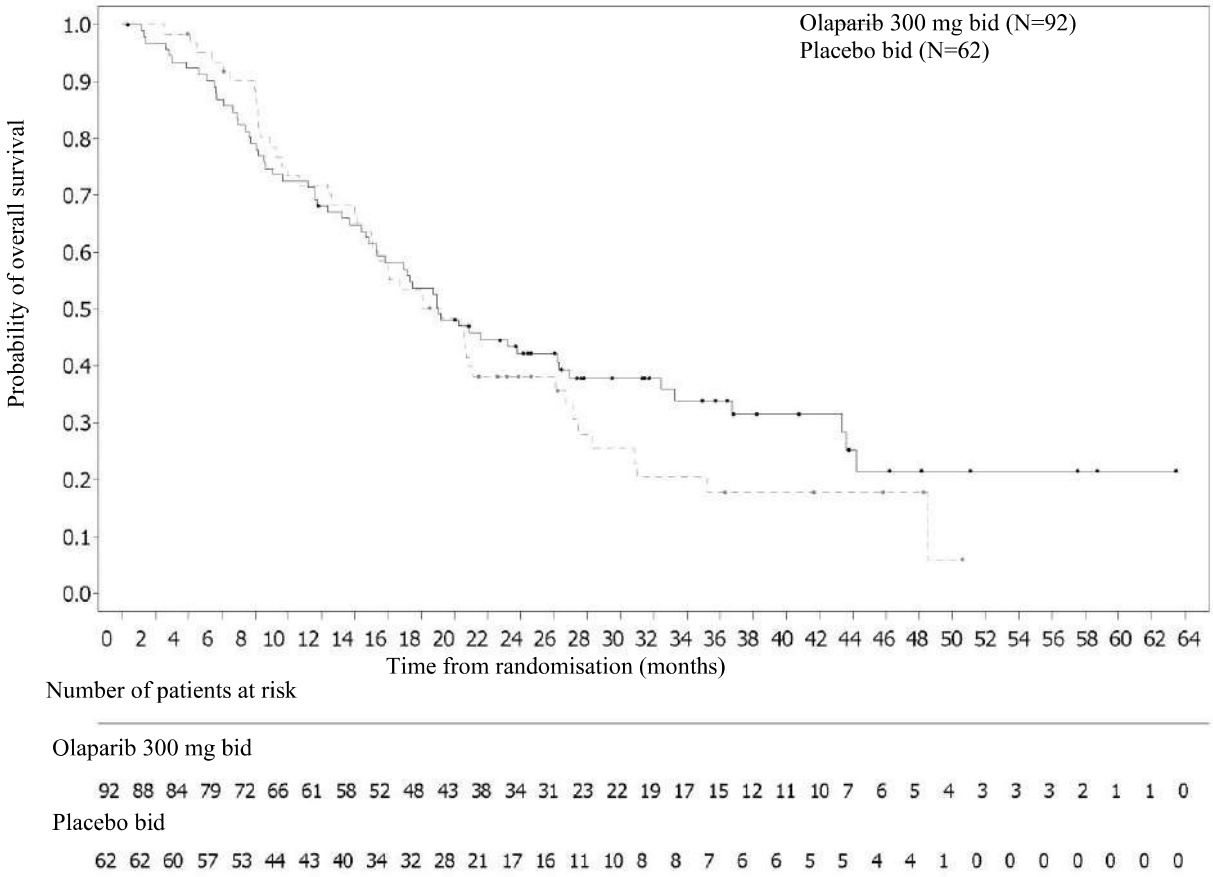
Figure 13 **POLO: Kaplan-Meier plot of PFS for patients with g*BRCAm* metastatic adenocarcinoma of the pancreas (68% maturity – BICR, DCO 15 January 2019)**



SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

Figure 14 **POLO: Kaplan-Meier plot of OS for patients with g*BRCAm* metastatic adenocarcinoma of the pancreas (70% maturity, DCO 21 July 2020)**



BRCA1/2-mutated metastatic castration-resistant prostate cancer:

PROfound Study

The safety and efficacy of olaparib were studied in men with metastatic castration-resistant prostate cancer (mCRPC) in a Phase III randomised, open-label, multicentre trial that evaluated the efficacy of Lynparza versus a comparator arm of investigator's choice of NHA ([new hormonal agent] enzalutamide or abiraterone acetate).

Patients needed to have progressed on prior NHA for the treatment of metastatic prostate cancer and/or CRPC. For inclusion in Cohort A, patients needed to have deleterious or suspected deleterious mutations in either *BRCA1* or *BRCA2* genes. Patients with *ATM* mutations were also randomised in Cohort A, but

positive benefit-risk could not be demonstrated in this subpopulation of patients. Patients with mutations in other genes were randomised in Cohort B.

In this study 387 patients were randomised 2:1 to receive either olaparib (300 mg [2 x 150 mg tablets] twice daily) or 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 *BRCA1*m, *BRCA2*m detected in their tumours were enrolled on the basis of prospective central testing, with the exception of 3 patients enrolled using a local test result. Of the 160 patients with a *BRCA1* or *BRCA2* mutation in PROfound, 114 patients were retrospectively tested to determine if the identified *BRCA1/2* mutation was germline or somatic in origin. Within these patients, 63 *BRCA1/2* mutations were identified in the germline blood sample and hence were determined to be germline in origin. The remaining 51 patients did not have a tumour detected *BRCA1/2* mutation identified in the germline blood sample and hence the *BRCA1/2* mutations are determined to be somatic in origin. For the remaining 46 patients, somatic or germline origin is unknown.

Demographics and baseline characteristics were generally well balanced between the olaparib and comparator arms in patients with *BRCA1/2* mutations. Median age was 68 years and 67 years in the olaparib and comparator arms, respectively. Prior therapy in the olaparib arm was 71% taxane, 41% enzalutamide, 37% abiraterone acetate and 20% both enzalutamide and abiraterone acetate. Prior therapy in the comparator arm was 60% taxane, 50% enzalutamide, 36% abiraterone acetate and 14% both enzalutamide and abiraterone acetate. Fifty-eight percent (58%) of patients in the olaparib arm and 55% in the comparator arm had measurable disease at study entry. The proportion of patients with bone, lymph node, respiratory and liver metastases was 89%, 62%, 23% and 12%, respectively in the olaparib arm and 86%, 71%, 16% and 17%, respectively in the comparator arm. Most patients in both treatment arms had an ECOG of 0 or 1 (93%). Baseline pain scores (BPI-SF worst pain) were 0-<2 (52%), 2-3 (10%) or >3 (34%) in the olaparib arm and 0-<2 (45%), 2-3 (7%) or >3 (45%) in the comparator arm. Median baseline PSA was 57.48 µg/L in the olaparib arm and 103.95 µg/L in the comparator.

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, rPFS by BICR, time to pain progression (TTPP) and overall survival (OS).

The study demonstrated a statistically significant improvement in BICR assessed rPFS and final OS for olaparib vs comparator in Cohort A.

Results for patients with *BRCA1/2* mutations are presented in Table 14. There was a statistically significant improvement in BICR assessed rPFS for olaparib vs the investigators choice of NHA arm in *BRCA1/2*m patients. The final analysis of OS showed a nominally statistically significant improvement in OS in *BRCA1/2*m patients randomised to Lynparza vs comparator.

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

Table 14 **Summary of key efficacy findings in patients with *BRCA1/2*-mutated mCRPC in PROfound**

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

[a] Not controlled for multiplicity

[b] rPFS 71% maturity

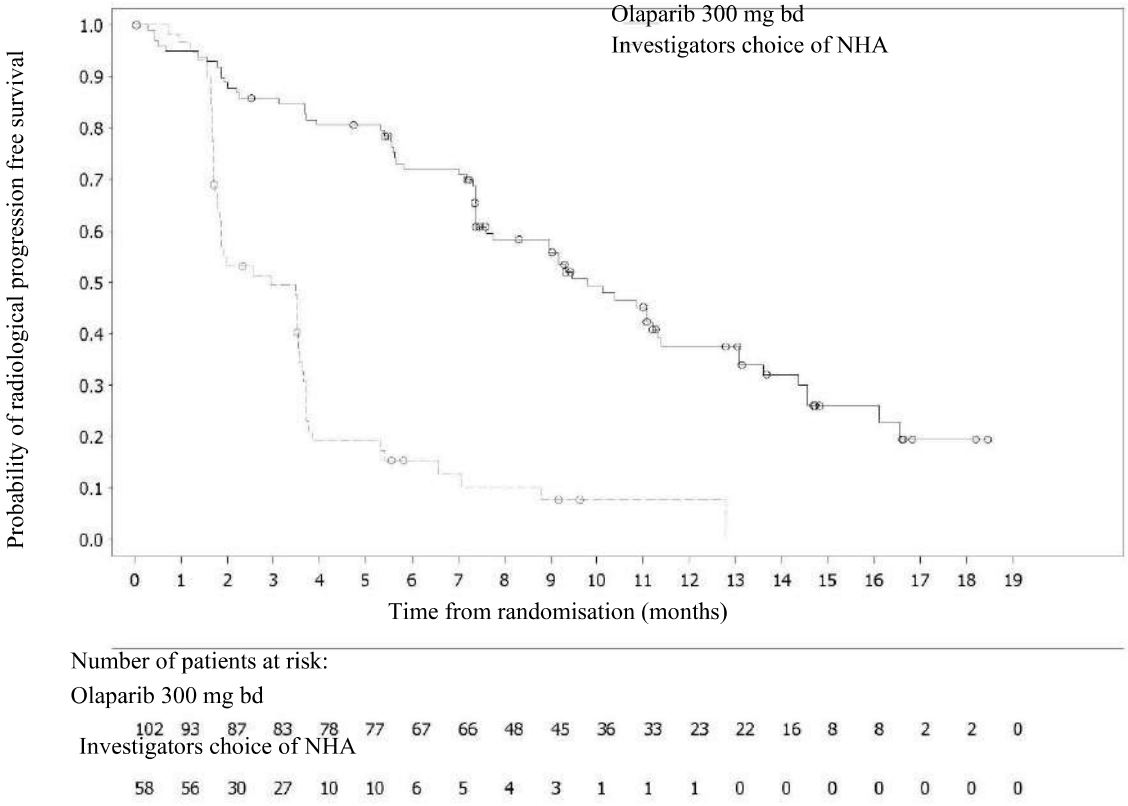
[c] The HR and CI were calculated using a Cox proportional hazards model that contains terms for treatment, factor and treatment by factor interaction.

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

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

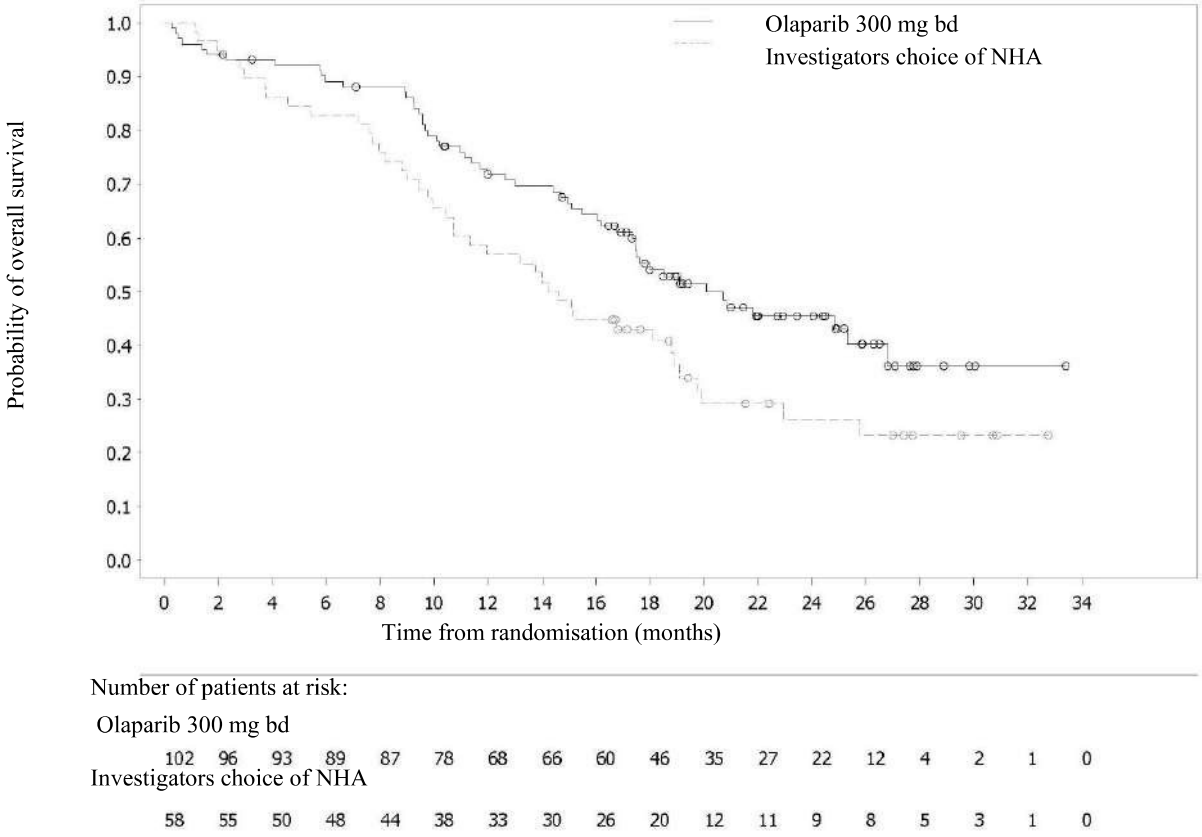
Figure 15 ***BRCA1/2*m patients: Kaplan-Meier plot of rPFS (by BICR)**



Number of patients at risk:

Olaparib 300 mg bd	102	93	87	83	78	77	67	66	48	45	36	33	23	22	16	8	8	2	2	0
Investigators choice of NHA	58	56	30	27	10	10	6	5	4	3	1	1	1	0	0	0	0	0	0	0

Figure 16 *BRCA1/2*m patients: Kaplan-Meier plot of OS



Treatment of patients in the first-line mCRPC setting

PROpel

The safety and efficacy of olaparib were studied in men with metastatic castration-resistant prostate cancer (mCRPC) in a Phase III randomised, double-blind, placebo-controlled, multicentre study that evaluated the efficacy of Lynparza (300 mg [2 x 150 mg tablets] twice daily) in combination with abiraterone (1000 mg [2 x 500 mg tablets] once daily) versus a comparator arm of placebo plus abiraterone. Patients in both arms also received either prednisone or prednisolone 5 mg twice daily.

The study randomised 796 patients (1:1 randomisation; 399 olaparib/abiraterone:397 placebo/ abiraterone) who had evidence of histologically confirmed prostate adenocarcinoma and metastatic status defined as at least one documented metastatic lesion on either a bone or CT/MRI scan and who were treatment naïve with no prior chemotherapy or NHA in the mCRPC setting. Prior to the mCRPC stage,

treatment with NHAs (except abiraterone) without PSA progression (clinical or radiological) during treatment was allowed, provided the treatment was stopped at least 12 months before randomisation. Treatment with first-generation antiandrogen agents (e.g., bicalutamide, nilutamide, flutamide) was also allowed, provided there was a washout period of 4 weeks. Docetaxel treatment was allowed during neoadjuvant/adjuvant treatment for localised prostate cancer and at metastatic hormone-sensitive prostate cancer (mHSPC) stage, as long as no signs of disease progression occurred during or immediately after such treatment. All patients received a GnRH analogue or had prior bilateral orchiectomy. Patients were stratified by metastases (bone only, visceral or other) and docetaxel treatment at mHSPC stage (yes or no). Treatment was continued until radiological progression of the underlying disease or unacceptable toxicity.

