Proposed packaging material		
Code	LYNPARZA 100 150 (56s) TAB-PI-03.01	
Submission	☐NDA ☐Renewal ☑Variation change detail no.: MU-104953-135498	
Code of previous version	LYNPARZA 100 150 (56s) TAB-PI-01.02	
Changes	Additional Indication of PROfound	
Reference	☑CDS version: V3.0 / Doc ID-004025980 ☐CPIL version:	☑SmPC country/version/date: EU SmPC/ Feb 2021/ Doc ID-004086888 v11. ☐GRL approval: 24 May 2021
Name & Date	MMN – 6 Jun 2022	

LYNPARZA™

Olaparib

Film-coated Tablet

1. NAME OF THE MEDICINAL PRODUCT

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

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Lynparza 100 mg film-coated tablets
Yellow to dark yellow, oval, bi-convex tablet, debossed with ‘OP100’ on one side and plain on the other side.

Lynparza 150 mg film-coated tablets
Green to green/grey, oval, bi-convex tablet, debossed with ‘OP150’