Demographic and baseline characteristics were balanced between the two treatment arms. The median age of patients was 69 years overall, and the majority (71%) of patients were in the ≥65 years age group. One hundred and eighty-nine patients (24%) had prior docetaxel treatment at mHSPC stage. In total, 434 (55%) patients had bone metastases (metastases in the bone and no other distant site), 105 (13%) patients had visceral metastases (distant soft tissue metastases in an organ e.g., liver, lung) and 257 (32%) patients had other metastases (this could include, for example, patients with bone metastases and distant lymph nodes or patients with disease present only in distant lymph nodes). Most patients in both arms (70%) had an ECOG performance status of 0. There were 103 (25.8%) symptomatic patients in the olaparib group and 80 (20.2%) patients in the placebo group. Symptomatic patients were characterized by Brief Pain Inventory-Short Form (BPI-SF) item #3 score ≥ 4 and/or opiate use at baseline.

Patient enrolment was not based on biomarker status. HRR gene mutation status was assessed retrospectively by ctDNA and tumour tissue tests to assess the consistency of treatment effect from the FAS population. Of the patients tested, 198 and 118 were HRRm as determined by ctDNA and tumour tissue, respectively. The distribution of HRRm patients was well balanced between the two arms.

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

The study met its primary endpoint demonstrating a statistically significant improvement in the risk of radiological disease progression or death for olaparib/abiraterone compared to placebo/abiraterone as assessed by the investigator with HR 0.66; 95% CI 0.54, 0.81; p<0.0001; median rPFS 24.8 months in the olaparib/abiraterone arm vs 16.6 months in the placebo/abiraterone arm. The investigator assessment of rPFS was supported with a blinded independent central radiological (BICR) review. The sensitivity analysis of rPFS by BICR was consistent with the investigator -based analysis with HR 0.61; 95% CI 0.49, 0.74; p<0.0001; median rPFS 27.6 months in the olaparib/abiraterone arm vs 16.4 months in the placebo/abiraterone arm, respectively.

Subgroup results were consistent with the overall results for olaparib/abiraterone compared to placebo/abiraterone in all pre-defined sub-groups, including patients with or without prior taxane at mHSPC stage, patients with different metastatic disease at baseline (bone only vs visceral vs other) and patients with or without HRRm (Figure 19).

Efficacy results are presented in Table 15, Table 16, Figure 17 and Figure 18.

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

Table 15 Summary of key efficacy findings for treatment of patients with mCRPC in PROpel

	Olaparib/abiraterone N = 399	**Placebo/abiraterone N = 397**
rPFS (by investigator assessment) (50% maturity) (DCO 30 July 2021)		
Number of events: Total number of patients (%)	168:399 (42.1)	226:397 (56.9)
Median time (95% CI) (months)	24.8 (20.5, 27.6)	16.6 (13.9, 19.2)
HR (95% CI)[a]	0.66 (0.54, 0.81)	
p-value[b]	<0.0001	
Interim OS (40% maturity) (DCO 14 March 2022)		
Number of events: Total number of patients (%)	148:399 (37.1)	171:397 (43.1)
Median time (95% CI) (months)	NC (NC, NC)	NC (NC, NC)
HR (95% CI)[a]	0.83 (0.66, 1.03)	
p-value[b]	p=0.1126	
% Alive at 36 months (95% CI) [c]	57.1 (50.6, 63.0)	51.6 (45.5, 57.3)

[a] The HR and CI were calculated using a Cox proportional hazards model adjusted for the variables selected in the primary pooling strategy: metastases, docetaxel treatment at mHSPC stage. The Efron approach was used for handling ties. A HR <1 favours olaparib 300 mg bd.

[b] The 2-sided p-value was calculated using the log-rank test stratified by the same variables selected in the primary pooling strategy.

[c] Calculated using the Kaplan-Meier technique.

Table 16 rPFS subgroup analyses by investigator assessment – PROpel (DCO 30 July 2021)

	Olaparib/abiraterone	**Placebo/abiraterone**
Radiological Progression-Free Survival (rPFS) by investigator assessment		
Aggregate HRRm Subgroup Analyses [a]		
HRRm	**N=111**	**N=115**
Number of events: Total number of patients (%)	43:111 (38.7)	73:115 (63.5)
Median (months)	NC	13.86
Hazard ratio (95% CI) [b]	0.50 (0.34, 0.73)	
Non-HRRm	**N=279**	**N=273**
Number of events: Total number of patients (%)	119:279 (42.7)	149:273 (54.6)
Median (months)	24.11	18.96
Hazard ratio (95% CI) [b]	0.76 (0.60, 0.97)	

SUMMARY OF PRODUCT CHARACTERISTICS

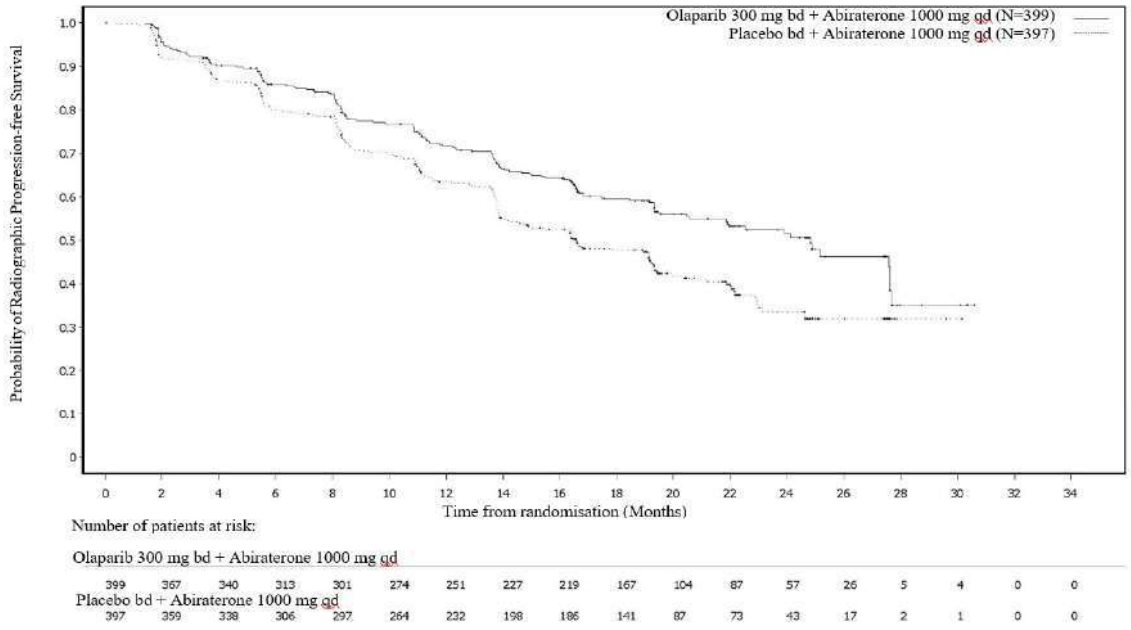
Printed for Certificate of Pharmaceutical Product

	Olaparib/abiraterone	Placebo/abiraterone
Aggregate BRCAm Subgroup Analyses [a]		
BRCAm	**N=47**	**N=38**
Number of events: Total number of patients (%)	14:47 (29.8)	28:38 (73.7)
Median (months)	NC	8.38
Hazard ratio (95% CI) [b]	0.23 (0.12, 0.43)	
Non-BRCAm	**N=343**	**N=350**
Number of events: Total number of patients (%)	148:343 (43.1)	194:350 (55.4)
Median (months)	24.11	18.96
Hazard ratio (95% CI) [b]	0.76 (0.61, 0.94)	

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

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

Figure 17 PROpel: Kaplan-Meier plot of rPFS (investigator assessed)

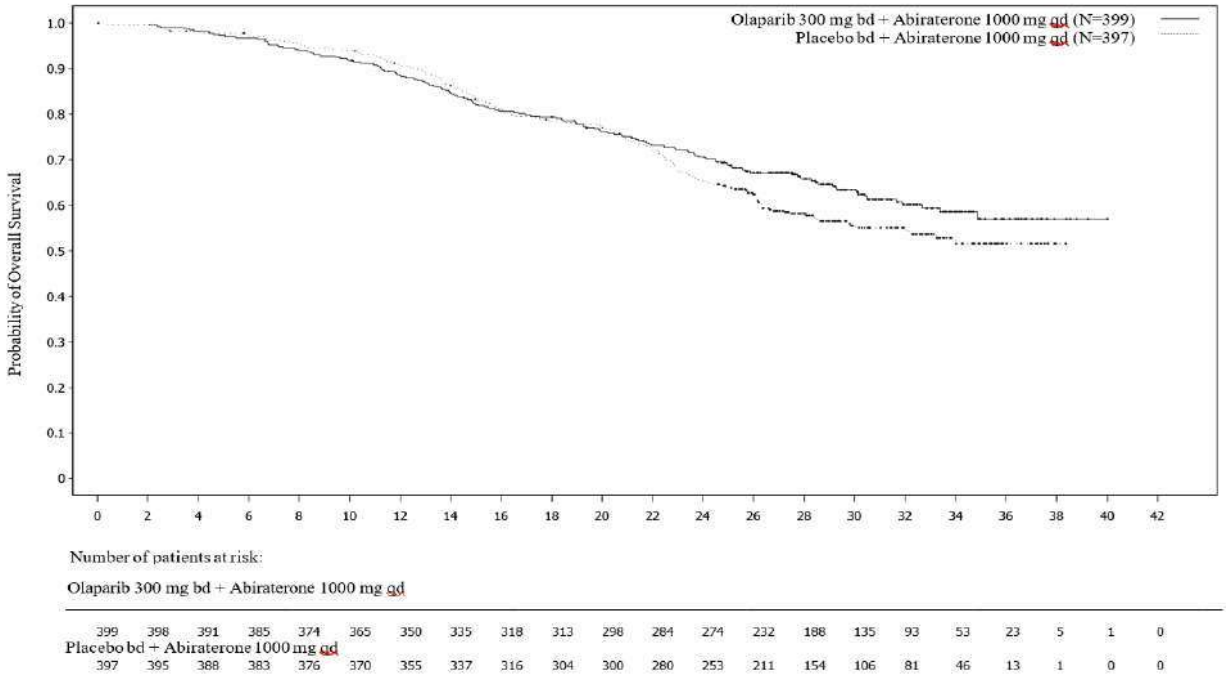


Olaparib 300 mg bd + Abiraterone 1000 mg qd (N=399)
Placebo bd + Abiraterone 1000 mg qd (N=397)

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

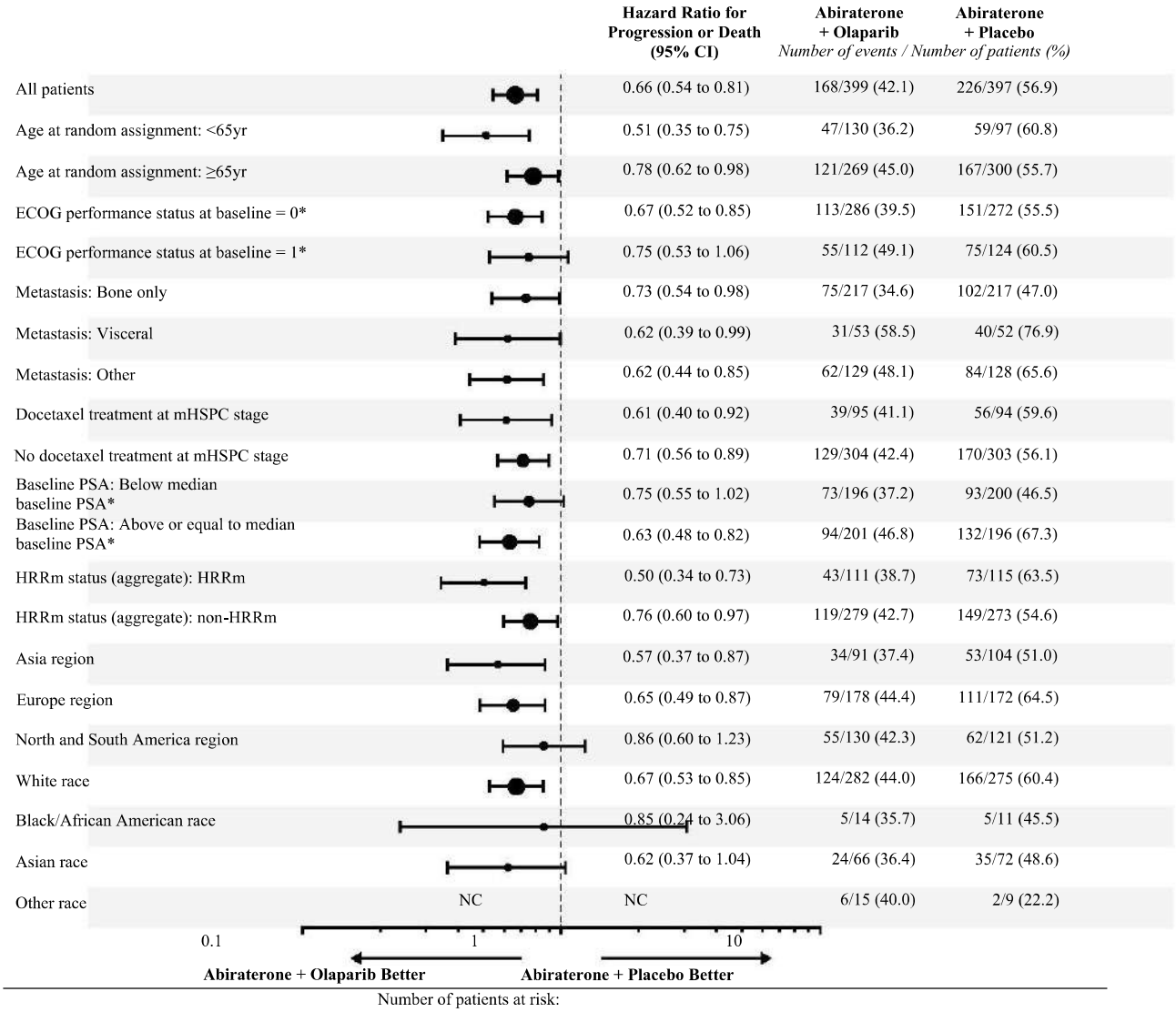
Figure 18 PROpel: Kaplan-Meier plot of OS



SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

Figure 19 PROpel: Forest plot of subgroup analysis of rPFS (investigator assessed)



Each subgroup analysis was performed using a Cox proportional hazards model that contained a term for treatment, factor, and treatment by factor interaction. A hazard ratio < 1 implies a lower risk of progression on olaparib. The size of a circle is proportional to the number of events.
*Excludes patients with no baseline assessment. CI: confidence interval, ECOG: Eastern Cooperative Oncology Group; HRRm: homologous recombination repair gene mutation; mHSPC: metastatic hormone-sensitive prostate cancer; NC: noncalculable; PSA: prostate-specific antigen.

Paediatric population

The Licensing 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).

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

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 UGT1A4, UGT1A9, 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

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.

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.

Carcinogenicity
Carcinogenicity studies have not been conducted with olaparib.
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.

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)

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

4 Years

6.4 Special precautions for storage

Store 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.

Pack sizes:
56 film-coated tablets (7 blisters).
Multipack containing 112 (2 packs of 56) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

Certificate Number: PP10185999

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

7 MARKETING AUTHORISATION HOLDER

AstraZeneca UK Limited,
1 Francis Crick Avenue,
Cambridge,
CB2 0AA,
UK.

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 17901/0333

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

17/10/2023

Lynparza 100 mg film-coated tablets
Lynparza 150 mg film-coated tablets
olaparib

1 INDICATIONS AND USAGE

1.1 First-Line Maintenance Treatment of *BRCA*-mutated Advanced Ovarian Cancer

Lynparza is indicated for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic *BRCA*-mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Selection of patients for therapy should be determined by an experienced laboratory using a validated test method *[see Dosage and Administration (2.1)]*.

1.2 First-line Maintenance Treatment of HRD-positive Advanced Ovarian Cancer in Combination with Bevacizumab

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

- a deleterious or suspected deleterious *BRCA* mutation, and/or
- genomic instability.

Selection of patients for therapy should be determined by an experienced laboratory using a validated test method *[see Dosage and Administration (2.1)]*.

1.3 Maintenance Treatment of *BRCA*-mutated Recurrent Ovarian Cancer

Lynparza is indicated for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic *BRCA*-mutated recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy. Selection of patients for therapy should be determined by an experienced laboratory using a validated test method *[see Dosage and Administration (2.1)]*.

1.4 Adjuvant Treatment of Germline *BRCA*-mutated HER2-negative High Risk Early Breast Cancer

Lynparza is indicated for the adjuvant treatment of adult patients with deleterious or suspected deleterious g*BRCA*m human epidermal growth factor receptor 2 (HER2)-negative high risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy. Selection of patients for therapy should be determined by an experienced laboratory using a validated test method *[see Dosage and Administration (2.1)]*.

1.5 Germline *BRCA*-mutated HER2-negative Metastatic Breast Cancer

Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious g*BRCA*m, HER2-negative metastatic breast cancer, who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer

should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Selection of patients for therapy should be determined by an experienced laboratory using a validated test method *[see Dosage and Administration (2.1)]*.

1.6 First-Line Maintenance Treatment of Germline *BRCA*-mutated Metastatic Pancreatic Adenocarcinoma

Lynparza is indicated for the maintenance treatment of adult patients with deleterious or suspected deleterious g*BRCA*m metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen. Selection of patients for therapy should be determined by an experienced laboratory using a validated test method *[see Dosage and Administration (2.1)]*.

1.7 HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone. Selection of patients for therapy should be determined by an experienced laboratory using a validated test method *[see Dosage and Administration (2.1)]*.

1.8 Treatment of *BRCA*-mutated Metastatic Castration-Resistant Prostate Cancer in Combination with Abiraterone and Prednisone or Prednisolone

Lynparza is indicated in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with deleterious or suspected deleterious *BRCA*-mutated (*BRCAm*) metastatic castration-resistant prostate cancer (mCRPC). Selection of patients for therapy should be determined by an experienced laboratory using a validated test method *[see Dosage and Administration (2.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for treatment with Lynparza based on the presence of deleterious or suspected deleterious HRR gene mutations, including *BRCA* mutations, or genomic instability based on the indication, biomarker, and sample type (Table 1).

Table 1 Biomarker Testing for Patient Selection*

Indication	Biomarker	Sample type		
		Tumour	Blood	Plasma (ctDNA)
First-line maintenance treatment of germline or somatic *BRCA*m advanced ovarian cancer	*BRCA1*m, *BRCA2*m	X	X	

First-line maintenance treatment of HRD-positive advanced ovarian cancer in combination with bevacizumab	*BRCA1*m, *BRCA2*m, and/or genomic instability	X		
Maintenance treatment of germline or somatic *BRCA*m recurrent ovarian cancer	*BRCA1*m, *BRCA2*m	X	X	
Adjuvant treatment of gBRCAm HER2-negative high risk early breast cancer	g*BRCA1*m, g*BRCA2*m		X	
g*BRCA*m HER2-negative metastatic breast cancer	*gBRCA1*m, *gBRCA2*m		X	
First-line maintenance treatment of germline *BRCA*-mutated metastatic pancreatic adenocarcinoma	*gBRCA1*m, *gBRCA2*m		X	
Germline or somatic HRR gene-mutated metastatic castration-resistant prostate cancer	*ATM*m, *BRCA1*m, *BRCA2*m, *BARD1*m, *BRIP1*m, *CDK12*m, *CHEK1*m, *CHEK2*m, *FANCL*m, *PALB2*m, *RAD51B*m, *RAD51C*m, *RAD51D*m, *RAD54L*m	X		
	g*BRCA1*m, g*BRCA2*m		X	
	*ATM*m, *BRCA1*m, *BRCA2*m			X
BRCA-mutated metastatic castration-resistant prostate cancer in combination with abiraterone and prednisone or prednisolone	*BRCA1*m, *BRCA2*m	X	X	X

* Where testing fails or tissue sample is unavailable/insufficient, or when germline testing is negative, consider using an alternative test, if available.

2.2 Recommended Dosage

The recommended dosage of Lynparza is 300 mg taken orally twice daily, with or without food.

If a patient misses a dose of Lynparza, instruct patient to take their next dose at its scheduled time. Instruct patients to swallow tablets whole. Do not chew, crush, dissolve, or divide tablet.

First-Line Maintenance Treatment of *BRCA*-mutated Advanced Ovarian Cancer

Continue treatment until disease progression, unacceptable toxicity, or completion of 2 years of treatment. 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 healthcare provider can derive further benefit from continuous treatment, can be treated beyond 2 years.

First-Line Maintenance Treatment of HRD-positive Advanced Ovarian Cancer in Combination with Bevacizumab

Continue Lynparza treatment until disease progression, unacceptable toxicity, or completion of 2 years of treatment. 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 healthcare provider can derive further benefit from continuous Lynparza treatment, can be treated beyond 2 years.

When used with Lynparza, the recommended dose of bevacizumab is 15 mg/kg every three weeks. Bevacizumab should be given for a total of 15 months including the period given with chemotherapy and given as maintenance. Refer to the Prescribing Information for bevacizumab when used in combination with Lynparza for more information.

Adjuvant Treatment of Germline *BRCA*-mutated HER2-negative High Risk Early Breast Cancer

Continue treatment for a total of 1 year, or until disease recurrence, or unacceptable toxicity, whichever occurs first. Patients receiving Lynparza for hormone receptor positive HER2-negative breast cancer should continue concurrent treatment with endocrine therapy as per current clinical practice guidelines.

Germline or Somatic *BRCA*-mutated Recurrent Ovarian Cancer, Germline *BRCA*-mutated HER2-negative Metastatic Breast Cancer, Germline *BRCA*-mutated Metastatic Pancreatic Adenocarcinoma, and HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

Continue treatment until disease progression or unacceptable toxicity for:

- Maintenance treatment of germline or somatic *BRCA*-mutated recurrent ovarian cancer
- Germline *BRCA*-mutated HER-2 negative metastatic breast cancer
- First-line maintenance treatment of germline *BRCA*-mutated metastatic pancreatic adenocarcinoma
- HRR gene-mutated metastatic castration-resistant prostate cancer

BRCA-mutated Metastatic Castration-Resistant Prostate Cancer in Combination with Abiraterone and Prednisone or Prednisolone

Continue treatment until disease progression or unacceptable toxicity.

When used with Lynparza, the recommended dose of abiraterone is 1000 mg taken orally once daily. Abiraterone should be given in combination with prednisone or prednisolone 5 mg orally twice daily. Refer to the Prescribing Information for abiraterone for dosing information.

Patients with mCRPC should also receive a gonadotropin-releasing hormone (GnRH) analogue concurrently or should have had bilateral orchiectomy.

2.3 Dosage Modifications for Adverse Reactions

To manage adverse reactions, consider interruption of treatment or dose reduction. The recommended dose reduction is 250 mg taken twice daily.

If a further dose reduction is required, then reduce to 200 mg taken twice daily.

2.4 Dosage Modifications for Concomitant Use with Strong or Moderate CYP3A Inhibitors

Avoid concomitant use of strong or moderate CYP3A inhibitors with Lynparza.

If concomitant use cannot be avoided, reduce Lynparza dosage to:

- 100 mg twice daily when used concomitantly with a strong CYP3A inhibitor.
- 150 mg twice daily when used concomitantly with a moderate CYP3A inhibitor.

After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume the Lynparza dose taken prior to initiating the CYP3A inhibitor *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

2.5 Dosage Modifications for Renal Impairment

Moderate Renal Impairment

In patients with moderate renal impairment (CLcr 31-50 mL/min), reduce the Lynparza dosage to 200 mg orally twice daily *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Tablets:

- 150 mg: green to green/grey film-coated, oval, bi-convex, tablet, debossed with ‘OP150’ on one side and plain on the reverse side.
- 100 mg: yellow to dark yellow film-coated, oval, bi-convex, tablet, debossed with ‘OP100’ on one side and plain on the reverse side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Myelodysplastic Syndrome/Acute Myeloid Leukaemia

Myelodysplastic syndrome (MDS)/Acute Myeloid Leukaemia (AML) has occurred in patients treated with Lynparza and some cases were fatal.

In clinical studies, among 2219 patients with various *BRCA*m, g*BRCA*m, HRR gene-mutated or HRD-positive cancers who received Lynparza as a single agent or as part of combination regimen, consistent with approved indications, the cumulative incidence of MDS/AML was approximately 1.2% (26/2219) *[see Adverse Reactions (6.1)]*. Of these, 54% (14/26) had a fatal outcome. The median duration of therapy with Lynparza in patients who developed MDS/AML was approximately 2 years (range: < 6 months to > 4 years). All of these patients had received previous chemotherapy with platinum agents and/or other DNA damaging agents including radiotherapy.

In SOLO1, patients with newly diagnosed advanced *BRCA*m ovarian cancer, the incidence of MDS/AML was 1.9% (5/260) in patients who received Lynparza and 0.8% (1/130) in patients who received placebo based on an updated analysis. In PAOLA-1, of patients with newly diagnosed advanced ovarian cancer with HRD-positive status, the incidence of MDS/AML was 1.6% (4/255) in patients who received Lynparza and 2.3% (3/131) in the control arm.

In SOLO2, patients with *BRCA*m platinum-sensitive relapsed ovarian cancer, the incidence of MDS/AML was 8% (15/195) in patients who received Lynparza and 4% (4/99) in patients who received placebo. The duration of Lynparza treatment prior to the diagnosis of MDS/AML ranged from 0.6 years to 4.5 years.

Do not start Lynparza until patients have recovered from haematological toxicity caused by previous chemotherapy (≤Grade 1). Monitor complete blood count for cytopenia at baseline and monthly thereafter for clinically significant changes during treatment. For prolonged haematological toxicities, interrupt Lynparza and monitor blood counts weekly until recovery. If the levels have not recovered to Grade 1 or less after 4 weeks, refer the patient to a haematologist for further investigations, including bone marrow analysis, and blood sample for cytogenetics. If MDS/AML is confirmed, discontinue Lynparza.

5.2 Pneumonitis

In clinical studies enrolling 2901 patients with various cancers who received Lynparza as a single agent *[see Adverse Reactions (6.1)]*, the incidence of pneumonitis, including fatal cases, was 0.8% (24/2901). If patients present with new or worsening respiratory symptoms such as dyspnoea, cough, and fever, or a radiological abnormality occurs, interrupt Lynparza treatment and promptly assess the source of the symptoms. If pneumonitis is confirmed, discontinue Lynparza treatment and treat the patient appropriately.

5.3 Venous Thromboembolism

Venous thromboembolism (VTE), including severe or fatal pulmonary embolism (PE), occurred in patients treated with Lynparza *[see Adverse Reactions (6.1)]*.

In the combined data of two randomised, placebo-controlled clinical studies (PROfound and PROpel) in patients with metastatic castration-resistant prostate cancer (N=1180), VTE occurred in 8% of patients who received Lynparza, including pulmonary embolism in 6%. In the control arms, VTE occurred in 2.5% including pulmonary embolism in 1.5%.

Monitor patients for clinical signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate, which may include long-term anticoagulation as clinically indicated.

5.4 Embryo-Foetal Toxicity

Lynparza can cause foetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. In an animal reproduction study, administration of olaparib to pregnant rats during the period of organogenesis caused teratogenicity and embryo-foetal toxicity at exposures below those in patients receiving the recommended human dose of 300 mg twice daily. Apprise pregnant women of the potential hazard to a foetus and the potential risk for loss of the pregnancy. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of Lynparza. Based on findings from genetic toxicity and animal reproduction studies, advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of Lynparza *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labelling:

- Myelodysplastic Syndrome/Acute Myeloid Leukaemia *[see Warnings and Precautions (5.1)]*
- Pneumonitis *[see Warnings and Precautions (5.2)]*
- Venous Thromboembolism *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Unless otherwise specified, the data described in the WARNINGS AND PRECAUTIONS reflect exposure to Lynparza as a single agent in 2901 patients; 2135 patients with exposure to 300 mg twice daily tablet dose including five controlled, randomised, trials (SOLO-1, SOLO-2, OlympiAD, POLO, and PROfound) and to 400 mg twice daily capsule dose in 766 patients in other trials that were pooled to conduct safety analyses. In addition to the 2901 patients, certain subsections in the WARNINGS AND PRECAUTIONS include adverse reactions observed with exposure to Lynparza with abiraterone (n=398)

in PROpel. All patients with metastatic castration resistant prostate cancer received concomitant ADT or previous bilateral orchiectomy.

In the pooled safety population, 56% of patients were exposed for 6 months or longer and 28% were exposed for greater than one year in the Lynparza group.

In this pooled safety population, the most common adverse reactions in ≥10% of patients were nausea (60%), fatigue (55%), anaemia (36%), vomiting (32%), diarrhoea (24%), decreased appetite (22%), headache (16%), dysgeusia (15%), cough (15%), neutropenia (14%), dyspnoea (14%), dizziness (12%), dyspepsia (12%), leukopenia (11%), and thrombocytopenia (10%).

First-Line Maintenance Treatment of *BRCA*-mutated Advanced Ovarian Cancer

SOLO-1

The safety of Lynparza for the maintenance treatment of patients with *BRCA*-mutated advanced ovarian cancer following first-line treatment with platinum-based chemotherapy was investigated in SOLO-1 *[see Clinical Studies (14.1)]*. Patients received Lynparza tablets 300 mg orally twice daily (n=260) or placebo (n=130) until disease progression or unacceptable toxicity. The median duration of study treatment was 25 months for patients who received Lynparza and 14 months for patients who received placebo.
Among patients who received Lynparza, dose interruptions due to an adverse reaction of any grade occurred in 52% and dose reductions due to an adverse reaction occurred in 28%. The most frequent adverse reactions leading to dose interruption or reduction of Lynparza were anaemia (23%), nausea (14%), and vomiting (10%). Discontinuation due to adverse reactions occurred in 12% of patients receiving Lynparza. The most frequent adverse reactions that led to discontinuation of Lynparza were fatigue (3.1%), anaemia (2.3%), and nausea (2.3%).

Tables 2 and 3 summarise adverse reactions and laboratory abnormalities in SOLO-1.

Table 2 Adverse Reactions[*] in SOLO-1 (≥10% of Patients Who Received Lynparza)

Adverse Reaction	Lynparza tablets n=260		Placebo n=130	
	All Grades (%)	Grades 3 – 4 (%)	All Grades (%)	Grades 3 – 4 (%)
Gastrointestinal Disorders				
Nausea	77	1	38	0
Abdominal pain[†]	45	2	35	1
Vomiting	40	0	15	1
Diarrhoea[‡]	37	3	26	0
Constipation	28	0	19	0
Dyspepsia	17	0	12	0
Stomatitis[§]	11	0	2	0

Adverse Reaction	Lynparza tablets n=260		Placebo n=130	
	All Grades (%)	Grades 3 – 4 (%)	All Grades (%)	Grades 3 – 4 (%)
General Disorders and Administration Site Conditions				
Fatigue[¶]	67	4	42	2
Blood and Lymphatic System Disorders				
Anaemia	38	21	9	2
Neutropenia[#]	17	6	7	3
Leukopenia[Þ]	13	3	8	0
Thrombocytopenia[ß]	11	1	4	2
Infections and Infestations				
Upper respiratory tract infection/ influenza/nasopharyngitis/bronchitis	28	0	23	0
UTI[à]	13	1	7	0
Nervous System Disorders				
Dysgeusia	26	0	4	0
Dizziness	20	0	15	1
Metabolism and Nutrition Disorders				
Decreased appetite	20	0	10	0
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnoea[è]	15	0	6	0

* Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0.

† Includes abdominal pain, abdominal pain lower, abdominal pain upper, abdominal distension, abdominal discomfort, and abdominal tenderness.

‡ Includes colitis, diarrhoea, and gastroenteritis.

§ Includes stomatitis, aphthous ulcer, and mouth ulceration.

¶ Includes: asthenia, fatigue, lethargy, and malaise.

Includes neutropenia and febrile neutropenia.

Þ Includes leukopenia and white blood cell count decreased.

ß Includes platelet count decreased and thrombocytopenia.

à Includes urosepsis, urinary tract infection, urinary tract pain, and pyuria.

è Includes dyspnoea and dyspnoea exertional.

Clinically relevant adverse reactions that occurred in <10% of patients receiving Lynparza were increased blood creatinine (8%), lymphopenia (6%), VTE (3%), hypersensitivity (2%), MDS/AML (1.9%), dermatitis (1%), and increased mean cell volume (0.4%).

Table 3 Laboratory Abnormalities Reported in ≥25% of Patients in SOLO-1

Laboratory Parameter[*]	Lynparza tablets n[†]=260	Placebo n[†]=130

	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Decrease in haemoglobin	87	19	63	2
Increase in mean corpuscular volume	87	-	43	-
Decrease in leucocytes	70	7	52	1
Decrease in lymphocytes	67	14	29	5
Decrease in absolute neutrophil count	51	9	38	6
Decrease in platelets	35	1	20	2
Increase in serum creatinine	34	0	18	0

* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.

† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.

First-line Maintenance Treatment of HRD-positive Advanced Ovarian Cancer in Combination with Bevacizumab

PAOLA-1

The safety of Lynparza in combination with bevacizumab for the maintenance treatment of patients with advanced ovarian cancer following first-line treatment containing platinum-based chemotherapy and bevacizumab was investigated in PAOLA-1 *[see Clinical Studies (14.2)]*. This study was a placebo-controlled, double-blind study in which 802 patients received either Lynparza 300 mg BID in combination with bevacizumab (n=535) or placebo in combination with bevacizumab (n=267) until disease progression or unacceptable toxicity. The median duration of treatment with Lynparza was 17.3 months and 11 months for bevacizumab post-randomisation on the Lynparza/bevacizumab arm.

Fatal adverse reactions occurred in 1 patient due to concurrent pneumonia and aplastic anaemia. Serious adverse reactions occurred in 31% of patients who received Lynparza/bevacizumab. Serious adverse reactions in >5% of patients included hypertension (19%) and anaemia (17%).

Dose interruptions due to an adverse reaction of any grade occurred in 54% of patients receiving Lynparza/bevacizumab and dose reductions due to an adverse reaction occurred in 41% of patients who received Lynparza/bevacizumab.

The most frequent adverse reactions leading to dose interruption in the Lynparza/bevacizumab arm were anaemia (21%), nausea (7%), vomiting (3%), and fatigue (3%), and the most frequent adverse reactions leading to reduction in the Lynparza/bevacizumab arm were anaemia (19%), nausea (7%), and fatigue (4%).

Discontinuation due to adverse reactions occurred in 20% of patients receiving Lynparza/bevacizumab. Specific adverse reactions that most frequently led to discontinuation in patients treated with Lynparza/bevacizumab were anaemia (4%) and nausea (3%).

The most common adverse reactions (≥ 10%) for patients receiving Lynparza/bevacizumab irrespective of the frequency compared with the placebo/bevacizumab arm were nausea (53%), fatigue (including asthenia) (53%), anaemia (41%), lymphopenia (24%), vomiting (22%), diarrhoea (18%), neutropenia (18%), leukopenia (18%), urinary tract infection (15%), and headache (14%).

Tables 4 and 5 summarise adverse reactions and laboratory abnormalities in PAOLA-1, respectively.

Table 4 Adverse Reactions* Occurring in ≥10% of Patients Treated with Lynparza/bevacizumab in PAOLA-1 and at ≥5% Frequency Compared to the Placebo/bevacizumab Arm

Adverse Reactions	Lynparza/bevacizumab n=535		Placebo/bevacizumab n=267	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
General Disorders and Administration Site Conditions				
Fatigue (including asthenia)†	53	5	32	1.5
Gastrointestinal Disorders				
Nausea	53	2.4	22	0.7
Vomiting	22	1.7	11	1.9
Blood and Lymphatic Disorders				
Anaemia‡	41	17	10	0.4
Lymphopenia§	24	7	9	1.1
Leukopenia¶	18	1.9	10	1.5

* Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0.

† Includes asthenia and fatigue.

‡ Includes anaemia, anaemia macrocytic, erythropenia, haematocrit decreased, haemoglobin decreased, normochromic anaemia, normochromic normocytic anaemia, normocytic anaemia, and red blood cell count decreased.

§ Includes B-lymphocyte count decreased, lymphocyte count decreased, lymphopenia, and T-lymphocyte count decreased.

¶ Includes leukopenia, and white blood cell count decreased.

Clinically relevant adverse reactions that occurred in <10% of patients receiving Lynparza/bevacizumab were dysgeusia (8%), dyspnoea (8%), stomatitis (5%), dyspepsia (4.3%), erythema (3%), dizziness (2.6%), hypersensitivity (1.7%), and MDS/AML (0.7%).

Venous thromboembolism occurred more commonly in patients receiving Lynparza/bevacizumab (5%) than in those receiving placebo/bevacizumab (1.9%).

Table 5 Laboratory Abnormalities Reported in ≥25% of Patients in PAOLA-1*

Laboratory Parameter†	Lynparza/bevacizumab n‡=535		Placebo/bevacizumab n‡=267	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Decrease in haemoglobin	79	13	55	0.4
Decrease in lymphocytes	63	10	42	3.0
Increase in serum creatinine	61	0.4	36	0.4
Decrease in leucocytes	59	3.4	45	2.2
Decrease in absolute neutrophil count	35	7	30	3.7
Decrease in platelets	35	2.4	28	0.4

* Reported within 30 days of the last dose.

† Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.

‡ This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.

Maintenance Treatment of *BRCA*-mutated Recurrent Ovarian Cancer

SOLO-2

The safety of Lynparza for the maintenance treatment of patients with platinum sensitive g*BRCA*m ovarian cancer was investigated in SOLO-2 *[see Clinical Studies (14.3)]*. Patients received Lynparza tablets 300 mg orally twice daily (n=195) or placebo (n=99) until disease progression or unacceptable toxicity. The median duration of study treatment was 19.4 months for patients who received Lynparza and 5.6 months for patients who received placebo.

Among patients who received Lynparza, dose interruptions due to an adverse reaction of any grade occurred in 45% and dose reductions due to an adverse reaction occurred in 27%. The most frequent adverse reactions leading to dose interruption or reduction of Lynparza were anaemia (22%), neutropenia (9%), and fatigue/asthenia (8%). Discontinuation due to an adverse reaction occurred in 11% of patients receiving Lynparza.

Tables 6 and 7 summarise adverse reactions and laboratory abnormalities in SOLO-2.

Table 6 Adverse Reactions* in SOLO-2 (≥20% of Patients Who Received Lynparza)

Adverse Reaction	Lynparza tablets n=195		Placebo n=99	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Gastrointestinal Disorders				
Nausea	76	3	33	0
Vomiting	37	3	19	1

Diarrhoea	33	2	22	0
Stomatitis†	20	1	16	0
General Disorders and Administration Site Conditions				
Fatigue including asthenia	66	4	39	2
Blood and Lymphatic Disorders				
Anaemia‡	44	20	9	2
Infections and Infestations				
Nasopharyngitis/URI/sinusitis/ rhinitis/influenza	36	0	29	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia/myalgia	30	0	28	0
Nervous System Disorders				
Dysgeusia	27	0	7	0
Headache	26	1	14	0
Metabolism and Nutrition Disorders				
Decreased appetite	22	0	11	0

* Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0.

† Represents grouped term consisting of abscess oral, aphthous ulcer, gingival abscess, gingival disorder, gingival pain, gingivitis, mouth ulceration, mucosal infection, mucosal inflammation, oral candidiasis, oral discomfort, oral herpes, oral infection, oral mucosal erythema, oral pain, oropharyngeal discomfort, and oropharyngeal pain.

‡ Represents grouped term consisting of anaemia, hematocrit decreased, haemoglobin decreased, iron deficiency, mean cell volume increased, and red blood cell count decreased.

Clinically relevant adverse reactions that occurred in <20% of patients receiving Lynparza were neutropenia (19%), cough (18%), leukopenia (16%), hypomagnesemia (14%), thrombocytopenia (14%), dizziness (13%), dyspepsia (11%), increased creatinine (11%), MDS/AML (8%), oedema (8%), rash (6%), VTE (5%), and lymphopenia (1%).

Table 7 Laboratory Abnormalities Reported in ≥25% of Patients in SOLO-2

Laboratory Parameter*	**Lynparza tablets n†=195**		**Placebo n†=99**	
	Grades 1-4 (%)	**Grades 3-4 (%)**	**Grades 1-4 (%)**	**Grades 3-4 (%)**
Increase in mean corpuscular volume‡	89	-	52	-
Decrease in haemoglobin	83	17	69	0
Decrease in leucocytes	69	5	48	1
Decrease in lymphocytes	67	11	37	1
Decrease in absolute neutrophil count	51	7	34	3
Increase in serum creatinine	44	0	29	0
Decrease in platelets	42	2	22	1

* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.

† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.

‡ Represents the proportion of subjects whose mean corpuscular volume was > upper limit of normal (ULN).

Adjuvant Treatment of germline *BRCA*-mutated HER2-negative High Risk Early Breast Cancer

OlympiA

The safety of Lynparza as monotherapy for the adjuvant treatment of patients with g*BRCA*-mutated HER2-negative high risk early breast cancer was investigated in OlympiA *[see Clinical Studies (14.4)]*. This study was a randomized, double-blind, multicentre study in which patients received either Lynparza tablets 300 mg orally twice daily (n=911) or placebo (n=904) for a total of 1 year, or until disease recurrence, or unacceptable toxicity. The median duration of treatment was 1 year in both arms.

Dose interruptions due to an adverse reaction of any grade occurred in 31% of patients receiving Lynparza; dose reductions due to an adverse reaction occurred in 23% of patients receiving Lynparza. The most frequent adverse reactions leading to dose interruption of Lynparza were anaemia (11%), neutropenia (6%), nausea (5%), leucopenia (3.5%), fatigue (3%), and vomiting (2.9%) and the most frequent adverse reactions leading to dose reduction of Lynparza were anaemia (8%), nausea (4.7%), neutropenia (4.2%), fatigue (3.3%), leucopenia (1.8%), and vomiting (1.5%). Discontinuation due to adverse reactions occurred in 10% of patients receiving Lynparza. The adverse reactions that most frequently led to discontinuation of Lynparza were nausea (2%), anaemia (1.8%), and fatigue (1.3%).

Tables 8 and 9 summarize the adverse reactions and laboratory abnormalities, respectively, in patients in OlympiA.

Table 8 Adverse Reactions[*] in OlympiA (≥ 10% of Patients Who Received Lynparza)

Adverse Reactions	Lynparza tablets n=911		Placebo n=904	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Gastrointestinal Disorders				
Nausea	57	0.8	23	0
Vomiting	23	0.7	8	0
Diarrhoea	18	0.3	14	0.3
Stomatitis[†]	10	0.1	4.5	0
General Disorders and Administration Site Conditions				
Fatigue (including asthenia)	42	1.8	28	0.7
Blood and Lymphatic Disorders				
Anaemia[‡]	24	9	3.9	0.3
Leucopenia[§]	17	3	6	0.3
Neutropenia[¶]	16	5	7	0.8
Nervous System Disorders				
Headache	20	0.2	17	0.1
Dysgeusia[#]	12	0	4.8	0
Dizziness	11	0.1	7	0.1
Metabolism and Nutrition Disorders				
Decreased appetite	13	0.2	6	0

[*] Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03

† Includes aphthous ulcer, mouth ulceration, and stomatitis.
‡ Includes anaemia, anaemia macrocytic, erythropenia, haematocrit decreased, haemoglobin decreased, normochromic anaemia, normochromic normocytic anaemia, normocytic anaemia, and red blood cell count decreased.
§ Includes leucopenia and white blood cell count decreased.
¶ Includes agranulocytosis, febrile neutropenia, granulocyte count decreased, granulocytopenia, idiopathic neutropenia, neutropenia, neutropenic infection, neutropenic sepsis, and neutrophil count decreased.
# Includes dysgeusia and taste disorder.

Clinically relevant adverse reactions that occurred in <10% of patients receiving Lynparza were cough (9.2%), lymphopenia (7%), dyspepsia (6%), upper abdominal pain (4.9%), rash (4.9%), dyspnoea (4.2%), thrombocytopenia (4.2%), increase in creatinine (2%), hypersensitivity (0.9%), VTE (0.5%), dermatitis (0.5%), increase in mean corpuscular volume (0.2%), and MDS/AML (0.2%).

Table 9 Laboratory Abnormalities Reported in ≥25% of Patients in OlympiA

Laboratory Parameter*	Lynparza tablets n†= 911		Placebo n†=904	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Decrease in lymphocytes	77	13	59	3.7
Increase in mean corpuscular volume‡	67	0	4.8	0
Decrease in haemoglobin	65	8	31	0.9
Decrease in leukocytes	64	5	42	0.7
Decrease in absolute neutrophil count	39	7	27	1.1

* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.
† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.
‡ Represents the proportion of subjects whose mean corpuscular volume was > ULN.

Germline *BRCA*-mutated HER2-negative Metastatic Breast Cancer

OlympiAD

The safety of Lynparza was evaluated in g*BRCA*m patients with HER2-negative metastatic breast cancer who had previously received up to two lines of chemotherapy for the treatment of metastatic disease in OlympiAD *[see Clinical Studies (14.5)]*. Patients received either Lynparza tablets 300 mg orally twice daily (n=205) or a chemotherapy (capecitabine, eribulin, or vinorelbine) of the healthcare provider's choice (n=91) until disease progression or unacceptable toxicity. The median duration of study treatment was 8.2 months in patients who received Lynparza and 3.4 months in patients who received chemotherapy.

Among patients who received Lynparza, dose interruptions due to an adverse reaction of any grade occurred in 35% and dose reductions due to an adverse reaction occurred in 25%. Discontinuation due to an adverse reaction occurred in 5% of patients receiving Lynparza.

Tables 10 and 11 summarise the adverse reactions and laboratory abnormalities in OlympiAD.

Table 10 Adverse Reactions* in OlympiAD (≥20% of Patients Who Received Lynparza)

Adverse Reaction	Lynparza tablets n=205		Chemotherapy n=91	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Gastrointestinal Disorders				
Nausea	58	0	35	1
Vomiting	30	0	15	1
Diarrhoea	21	1	22	0
Blood and Lymphatic Disorders				
Anaemia†	40	16	26	4
Neutropenia‡	27	9	50	26
Leucopenia§	25	5	31	13
General Disorders and Administration Site Conditions				
Fatigue (including asthenia)	37	4	36	1
Infections and Infestations				
Respiratory tract infection¶	27	1	22	0
Nervous System Disorders				
Headache	20	1	15	2

* Graded according to NCI CTCAE v4.0.
† Represents grouped terms consisting of anaemia (anaemia erythropenia, hematocrit decreased, haemoglobin decreased, and red blood cell count decreased).
‡ Represents grouped terms consisting of neutropenia (febrile neutropenia, granulocyte count decreased, granulocytopenia, neutropenia, neutropenic infection, neutropenic sepsis, and neutrophil count decreased).
§ Represents grouped terms consisting of leucopenia (leucopenia and white blood cell count decreased).
¶ Represents grouped terms consisting of bronchitis, influenza, lower respiratory tract infection, nasopharyngitis, pharyngitis, respiratory tract infection, rhinitis, sinusitis, upper respiratory tract infection, and upper respiratory tract infection bacterial.

Clinically relevant adverse reactions that occurred in <20% of patients receiving Lynparza were cough (18%), decreased appetite (16%), thrombocytopenia (11%), dysgeusia (9%), lymphopenia (8%), dyspepsia (8%), dizziness (7%), stomatitis (7%), upper abdominal pain (7%), rash (5%), increase in serum creatinine (3%), dermatitis (1%), and VTE (1%).

Table 11 Laboratory Abnormalities Reported in ≥25% of Patients in OlympiAD

Laboratory Parameter*	Lynparza tablets n†= 205		Chemotherapy n†= 91	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Decrease in haemoglobin	82	17	66	3
Decrease in lymphocytes	73	21	63	3
Decrease in leucocytes	71	8	70	23
Increase in mean corpuscular volume‡	71	-	33	-
Decrease in absolute neutrophil count	46	11	65	38
Decrease in platelets	33	3	28	0

* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.

† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.
‡ Represents the proportion of subjects whose mean corpuscular volume was > ULN.

First-line Maintenance Treatment of Germline *BRCA*-mutated Metastatic Pancreatic Adenocarcinoma

POLO

The safety of Lynparza as maintenance treatment of germline *BRCA*-mutated metastatic pancreatic adenocarcinoma following first-line treatment with platinum-based chemotherapy was evaluated in POLO *[see Clinical Studies (14.6)]*. Patients received Lynparza tablets 300 mg orally twice daily (n=90) or placebo (n=61) until disease progression or unacceptable toxicity. Among patients receiving Lynparza, 34% were exposed for 6 months or longer and 25% were exposed for greater than one year.

Among patients who received Lynparza, dosage interruptions due to an adverse reaction of any grade occurred in 35% and dosage reductions due to an adverse reaction occurred in 17%. The most frequent adverse reactions leading to dosage interruption or reduction in patients who received Lynparza were anaemia (11%), vomiting (5%), abdominal pain (4%), asthenia (3%), and fatigue (2%). Discontinuation due to adverse reactions occurred in 6% of patients receiving Lynparza. The most frequent adverse reaction that led to discontinuation of Lynparza was fatigue (2.2%).

Tables 12 and 13 summarise the adverse reactions and laboratory abnormalities in patients in POLO.

Table 12 Adverse Reactions* in POLO (Occurring in ≥10% of Patients who Received Lynparza)

Adverse Reaction	Lynparza tablets (n=91)†		Placebo (n=60)†	
	All Grades (%)	Grades 3 – 4 (%)	All Grades (%)	Grades 3 – 4 (%)
General Disorders and Administration Site Conditions				
Fatigue‡	60	5	35	2
Gastrointestinal Disorders				
Nausea	45	0	23	2
Abdominal pain§	34	2	37	5
Diarrhoea	29	0	15	0
Constipation	23	0	10	0
Vomiting	20	1	15	2
Stomatitis¶	10	0	5	0
Blood and Lymphatic System Disorders				
Anaemia	27	11	17	3
Thrombocytopenia#	14	3	7	0
Neutropenia‧	12	4	8	3
Metabolism and Nutrition Disorders				

Adverse Reaction	Lynparza tablets (n=91)†		Placebo (n=60)†	
	All Grades (%)	Grades 3 – 4 (%)	All Grades (%)	Grades 3 – 4 (%)
Decreased appetite	25	3	7	0
Musculoskeletal and Connective Tissue Disorders				
Back pain	19	0	17	2
Arthralgia	15	1	10	0
Skin and Subcutaneous Tissue Disorder				
Rashß	15	0	5	0
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnoeaà	13	0	5	2
Infections and Infestations				
Nasopharyngitis	12	0	3	0
Nervous System Disorders				
Dysgeusia	11	0	5	0

* Graded according to NCI CTCAE, version 4.0.
† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.
‡ Includes asthenia and fatigue.
§ Includes abdominal pain, abdominal pain upper, and abdominal pain lower.
¶ Includes stomatitis and mouth ulceration.
# Includes platelets count decreased and thrombocytopenia.
Þ Includes neutropenia, febrile neutropenia, and neutrophil count decreased.
ß Includes rash erythematous, rash macular, and rash maculo-papular.
à Includes dyspnoea and dyspnoea exertional.

Clinically relevant adverse reactions that occurred in <10% of patients receiving Lynparza were cough (9%), abdominal pain upper (7%), blood creatinine increased (7%), dizziness (7%), headache (7%), dyspepsia (5%), leukopenia (5%), VTE (3%), hypersensitivity (2%), and lymphopenia (2%).

Table 13 Laboratory Abnormalities Reported in ≥25% of Patients in POLO

Laboratory Parameter*	Lynparza tablets n†=91		Placebo n†=60	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Increase in serum creatinine	99	2	85	0
Decrease in haemoglobin	86	11	65	0
Increase in mean corpuscular volume‡	71	-	30	-
Decrease in lymphocytes	61	9	27	0
Decrease in platelets	56	2	39	0

Decrease in leucocytes	50	3	23	0
Decrease in absolute neutrophil count	25	3	10	0

* Patients were allowed to enter POLO with haemoglobin ≥9 g/dL (CTCAE Grade 2) and other laboratory values of CTCAE Grade 1.

† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.

‡ Represents the proportion of subjects whose mean corpuscular volume was > ULN.

HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

PROfound

The safety of Lynparza as monotherapy was evaluated in patients with mCRPC and HRR gene mutations who have progressed following prior treatment with enzalutamide or abiraterone in PROfound *[see Clinical Studies (14.7)]*. This study was a randomised, open-label, multicentre study in which 386 patients received either Lynparza tablets 300 mg orally twice daily (n=256) or investigator's choice of enzalutamide or abiraterone acetate (n=130) until disease progression or unacceptable toxicity. Among patients receiving Lynparza, 62% were exposed for 6 months or longer and 20% were exposed for greater than one year.

Fatal adverse reactions occurred in 4% of patients treated with Lynparza. These included pneumonia (1.2%), cardiopulmonary failure (0.4%), aspiration pneumonia (0.4%), intestinal diverticulum (0.4%), septic shock (0.4%), Budd-Chiari Syndrome (0.4%), sudden death (0.4%), and acute cardiac failure (0.4%).

Serious adverse reactions occurred in 36% of patients receiving Lynparza. The most frequent serious adverse reactions (≥2%) were anaemia (9%), pneumonia (4%), pulmonary embolism (2%), fatigue/asthenia (2%), and urinary tract infection (2%).

Dose interruptions due to an adverse reaction of any grade occurred in 45% of patients receiving Lynparza; dose reductions due to an adverse reaction occurred in 22% of Lynparza patients. The most frequent adverse reactions leading to dose interruption of Lynparza were anaemia (25%) and thrombocytopenia (6%) and the most frequent adverse reaction leading to reduction of Lynparza was anaemia (16%). Discontinuation due to adverse reactions occurred in 18% of Lynparza. The adverse reaction that most frequently led to discontinuation of Lynparza was anaemia (7%).

Tables 14 and 15 summarise the adverse reactions and laboratory abnormalities, respectively, in patients in PROfound.

Table 14 Adverse Reactions* Reported in ≥10% of Patients in PROfound

Adverse Reactions	Lynparza tablets n=256		Enzalutamide or abiraterone n=130	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Blood and lymphatic disorders				
Anaemia†	46	21	15	5
Thrombocytopenia‡	12	4	3	0
Gastrointestinal disorders				
Nausea	41	1	19	0
Diarrhoea	21	1	7	0
Vomiting	18	2	12	1
General disorders and administration site conditions				
Fatigue (including asthenia)	41	3	32	5
Metabolism and nutrition disorders				
Decreased appetite	30	1	18	1
Respiratory, thoracic, and mediastinal disorders				
Cough	11	0	2	0
Dyspnoea	10	2	3	0

* Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.
† Includes anaemia and haemoglobin decreased.
‡ Includes platelet count decreased and thrombocytopenia.

Clinically relevant adverse reactions that occurred in <10% of patients receiving Lynparza were neutropenia (9%), VTE (7%), dizziness (7%), dysgeusia (7%), dyspepsia (7%), headache (6%), pneumonia (5%), stomatitis (5%), rash (4%), blood creatinine increase (4%), pneumonitis (2%), upper abdominal pain (2%), and hypersensitivity (1%).

Table 15 Laboratory Abnormalities Reported in ≥25% of Patients in PROfound

Laboratory Parameter*	Lynparza tablets n†= 256		Enzalutamide or abiraterone n†=130	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Decrease in haemoglobin	98	13	73	4
Decrease in lymphocytes	62	23	34	13
Decrease in leucocytes	53	4	21	0
Decrease in absolute neutrophil count	34	3	9	0

* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.
† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.

Treatment of *BRCA*-mutated Metastatic Castration-Resistant Prostate Cancer in Combination with Abiraterone and Prednisone or Prednisolone

PROpel

The safety of Lynparza in combination with abiraterone and prednisone or prednisolone for the treatment of patients in the first-line mCRPC setting was investigated in PROpel *[see Clinical Studies (14.8)]*. Patients were randomised to receive either Lynparza tablets 300 mg orally twice daily plus abiraterone tablets 1000 mg once daily (Lynparza/abiraterone) (n=398), or placebo plus abiraterone 1000 mg once daily (placebo/abiraterone) (n=396) until disease progression or unacceptable toxicity. Patients in both arms also received either prednisone or prednisolone 5 mg twice daily.

Fatal adverse reactions occurred in 6% of patients, including COVID-19 (3%) and pneumonias (0.5%).

Serious adverse reactions occurred in 39% of patients. Serious adverse reactions reported in > 2% of patients included anaemia (6%), COVID-19 (6%), pneumonia (4.5%), pulmonary embolism (3.5%), and urinary tract infection (3%).

Permanent discontinuation of Lynparza due to adverse reactions occurred in 16% of patients treated in the Lynparza with abiraterone arm. The most common adverse reactions which resulted in permanent discontinuation of Lynparza were anaemia (4.3%) and pneumonia (1.5%).

Dosage interruption of Lynparza due to adverse reactions occurred in 48% of patients treated in the Lynparza with abiraterone arm. The most common (>2%) adverse reactions requiring dosage interruption of Lynparza were anaemia (16%), COVID-19 (6%) fatigue (3.5%), nausea (2.8%), pulmonary embolism (2.3%), and diarrhoea (2.3%).

Dose reduction of Lynparza due to adverse reactions occurred in 21% of patients treated in the Lynparza with abiraterone arm. The most common (>2%) adverse reactions requiring dosage reductions of Lynparza were anaemia (11%) and fatigue (2.5%).

The most common adverse reactions (≥10%) in patients who received Lynparza/abiraterone were anaemia (48%), fatigue (38%), nausea (30%), diarrhoea (19%), decreased appetite (16%), lymphopenia (14%), abdominal pain (13%), and dizziness (14%).

Tables 16 and 17 summarize adverse reactions and laboratory abnormalities in PROpel, respectively.

Table 16 Adverse Reactions (≥10%) in Patients Who Received Lynparza (with a Difference of ≥5% Compared to Placebo) in PROpel

Adverse Reactions*	**Lynparza/abiraterone n=398**		**Placebo/abiraterone n=396**	
	Grades 1-4 (%)	**Grades 3-4 (%)**	**Grades 1-4 (%)**	**Grades 3-4 (%)**
Blood and Lymphatic Disorders				
Anaemia†	48	16	18	3.3
Lymphopenia‡	14	5	6	1.8
General Disorders and Administration Site Conditions				
Fatigue (including asthenia)	38	2.3	30	1.5

Gastrointestinal Disorders				
Nausea	30	0.3	14	0.3
Diarrhoea	19	1	10	0.3
Abdominal pain[§]	13	0	7	0.5
Metabolism and nutrition disorders				
Decreased appetite	16	1	7	0
Nervous System Disorders				
Dizziness[¶]	14	0.3	7	0

* Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.

† Includes anaemia, anaemia macrocytic, and red blood cell count decreased

‡ Includes lymphocyte count decreased and lymphopenia

§ Includes abdominal discomfort, abdominal pain, abdominal pain upper, and abdominal pain lower

¶ Includes dizziness and vertigo.

Clinically relevant adverse reactions that occurred in <10% for patients receiving Lynparza plus abiraterone were headache (9%), VTE (8%), rash (7%), dysgeusia (6%), acute kidney injury (3%), and stomatitis (2.5%).

Table 17 Selected Laboratory Abnormalities Reported in ≥20% of Patients in PROpel

Laboratory Parameter	**Lynparza/abiraterone n=398***		**Placebo/abiraterone n=396***	
	Grades 1-4 (%)	**Grades 3-4 (%)**	**Grades 1-4 (%)**	**Grades 3-4 (%)**
Decrease in haemoglobin	97	12	81	1.3
Decrease in lymphocytes	70	23	49	11
Decrease in platelets	23	1.2	20	0.3
Decrease in absolute neutrophil count	23	5	6	0

* This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Lynparza. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: Hypersensitivity including angioedema.

Skin and subcutaneous tissue disorders: Erythema nodosum, rash, dermatitis.

7 DRUG INTERACTIONS

7.1 Use with Anticancer Agents

Clinical studies of Lynparza with other myelosuppressive anticancer agents, including DNA damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity.

7.2 Effect of Other Drugs on Lynparza

Strong and Moderate CYP3A Inhibitors

Coadministration of CYP3A inhibitors can increase olaparib concentrations, which may increase the risk for adverse reactions *[see Clinical Pharmacology (12.3)]*. Avoid coadministration of strong or moderate CYP3A inhibitors. If the strong or moderate inhibitor must be coadministered, reduce the dose of Lynparza *[see Dosage and Administration (2.4)]*.

Strong and Moderate CYP3A Inducers

Concomitant use with a strong or moderate CYP3A inducer decreased olaparib exposure, which may reduce Lynparza efficacy *[see Clinical Pharmacology (12.3)]*. Avoid coadministration of strong or moderate CYP3A inducers.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action *[see Clinical Pharmacology (12.1)]*, Lynparza can cause foetal harm when administered to a pregnant woman. There are no available data on Lynparza use in pregnant women to inform the drug-associated risk. In an animal reproduction study, the administration of olaparib to pregnant rats during the period of organogenesis caused teratogenicity and embryo-foetal toxicity at exposures below those in patients receiving the recommended human dose of 300 mg twice daily *(see Data)*. Apprise pregnant women of the potential hazard to the foetus and the potential risk for loss of the pregnancy.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

In a fertility and early embryonic development study in female rats, olaparib was administered orally for 14 days before mating through to Day 6 of pregnancy, which resulted in increased post-implantation loss at a dose level of 15 mg/kg/day (with maternal systemic exposures approximately 7% of the human exposure ($AUC_{0\text{-}24h}$) at the recommended dose).

In an embryo-foetal development study, pregnant rats received oral doses of 0.05 and 0.5 mg/kg/day olaparib during the period of organogenesis. A dose of 0.5 mg/kg/day (with maternal systemic exposures

approximately 0.18% of human exposure (AUC_{0-24h}) at the recommended dose) caused embryo-foetal toxicities including increased post-implantation loss and major malformations of the eyes (anophthalmia, microphthalmia), vertebrae/ribs (extra rib or ossification centre; fused or absent neural arches, ribs, and sternebrae), skull (fused exoccipital), and diaphragm (hernia). Additional abnormalities or variants included incomplete or absent ossification (vertebrae/sternebrae, ribs, limbs) and other findings in the vertebrae/sternebrae, pelvic girdle, lung, thymus, liver, ureter, and umbilical artery. Some findings noted above in the eyes, ribs and ureter were observed at a dose of 0.05 mg/kg/day olaparib at lower incidence.

8.2 Lactation

Risk Summary

No data are available regarding the presence of olaparib in human milk, or on its effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in the breastfed infants from Lynparza, advise a lactating woman not to breastfeed during treatment with Lynparza and for one month after receiving the last dose.

8.3 Females and Males of Reproductive Potential

Lynparza can cause foetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status of females of reproductive potential prior to initiating treatment with Lynparza.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with Lynparza and for 6 months following the last dose.

Males

Based on findings in genetic toxicity and animal reproduction studies, advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of Lynparza. Advise male patients not to donate sperm during therapy and for 3 months following the last dose of Lynparza *[see Use in Specific Populations (8.1) and Nonclinical Toxicology (13.1)]*.

8.4 Paediatric Use

Safety and effectiveness of Lynparza have not been established in paediatric patients.

8.5 Geriatric Use

Of the 2901 patients with advanced solid tumours who received Lynparza as a single agent, 680 (23%) patients were aged ≥65 years, and this included 206 (7%) patients who were aged ≥75 years. Thirteen (0.4%) patients were aged ≥85 years.

Of the 535 patients with advanced solid tumours who received Lynparza tablets 300 mg orally twice daily in combination with bevacizumab (PAOLA-1), 204 (38%) patients were aged ≥65 years, and this included 31 (6%) patients who were aged ≥75 years.

Of the 398 patients with advanced solid tumors who received Lynparza tablets 300 mg orally twice daily in combination with abiraterone and prednisone or prednisolone (PROpel), 268 (67%) patients were aged ≥65 years, and this included 95 (24%) patients who were aged ≥75 years.

No overall differences in the safety or effectiveness of Lynparza were observed between these patients and younger patients.

8.6 Renal Impairment

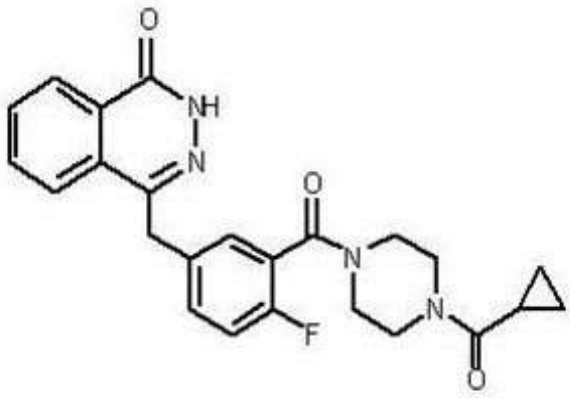
No dosage modification is recommended in patients with mild renal impairment (CLcr 51 to 80 mL/min estimated by Cockcroft-Gault). Reduce Lynparza dosage to 200 mg twice daily in patients with moderate renal impairment (CLcr 31 to 50 mL/min) *[see Dosage and Administration (2.5)]*. There are no data in patients with severe renal impairment or end-stage disease (CLcr ≤30 mL/min) *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No adjustment to the starting dose is required in patients with mild or moderate hepatic impairment (Child-Pugh classification A and B). There are no data in patients with severe hepatic impairment (Child-Pugh classification C) *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

Olaparib is a poly (ADP-ribose) polymerase (PARP) inhibitor. The chemical name is 4-[(3-{[4-(cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2*H*)-one. The empirical molecular formula for Lynparza is $C_{24}H_{23}FN_4O_3$ and the relative molecular mass is 434.46. It has the following chemical structure:



Olaparib is a crystalline solid, is non-chiral, and shows pH-independent low solubility across the physiological pH range.

Lynparza (olaparib) tablets for oral use contain 100 mg or 150 mg of olaparib. Inactive ingredients in the tablet core are copovidone, mannitol, colloidal silicon dioxide and sodium stearyl fumarate. The tablet coating consists of hypromellose, polyethylene glycol 400, titanium dioxide, ferric oxide yellow, and ferrosoferric oxide (150 mg tablet only).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Olaparib is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1, PARP2, and PARP3. PARP enzymes are involved in normal cellular functions, such as DNA transcription and DNA repair. Olaparib has been shown to inhibit growth of select tumour cell lines in vitro and decrease tumour growth in mouse xenograft models of human cancer, both as monotherapy or following platinum-based chemotherapy. Increased cytotoxicity and anti-tumour activity following treatment with olaparib were noted in cell lines and mouse tumour models with deficiencies in *BRCA1/2, ATM*, or other genes involved in the homologous recombination repair (HRR) of DNA damage and correlated with platinum response. In vitro studies have shown that olaparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes, resulting in DNA damage and cancer cell death. In prostate cancer models, PARP1 has been shown to contribute to androgen receptor (AR) activity regulation; the combination of olaparib and AR inhibition resulted in cytotoxicity in vitro and anti-tumour activity in mouse xenograft models.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of olaparib on cardiac repolarization was assessed in 119 patients following a single dose of 300 mg and in 109 patients following multiple dosing of 300 mg twice daily. No clinically relevant effect of olaparib on QT interval was observed.

12.3 Pharmacokinetics

The area under the curve (AUC) of olaparib increases approximately proportionally following administration of single doses of 25 mg to 450 mg (0.08 to 1.5 times the recommended dose) and maximal concentrations (C_{max}) increased slightly less than proportionally for the same dose range. Olaparib showed time-dependent pharmacokinetics and an AUC mean accumulation ratio of 1.8 is observed at steady state following a dose of 300 mg twice daily.

The mean (CV%) olaparib C_{max} is 5.4 µg/mL (32%) and AUC is 39.2 µg*h/mL (44%) following a single 300 mg dose. The mean steady state olaparib C_{max} and AUC is 7.6 µg/mL (35%) and 49.2 µg*h/mL (44%), following a dose of 300 mg twice daily.

Absorption

Following oral administration of olaparib, the median time to peak plasma concentration is 1.5 hours.

Effect of Food

Co-administration of a high fat and high calorie meal (800-1000 kcal, 50% of the calorie content made up

from fat) with olaparib slowed the rate (t_{max} delayed by 2.5 hours) of absorption, but did not significantly alter the extent of olaparib absorption (mean AUC increased by approximately 8%).

Distribution

The mean (± standard deviation) apparent volume of distribution of olaparib is 158 ± 136 L following a single 300 mg dose of Lynparza. The protein binding of olaparib is approximately 82% in vitro.

Elimination

The mean (± standard deviation) terminal plasma half-life of olaparib is 14.9 ± 8.2 hours and the apparent plasma clearance is 7.4 ± 3.9 L/h following a single 300 mg dose of Lynparza.

Metabolism

Olaparib is metabolised by cytochrome P450 (CYP) 3A in vitro.

Following an oral dose of radiolabelled olaparib to female patients, unchanged olaparib accounted for 70% of the circulating radioactivity in plasma. It was extensively metabolised with unchanged drug accounting for 15% and 6% of radioactivity in urine and faeces, respectively. The majority of the metabolism is attributable to oxidation reactions with a number of the components produced undergoing subsequent glucuronide or sulphate conjugation.

Excretion

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

Specific Populations

Patients with Renal Impairment

In a renal impairment trial, the mean AUC increased by 24% and C_{max} by 15%, when olaparib was dosed in patients with mild renal impairment (CLcr=51-80 mL/min defined by the Cockcroft-Gault equation; n=13) and by 44% and 26%, respectively, when olaparib was dosed in patients with moderate renal impairment (CLcr=31-50 mL/min; n=13), compared to those with normal renal function (CLcr ≥81 mL/min; n=12). There was no evidence of a relationship between the extent of plasma protein binding of olaparib and creatinine clearance. There are no data in patients with severe renal impairment or end-stage renal disease (CLcr ≤30 mL/min).

Patients with Hepatic Impairment

In a hepatic impairment trial, the mean AUC increased by 15% and the mean C_{max} increased by 13% when olaparib was dosed in patients with mild hepatic impairment (Child-Pugh classification A; n=10) and the mean AUC increased by 8% and the mean C_{max} decreased by 13% when olaparib was dosed in patients with moderate hepatic impairment (Child-Pugh classification B; n=8), compared to patients with normal hepatic function (n=13). Hepatic impairment has no effect on the protein binding of olaparib and, therefore, total plasma exposure was representative of free drug. There are no data in patients with severe

hepatic impairment (Child-Pugh classification C).

Drug Interaction Studies

Clinical Studies

CYP3A Inhibitors: Concomitant use of itraconazole (strong CYP3A inhibitor) increased olaparib C_{max} by 42% and AUC by 170%. Concomitant use of fluconazole (moderate CYP3A inhibitor) is predicted to increase olaparib C_{max} by 14% and AUC by 121%.

CYP3A Inducers: Concomitant use of rifampicin (strong CYP3A inducer) decreased olaparib C_{max} by 71% and AUC by 87%. Concomitant use of efavirenz (moderate CYP3A inducer) is predicted to decrease olaparib C_{max} by 31% and AUC by 60%.

In vitro Studies

CYP Enzymes: Olaparib is both an inhibitor and inducer of CYP3A and an inducer of CYP2B6. Olaparib is predicted to be a weak CYP3A inhibitor in humans.

UGT Enzymes: Olaparib is an inhibitor of UGT1A1.

Transporters: Olaparib is an inhibitor of BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1, and MATE2K. Olaparib is a substrate and inhibitor of the efflux transporter P-gp. The potential for olaparib to induce P-gp has not been evaluated.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with olaparib.

Olaparib was clastogenic in an in vitro chromosomal aberration assay in mammalian Chinese hamster ovary (CHO) cells and in an in vivo rat bone marrow micronucleus assay. This clastogenicity is consistent with genomic instability resulting from the primary pharmacology of olaparib and indicates potential for genotoxicity in humans. Olaparib was not mutagenic in a bacterial reverse mutation (Ames) test.

In a fertility study, female rats received oral olaparib at doses of 0.05, 0.5, and 15 mg/kg/day for at least 14 days before mating through the first week of pregnancy. There were no adverse effects on mating and fertility rates at doses up to 15 mg/kg/day (maternal systemic exposures approximately 7% of the human exposure (AUC_{0-24h}) at the recommended dose).

In a male fertility study, olaparib had no effect on mating and fertility in rats at oral doses up to 40 mg/kg/day following at least 70 days of olaparib treatment (with systemic exposures of approximately 5% of the human exposure (AUC_{0-24h}) at the recommended dose).

14 CLINICAL STUDIES

14.1 First-Line Maintenance Treatment of *BRCA*-mutated Advanced Ovarian Cancer

The efficacy of Lynparza was evaluated in SOLO-1 (NCT01844986), a randomised (2:1), double-blind, placebo-controlled, multicentre trial in patients with *BRCA*-mutated advanced ovarian, fallopian tube, or primary peritoneal cancer following first-line platinum-based chemotherapy. Patients were randomised to receive Lynparza tablets 300 mg orally twice daily or placebo. Treatment was continued for up to 2 years or until disease progression or unacceptable toxicity; however, patients with evidence of disease at 2 years, who in the opinion of the treating healthcare provider could derive further benefit from continuous treatment, could be treated beyond 2 years. Randomisation was stratified by response to first-line platinum-based chemotherapy (complete or partial response). The major efficacy outcome was investigator-assessed progression-free survival (PFS) evaluated according to Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1.

A total of 391 patients were randomised, 260 to Lynparza and 131 to placebo. The median age of patients treated with Lynparza was 53 years (range: 29 to 82) and 53 years (range: 31 to 84) among patients on placebo. The ECOG performance status (PS) was 0 in 77% of patients receiving Lynparza and 80% of patients receiving placebo. Of all patients, 82% were White, 36% were enrolled in the U.S. or Canada, and 82% were in complete response to their most recent platinum-based regimen. The majority of patients (n=389) had germline *BRCA* mutation (g*BRCA*m), and 2 patients had somatic *BRCA*m (s*BRCA*m).

Of the 391 patients randomised in SOLO-1, 386 were retrospectively or prospectively tested with a Myriad BRACAnalysis test and 383 patients were confirmed to have deleterious or suspected deleterious g*BRCA*m status; 253 were randomised to the Lynparza arm and 130 to the placebo arm. Two out of 391 patients randomised in SOLO-1 were confirmed to have s*BRCA*m based on an investigational Foundation Medicine tissue test.

SOLO-1 demonstrated a statistically significant improvement in investigator-assessed PFS for Lynparza compared to placebo. Results from a blinded independent review were consistent. At the time of the analysis of PFS, overall survival (OS) data were not mature (21% of patients had died). Efficacy results are presented in Table 18.

Table 18 Efficacy Results – SOLO-1 (Investigator Assessment)

	Lynparza tablets (n=260)	**Placebo (n=131)**
Progression-Free Survival*		
Number of events (%)	102 (39%)	96 (73%)
Median, months	NR	13.8
Hazard ratio† (95% CI)	0.30 (0.23, 0.41)	

	Lynparza tablets (n=260)	Placebo (n=131)
p-value‡	<0.0001	

* Median follow up of 41 months in both treatment arms.
† A value <1 favours olaparib. Hazard ratio from a Cox proportional hazards model including response to previous platinum chemotherapy (complete response versus partial response) as a covariate.
‡ The p-value is derived from a stratified log-rank test.
NR not reached; CI Confidence Interval.

14.2 First-line Maintenance Treatment of HRD-positive Advanced Ovarian Cancer in Combination with Bevacizumab

PAOLA-1 (NCT02477644) was a randomised, double-blind, placebo-controlled, multicentre trial that compared the efficacy of Lynparza in combination with bevacizumab versus placebo/bevacizumab for the maintenance treatment of advanced high-grade epithelial ovarian cancer, fallopian tube or primary peritoneal cancer following first-line platinum-based chemotherapy and bevacizumab. Randomisation was stratified by first-line treatment outcome (timing and outcome of cytoreductive surgery and response to platinum-based chemotherapy) and t*BRCAm* status, determined by prospective local testing. All available clinical samples were retrospectively tested with Myriad myChoice® CDx. Patients were required to have no evidence of disease (NED) due to complete surgical resection, or who were in complete response (CR), or partial response (PR) following completion of first-line platinum-containing chemotherapy and bevacizumab. Patients were randomised (2:1) to receive Lynparza tablets 300 mg orally twice daily in combination with bevacizumab (n=537) 15 mg/kg every three weeks or placebo/bevacizumab (n=269). 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. Lynparza treatment was continued for up to 2 years or until progression of the underlying disease or unacceptable toxicity. Patients who in the opinion of the treating physician could derive further benefit from continuous treatment could be treated beyond 2 years. Treatment with bevacizumab was for a total of up to 15 months, including the period given with chemotherapy and given as maintenance.

The major efficacy outcome measure was investigator-assessed PFS evaluated according to RECIST, version 1.1. An additional efficacy endpoint was overall survival (OS).

A statistically significant difference in PFS was observed in the intent-to-treat (ITT) population. Planned exploratory analyses of PFS and OS were conducted in patients with known HRD status. The PFS hazard ratio (HR) for patients with HRD-negative tumors (277/806; 34%) was 1.00 (95% CI: 0.75, 1.34) and the OS HR was 1.18 (95% CI: 0.87, 1.60) indicating that the clinical benefit was primarily attributed to the results seen in the HRD-positive population. Efficacy results in patients with HRD-positive tumors are summarized in Table 19.

Among the 387 patients (48%) with HRD-positive tumors identified post-randomization using the Myriad myChoice® HRD Plus tumor test the median age was 58 years in both arms (range 32-82). Ovarian cancer was the primary tumour type in 87% of patients in both arms. Ninety-five per cent (95%) were serous histological type. The ECOG performance score was 0 in 75% of patients and 1 in 24% of patients. All

patients had received first-line platinum-based therapy and bevacizumab. First-line treatment outcomes at screening indicated that patients had no evidence of disease with complete macroscopic resection at initial debulking surgery (36%), no evidence of disease/CR with complete macroscopic resection at interval debulking surgery (29%, both arms), no evidence of disease/CR in patients who had either incomplete resection (at initial or interval debulking surgery) or no debulking surgery (16%, both arms) and patients with a partial response (19%, both arms). Sixty-two (62%) of patients in the Lynparza/bevacizumab arm and 58% of patients in placebo/bevacizumab arm had tumors with a deleterious *BRCA* mutation. Patients were not restricted by the surgical outcome with 67% having complete cytoreduction at initial or interval debulking surgery and 33% having residual macroscopic disease.

Table 19 Efficacy Results – PAOLA-1 (HRD-positive status, Investigator Assessment)

	Lynparza/bevacizumab (n=255)	**Placebo/bevacizumab (n=132)**
Progression-Free Survival*		
Number of events (%)	87 (34%)	92 (70%)
Median, months	37.2	17.7
Hazard ratio† (95% CI)	0.33 (0.25, 0.45)	
Overall Survival‡		
Number of events (%)	93 (36%)	69 (52%)
Median, months	75.2	57.3
Hazard ratio† (95% CI)	0.62 (0.45, 0.85)	

* Results from a blinded independent review of PFS were consistent with those from investigator-assessed PFS.
† The analysis was performed using an unstratified Cox proportional hazards model.
‡ Based on final OS subgroup analysis.
CI Confidence interval.

14.3 Maintenance Treatment of *BRCA*-mutated Recurrent Ovarian Cancer

The efficacy of Lynparza was evaluated in SOLO-2 (NCT01874353), a randomised (2:1) double-blind, placebo-controlled trial in patients with *BRCA*m ovarian, fallopian tube, or primary peritoneal cancer who were in response to platinum based therapy. Patients were randomised to Lynparza tablets 300 mg orally twice daily or placebo until unacceptable toxicity or progressive disease. Randomisation was stratified by response to last platinum chemotherapy (complete versus partial) and time to disease progression in the penultimate platinum-based chemotherapy prior to enrollment (6-12 months versus >12 months). All patients had received at least two prior platinum-containing regimens and were in response (complete or

partial) to their most recent platinum-based regimen. The major efficacy outcome measure was investigator-assessed PFS evaluated according to RECIST, version 1.1. An additional efficacy outcome measure was OS.

A total of 295 patients were randomised, 196 to Lynparza and 99 to placebo. The median age of patients treated with Lynparza was 56 years (range: 28 to 83) and 56 years (range: 39 to 78) among patients treated with placebo. The ECOG PS was 0 in 83% of patients receiving Lynparza and 78% of patients receiving placebo. Of all patients, 89% were White, 17% were enrolled in the U.S. or Canada, 47% were in complete response to their most recent platinum-based regimen, and 40% had a progression-free interval of 6-12 months since their penultimate platinum regimen. Prior bevacizumab therapy was reported for 17% of those treated with Lynparza and 20% of those receiving placebo. Approximately 44% of patients on the Lynparza arm and 37% on placebo had received three or more lines of platinum-based treatment. All (100%) patients enrolled had g*BRCA* mutations.

All patients had a deleterious or suspected deleterious germline *BRCA* mutation as detected either by a local test (n=236) or central Myriad CLIA test (n=59), subsequently confirmed by BRACAnalysis CDx® (n=286).

SOLO-2 demonstrated a statistically significant improvement in investigator-assessed PFS in patients randomised to Lynparza as compared with placebo. Results from a blinded independent review were consistent. The final analysis of OS did not reach statistical significance. Efficacy results are presented in Table 20.

Table 20 Efficacy Results – SOLO-2 (Investigator Assessment)

	Lynparza tablets (n=196)	**Placebo (n=99)**
Progression-Free Survival		
Number of events (%)	107 (55%)	80 (81%)
Median, months	19.1	5.5
Hazard ratio* (95% CI)	0.30 (0.22, 0.41)	
p-value†	<0.0001	
Overall Survival		
Number of events (%)	116 (59)	65(66)
Median, months	51.7	38.8

	Lynparza tablets (n=196)	Placebo (n=99)
Hazard ratio* (95% CI)	0.74 (0.54, 1.00)	
p-value†	0.0537	

* Hazard ratio from a Cox proportional hazards model including response to last platinum chemotherapy (complete response versus partial response) and time to disease progression in the penultimate platinum-based chemotherapy prior to enrollment (6-12 month versus >12 months) as covariates.
† The p-value is derived from a stratified log-rank test.

14.4 Adjuvant Treatment of Germline *BRCA*-mutated HER2-negative High Risk Early Breast Cancer

The efficacy of Lynparza was evaluated in OlympiA (NCT02032823), a randomized (1:1), double-blind, placebo-controlled, international study in patients with g*BRCA*m HER2-negative high risk early breast cancer who had completed definitive local treatment and neoadjuvant or adjuvant chemotherapy. Patients were randomized to receive Lynparza tablets 300 mg orally twice daily or placebo. Treatment was continued for up to 1 year, or until disease recurrence, or unacceptable toxicity. 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. Patients with high-risk early breast cancer were defined as follows:

- patients who received prior neoadjuvant chemotherapy: patients with either triple negative breast cancer (TNBC) or hormone receptor positive breast cancer must have had residual invasive cancer in the breast and/or the resected lymph nodes (non-pathologic complete response) at the time of surgery. Additionally, patients with hormone receptor positive breast cancer must have had a score of ≥3 based on pre-treatment clinical and post-treatment pathologic stage (CPS), estrogen receptor (ER) status, and histologic grade as shown in Table 21.

Table 21 Early Breast Cancer Stage, Receptor Status, and Grade Scoring Requirements for Study Enrollment*

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

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

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

Randomisation was stratified by hormone receptor status (hormone receptor positive versus triple negative), by prior neoadjuvant versus adjuvant chemotherapy, and by prior platinum use for breast cancer (yes versus no).

The major efficacy outcome measure 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. An additional efficacy outcome measure was OS.

A total of 1836 patients were randomised, 921 to Lynparza and 915 to placebo. Demographic and baseline characteristics were well balanced between arms. The median age was 42 years. Sixty-seven percent (67%) of patients were White, 29% were Asian, and 3% were Black. Three percent (3%) of patients were Hispanic or Latino. Two patients (0.2%) in the Lynparza arm and four patients (0.4%) in the placebo arm were male. Sixty-one percent (61%) of patients were pre-menopausal. Eighty-nine percent (89%) of patients were ECOG performance status 0 and 11% ECOG PS 1. Eighty-two percent (82%) of patients had TNBC and 18% had hormone receptor-positive disease. 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 chemotherapy. Twenty-six (26%) of patients overall had received prior platinum for breast cancer. Ninety percent (90%) of patients with hormone receptor positive breast cancer received concurrent endocrine therapy.

Patients enrolled based on local g*BRCA* test results provided a sample for retrospective confirmatory central testing with BRACAnalysis®. Out of 1836 patients enrolled into OlympiA, 1623 were confirmed as g*BRCAm* by Myriad BRACAnalysis®, either prospectively or retrospectively.

A statistically significant improvement in IDFS and OS was demonstrated in patients in the Lynparza arm compared with the placebo arm. Efficacy data for OlympiA (FAS) is presented in Table 22.

Table 22 Efficacy Results – OlympiA

	Lynparza tablets (N=921)	**Placebo (N=915)**
Invasive Disease Free Survival (IDFS)*		
Number of events (%)	106 (12)	178 (20)
Hazard ratio (95% CI)†	0.58 (0.46, 0.74)	
p-value (2-sided)‡	< 0.0001	
3-year event-free rate, % (95% CI)§	86 (82.8, 88.4)	77 (73.7, 80.1)
Overall Survival¶		
Number of events (%)	75 (8)	109 (12)
Hazard ratio (95% CI)†	0.68 (0.50, 0.91)	
p-value (2-sided)‡	0.0091	
3-year event-free rate, % (95% CI)§	93 (90.8, 94.4)	89 (86.7, 91)

* Data from the pre-specified interim analysis (86% of the number of events for the planned final analysis).
† Based on the stratified Cox's Proportional Hazards Model.
‡ p-value from a stratified log-rank test. Compared with the allocated alpha of 0.005 for IDFS and 0.015 for OS.
§ Percentage are calculated using Kaplan-Meier estimates.
¶ Data from the pre-specified second interim analysis of OS (at ~330 IDFS events).
CI = confidence interval.

14.5 Treatment of Germline *BRCA*-mutated HER2-negative Metastatic Breast Cancer

The efficacy of Lynparza was evaluated in OlympiAD (NCT02000622), an open-label randomised (2:1) study in patients with g*BRCA*m HER2-negative metastatic breast cancer. Patients were required to have received treatment with an anthracycline (unless contraindicated) and a taxane, in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor-positive disease must have progressed on at least 1 endocrine therapy (adjuvant or metastatic) or have disease that the treating healthcare provider believed to be inappropriate for endocrine therapy. Patients with prior platinum therapy were required to have no evidence of disease progress during platinum treatment. No prior treatment with a PARP inhibitor was permitted. Patients were randomised to Lynparza tablets 300 mg orally twice daily or healthcare provider's choice of chemotherapy (capecitabine, eribulin, or vinorelbine, at standard doses) until progression or unacceptable toxicity. Randomisation was stratified by prior use of chemotherapy for metastatic disease (yes vs no), hormone receptor status (hormone receptor positive vs triple negative), and previous use of platinum-based chemotherapy (yes vs no). The major efficacy outcome measure was PFS assessed by blinded independent central review (BICR) using RECIST version 1.1.

A total of 302 patients were randomised, 205 to Lynparza and 97 to chemotherapy. Among the 205 patients treated with Lynparza, the median age was 44 years (range: 22 to 76), 65% were White, 4% were males, and all the patients had an ECOG PS of 0 or 1. Approximately 50% of patients had triple-negative tumours and 50% had oestrogen receptor and/or progesterone receptor positive tumours and the proportions were balanced across treatment arms. Patients in each treatment arm had received a median of 1 prior chemotherapy regimen for metastatic disease; approximately 30% had not received a prior chemotherapy regimen for metastatic breast cancer. Twenty-one per cent of patients in the Lynparza arm and 14% in the chemotherapy arm had received platinum therapy for metastatic disease. Seven per cent of patients in each treatment arm had received platinum therapy for localised disease.

Of the 302 patients randomised onto OlympiAD, 299 were tested with the BRACAnalysis CDx® and 297 were confirmed to have deleterious or suspected deleterious g*BRCA*m status; 202 were randomised to the Lynparza arm and 95 to the healthcare provider's choice of chemotherapy arm.

A statistically significant improvement in PFS was demonstrated for the Lynparza arm compared to the chemotherapy arm. Efficacy data for OlympiAD are displayed in Table 23. Consistent results were observed across patient subgroups defined by study stratification factors. An exploratory analysis of investigator-assessed PFS was consistent with the BICR-assessed PFS results.

Table 23 Efficacy Results - OlympiAD (BICR-assessed)

	Lynparza tablets (n=205)	Chemotherapy (n=97)
Progression-Free Survival		
Number of events (%)	163 (80%)	71 (73%)
Median, months	7.0	4.2
Hazard ratio (95% CI)*	0.58 (0.43, 0.80)	
p-value†	0.0009	
Patients with Measurable Disease	n=167	n=66
Objective Response Rate (95% CI)‡	52% (44, 60)	23% (13, 35)
Overall Survival		
Number of events (%)	130 (63%)	62 (64%)
Median, months	19.3	17.1
Hazard ratio (95% CI)*	0.90 (0.66, 1.23)	

* Hazard ratio is derived from a stratified log-rank test, stratified by ER, PgR negative versus ER and or PgR positive and prior chemotherapy (yes versus no).
† For PFS, p-value (2-sided) was compared to 0.05.
‡ Response based on confirmed responses. The confirmed complete response rate was 7.8% for Lynparza compared to 1.5% for chemotherapy arm.

14.6 First-Line Maintenance Treatment of Germline *BRCA*-mutated Metastatic Pancreatic Adenocarcinoma

The efficacy of Lynparza was evaluated in POLO (NCT02184195), a randomised (3:2), double-blind placebo-controlled, multicentre trial. Patients were required to have metastatic pancreatic adenocarcinoma with a deleterious or suspected deleterious germline *BRCA* mutation (g*BRCA*m) and absence of disease progression after receipt of first-line platinum-based chemotherapy for at least 16 weeks. Patients were randomised to receive Lynparza tablets 300 mg orally twice daily or placebo until disease progression or unacceptable toxicity. The major efficacy outcome measure was PFS by BICR using RECIST, version 1.1 modified to assess patients with clinical complete response at entry who were assessed as having no evidence of disease unless they had progressed based on the appearance of new lesions. Additional efficacy outcome measures were OS and ORR.

A total of 154 patients were randomised, 92 to Lynparza and 62 to placebo. The median age was 57 years (range 36 to 84); 54% were male; 92% were White, 4% were Asian, and 3% were Black; baseline ECOG

PS was 0 (67%) or 1 (31%). The median time from initiation of first-line platinum-based chemotherapy to randomisation was 5.8 months (range 3.4 to 33.4 months). Seventy-five per cent (75%) of patients received FOLFIRINOX with a median of 9 cycles (range 4-61), 8% received FOLFOX or XELOX, 4% received GEMOX, and 3% received gemcitabine plus cisplatin; 49% achieved a complete or partial response to platinum-based chemotherapy.

All patients had a deleterious or suspected deleterious germline *BRCA*-mutation as detected by the Myriad BRACAnalysis® or BRACAnalysis CDx® at a central laboratory only (n=106), local *BRCA* test only (n=4), or both local and central testing (n=44). Among the 150 patients with central test results, 30% had a mutation in *BRCA1;* 69% had a mutation in *BRCA2*; and 1 patient (1%) had mutations in both *BRCA1* and *BRCA2*.

POLO demonstrated a statistically significant improvement in BICR-assessed PFS in patients randomized to Lynparza as compared with placebo. The final analysis of OS did not reach statistical significance. Efficacy results of POLO are provided in Table 24.

Table 24 Efficacy Results - POLO (BICR-assessed)

	Lynparza tablets (n=92)	**Placebo (n=62)**
Progression-Free Survival		
Number of events (%)*	60 (65)	44 (71)
Median, months (95% CI)	7.4 (4.1, 11.0)	3.8 (3.5, 4.9)
Hazard ratio† (95% CI)	0.53 (0.35, 0.81)	
p-value	0.0035	
Overall Survival		
Number of events (%)	61 (66)	47 (76)
Median, months (95% CI)	19.0 (15.3, 26.3)	19.2 (14.3, 26.1)
Hazard ratio† (95% CI)	0.83 (0.56, 1.22)	
p-value	0.3487	
Patients with Measurable Disease	n=78	n=52

	Lynparza tablets (n=92)	Placebo (n=62)
Objective Response Rate (95% CI)	23% (14, 34)	12% (4, 23)
Complete response (%)	2 (2.6)	0
Partial response (%)	16 (21)	6 (12)
Duration of Response (DOR)		
Median time in months (95% CI)	25 (15, NC)	4 (2, NC)

* Number of events: Progression – Lynparza 55, placebo 44; death before BICR-documented progression – Lynparza 5, placebo 0.
† Hazard ratio, 95% CI, and p-value calculated from a log-rank test. A hazard ratio <1 favours Lynparza.
NC Not calculable.

14.7 HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

The efficacy of Lynparza was evaluated in PROfound (NCT02987543), randomised, open-label, multicentre trial that evaluated the efficacy of Lynparza 300 mg twice daily versus a comparator arm of investigator's choice of enzalutamide or abiraterone acetate in men with metastatic castration-resistant prostate cancer (mCRPC). All patients received a GnRH analogue or had prior bilateral orchiectomy. Patients needed to have progressed on prior enzalutamide or abiraterone 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 assigned to 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 risk-benefit. Patients were randomised (2:1), 256 to Lynparza arm and 131 to enzalutamide or abiraterone acetate arm; in Cohort A there were 245 (162 Lynparza arm and 83 in enzalutamide or abiraterone acetate arm) and in Cohort B there were 142 patients (94 in Lynparza arm and 48 in enzalutamide or abiraterone acetate arm). Randomisation was stratified by prior receipt of taxane chemotherapy and presence of measurable disease by RECIST 1.1. Treatment was continued until objective radiological disease progression determined by BICR. Upon radiological progression confirmed by BICR, patients randomised to enzalutamide or abiraterone acetate were given the option to switch to olaparib. Patients with HRR gene mutations were identified by tissue-based testing using the Foundation Medicine FoundationOne® clinical trial HRR assay performed at a central laboratory.

Determination of deleterious or suspected deleterious somatic or germline HRR mutation status in line with the FDA approved mutation classification and testing criteria for the Foundation Medicine F1CDx

tissue-based assay and assessment of the germline-*BRCA* status using the Myriad BRACAnalysis CDx blood-based assay was performed retrospectively. Representation of individual gene mutations by cohort is provided in Table 25. No patients were enrolled who had mutations in two of the 15 pre-specified HRR genes: *FANCL* and *RAD51C*.

Table 25 Frequency of Patients with HRR Mutations Enrolled in PROfound

HRR Mutation	Cohort A N=245 n (%)	Cohort B* N=142 n (%)
Single mutation	224 (91)	135 (95)
BRCA2	127 (52)	1 (<1)
ATM	84 (34)	2 (1)
BRCA1	13 (5)	0
CDK12	0	89 (63)
CHEK2	0	12 (8)
PPP2R2A†	0	10 (7)
RAD51B	0	5 (4)
RAD54L	0	5 (4)
PALB2	0	4 (3)
BRIP1	0	3 (2)
CHEK1	0	2 (1)
BARD1	0	1 (<1)
RAD51D	0	1 (<1)
Co-occurring mutation‡	21 (9)	7 (5)

* Three patients with single *BRCA2* or *ATM* gene mutations and 1 patient with co-occurring *BRCA2*+*CDK12* gene mutations were incorrectly assigned to Cohort B.

† Lynparza is not indicated for patients with *PPP2R2A* mutations.

‡ Patients with co-occurring mutations (*BRCA1*, *BRCA2*, or *ATM* plus a Cohort B gene) were assigned to Cohort A.

In Cohort A+B, the median age was 69 years (range: 47 to 91 years) in both arms; 69% were White, 29% were Asian, and 1% were Black. The ECOG performance score was 0 or 1 in most patients (95%) in both arms. In patients treated with Lynparza, the proportion of patients with RECIST 1.1 measurable disease at baseline was 58%, including 17% with lung and 10% with liver metastases, respectively. At randomisation, 66% of patients had received prior taxane chemotherapy, 40% had received enzalutamide, 38% had received abiraterone acetate, and 20% had received both enzalutamide and abiraterone acetate. Patient characteristics were well-balanced between arms.

The major efficacy outcome of the study was radiological progression free survival (rPFS) (Cohort A) as determined by BICR using RECIST version 1.1 and Prostate Cancer Clinical Trials Working Group 3 (PCWG3) (bone) criteria. Additional efficacy outcomes included confirmed objective response rate (ORR) (Cohort A), rPFS (combined Cohorts A+B) as assessed by BICR, and overall survival (OS) (Cohort A).

PROfound demonstrated a statistically significant improvement in BICR-assessed rPFS for Lynparza compared to investigator's choice of enzalutamide or abiraterone acetate in Cohort A and Cohort A+B. In an exploratory analysis for patients in Cohort B, the median rPFS was 4.8 months for Lynparza vs 3.3 months for comparator with a HR of 0.88 (95% CI 0.58, 1.36). The major efficacy outcome was

supported by a statistically significant improvement in ORR by BICR for patients with measurable disease at baseline in Cohort A. In Cohort B, ORR by BICR was 3.7% (95% CI 0.5, 12.7) in Lynparza treated patients and 8.3% (95% CI 1.0, 27.0) in patients treated with enzalutamide or abiraterone acetate.

The final analysis of overall survival (OS) demonstrated a statistically significant improvement in OS in patients randomised to Lynparza compared to patients in the enzalutamide or abiraterone acetate arm in Cohort A.

Efficacy results of PROfound are provided in Tables 26 and 27.

Table 26 Efficacy Results - PROfound (BICR-assessed)

	Cohort A		**Cohort A+B***	
	Lynparza tablets (n=162)	**Enzalutamide or Abiraterone acetate (n=83)**	**Lynparza tablets (n=256)**	**Enzalutamide or Abiraterone acetate (n=131)**
Radiological Progression-Free Survival (rPFS)				
Number of events (%)	106 (65)	68 (82)	180 (70)	99 (76)
Median (95% CI), in 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)
Hazard ratio (95% CI)†	0.34 (0.25, 0.47)		0.49 (0.38, 0.63)	
p-value‡	<0.0001		<0.0001	
Confirmed ORR				
Patients with measurable disease at baseline	n=84	n=43	-	-
ORR, n (%)	28 (33)	1 (2)	-	-
(95% CI)	(23, 45)	(0, 12)	-	-
p-value	<0.0001		-	
Overall Survival	n=162	n=83	-	-
Number of events (%)	91 (56)	57 (69)	-	-

	Cohort A		Cohort A+B*	
	Lynparza tablets (n=162)	**Enzalutamide or Abiraterone acetate (n=83)**	**Lynparza tablets (n=256)**	**Enzalutamide or Abiraterone acetate (n=131)**
Median (95% CI), in months	19.1 (17.4, 23.4)	14.7 (11.9, 18.8)	-	-
Hazard ratio (95% CI)†	0.69 (0.50, 0.97)		-	
p-value‡	0.0175		-	

* Although 10 patients with *PPP2R2A* mutation were included in all analyses of Cohort A+B, Lynparza is not indicated for this population due to unfavourable risk-benefit.
† The HR and CI were calculated using a Cox proportional hazards model adjusted for prior taxane use and measurable disease. An HR <1 favours Lynparza 300 mg taken orally twice daily.
‡ The analysis was performed using the log-rank test stratified by prior taxane use and measurable disease.
CI Confidence interval.

Consistent results were observed in exploratory analyses of rPFS for patients who received or did not receive prior taxane therapy and for those with germline-*BRCA* mutations identified using the Myriad BRACAnalysis CDx assay compared with those with *BRCA* mutations identified using the Foundation Medicine F1CDx assay.

Response data by HRR mutations for patients in the Lynparza arm are presented in Table 27. In the comparator arm of Cohorts A and B, a total of three patients achieved a partial response, including one patient with an *ATM* mutation alone and 2 patients with co-occurring mutations (one with *PALB2*+*PPP2R2A* and one with *CDK12*+*PALB2*).

Table 27 Response Rate and Duration of Response by HRR Mutation in Patients with Measurable Disease at Baseline on the Lynparza Arm – PROfound (BICR-assessed)

HRR mutation*	**Patients (N=138)**	**Confirmed ORR†**	
		n (%)	**95% CI**
Single mutation			
BRCA2	43	24 (56)	(40, 71)
ATM	30	3 (10)	(2, 27)
CDK12	34	2 (6)	(1, 20)
BRCA1	6	SD, PD (4), NE	NA
CHEK2	4	SD (2), PD (2)	NA
BRIP1	2	SD, PD	NA
PALB2	2	SD, PD	NA
CHEK1	1	PD	NA

RAD51B	1	SD	NA
RAD51D	1	PD	NA
RAD54L	1	SD	NA
Co-occurring mutations			
BRCA2/CDK12	2	PR, SD	NA
BRCA2/ATM	2	SD, SD	NA
BRCA2/BARD1	1	PD	NA
BRCA2/CHEK2	1	SD	NA
CDK12/CHEK1	1	SD	NA
CDK12/PALB2	1	PD	NA
BRCA2/CDK12/CHEK2	1	PD	NA
BRCA2/CHEK2/RAD51D	1	SD	NA

* No patients with *FANCL* or *RAD51C* enrolled. Three patients with *PPP2R2A* mutations had measurable disease, however, Lynparza is not indicated for patients with *PPP2R2A* mutation.
† In patients with a single *BRCA*2 mutation the median duration of response in the Lynparza arm (n=24) was 5.6 months (95% C.I: 5.5, 9.2). In the 3 responders with a single ATM mutation in the Lynparza arm, the duration of response ranged from 5.8+ to 9.0 months. In the 2 responders with a single CDK12 mutation in the Lynparza arm, the duration of response was 3.7 and 7.2 months. + denotes ongoing response.
PR Partial response; SD Stable disease; PD Progressive disease; NE Not evaluable; NA Not applicable due to small numbers or lack of response.

14.8 Treatment of *BRCA*-mutated Metastatic Castration-Resistant Prostate Cancer in Combination with Abiraterone and Prednisone or Prednisolone

The efficacy of Lynparza in the treatment of patients with mCRPC was investigated in PROpel (NCT03732820), a randomised, double-blind, placebo-controlled, multicentre study that compared the efficacy of Lynparza in combination with abiraterone with placebo plus abiraterone for patients with mCRPC. Patients (n=796) were randomised (1:1) to receive Lynparza tablets 300 mg orally twice daily in combination with abiraterone 1000 mg daily (n=399) compared with placebo plus abiraterone (n=397). All patients received either prednisone or prednisolone 5 mg twice daily, and a GnRH analog or prior bilateral orchiectomy. Patients with prior treatment with abiraterone were excluded. Prior docetaxel for localized or metastatic hormone-sensitive prostate cancer (mHSPC) was allowed. Randomisation was stratified by metastases (bone only, visceral, or other) and docetaxel treatment at mHSPC stage (yes or no). Lynparza treatment was continued until objective radiological disease progression determined by investigator or unacceptable toxicity.

BRCA gene mutation (*BRCA*m) status was assessed after randomization and before primary analysis by both NGS-based tumour tissue and ctDNA tests. *BRCA*m classification criteria in line with the FDA approved assays were used to determine the deleterious and suspected deleterious somatic or germline mutation status of patients.

The major efficacy outcome measure was investigator-assessed rPFS evaluated according to RECIST, version 1.1 and Prostate Cancer Working Group (PCWG3) (bone) criteria. Overall survival (OS) was an additional efficacy outcome measure.

Of the 796 patients tested, 85 (11%) had *BRCAm* determined by either a positive ctDNA test (9%) or a tumour tissue test (6%). Among these 85 patients, the median age was 68 years (range 43 to 85), and 67% were 65 years or older; 72% were White, 22% Asian, and 2% Black or African American; 66% had

ECOG performance status (PS) 0 and 34% had ECOG PS 1; 25% had prior docetaxel treatment for mHSPC; 53% had bone-only metastases, 15% had visceral metastases, and 32% had other metastases.

A statistically significant improvement in rPFS for Lynparza/abiraterone compared to placebo/abiraterone was observed in the intention to treat (ITT) population. In an exploratory analysis in the subgroup of 711 patients without an identified *BRCA*m, the rPFS hazard ratio was 0.77 (95% CI: 0.63, 0.96) and the OS hazard ratio was 0.92 (95% CI: 0.74, 1.14), indicating that the improvement in the ITT population was primarily attributed to the results seen in the subgroup of patients with *BRCA*m.

Results of an exploratory analysis in the subgroup of 85 patients on PROpel with *BRCA*m are summarized in Table 28.

Results from the BICR assessment were consistent with the investigator-assessed rPFS results.

Table 28 Efficacy Results – PROpel (Patients with *BRCA*m)

	Lynparza/abiraterone N = 47	**Placebo/abiraterone** N = 38
Radiological Progression-Free Survival (rPFS)*		
Events, n (%)	14 (30)	28 (74)
Median (95% CI), months	NR (NR, NR)	8 (6, 15)
Hazard ratio (95% CI)†	0.24 (0.12, 0.45)	
Overall Survival (OS)		
Events, n (%)	13 (28)	25 (66)
Median (95% CI), months	NR (NR, NR)	23 (18, 34)
Hazard ratio (95% CI)†	0.30 (0.15, 0.59)	

* Investigator-assessed.
NR: Not reached.
† Calculated using an unstratified univariable Cox proportional hazards model.

16 HOW SUPPLIED/STORAGE AND HANDLING

Lynparza is available as 150 mg and 100 mg tablets.

Lynparza is supplied in packs containing 56 film-coated tablets (7 blisters with 8 tablets each). Keep this medicine out of the sight and reach of children. Do not use this medicine after the expiry date which is stated on the carton and the blister after EXP. The expiry date refers to the last day of that month.

Do not store above 30°C.

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

17 PATIENT COUNSELING INFORMATION

MDS/AML

Advise patients to contact their healthcare provider if they experience weakness, feeling tired, fever, weight loss, frequent infections, bruising, bleeding easily, breathlessness, blood in urine or stool, and/or laboratory findings of low blood cell counts, or a need for blood transfusions. This may be a sign of haematological toxicity or a more serious uncommon bone marrow problem called 'myelodysplastic syndrome' (MDS) or 'acute myeloid leukaemia' (AML) which have been reported in patients treated with Lynparza *[see Warnings and Precautions (5.1)]*.

Pneumonitis

Advise patients to contact their healthcare provider if they experience any new or worsening respiratory symptoms including shortness of breath, fever, cough, or wheezing *[see Warnings and Precautions (5.2)]*.

Venous Thromboembolism

Advise patients to immediately report any signs or symptoms of thromboembolism such as pain or swelling in an extremity, shortness of breath, chest pain, tachypnea, and tachycardia *[see Warnings and Precautions (5.3)]*.

Embryo-Foetal Toxicity

Inform pregnant women of the risk to a foetus and potential loss of the pregnancy. Advise females to inform their healthcare provider of known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use effective contraception during treatment with Lynparza and for 6 months after the last dose *[see Use in Specific Populations (8.3)]*.

Advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months after receiving the last dose of Lynparza. Advise male patients not to donate sperm during therapy and for 3 months following the last dose of Lynparza *[see Warnings and Precautions (5.4) and Use in Specific Population (8.3)]*.

Lactation

Advise patients not to breastfeed while taking Lynparza and for one month after receiving the last dose *[see Use in Specific Populations (8.2)]*.

Drug Interactions

Advise patients and caregivers to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Inform patients

to avoid grapefruit, grapefruit juice, Seville oranges, and Seville orange juice while taking Lynparza *[see Drug Interactions (7.2)]*.

Nausea/Vomiting

Advise patients that mild or moderate nausea and/or vomiting is very common in patients receiving Lynparza and that they should contact their healthcare provider who will advise on available antiemetic treatment options *[see Adverse Reactions (6.1)]*.

Manufactured by

AbbVie Limited, KM 58.0, Carretera 2, Cruce Davila, Barceloneta, Puerto Rico (PR) 00617, United States, for AstraZeneca UK Limited.

Date of revision of the text
February 2024

Doc ID-004169187 V10.0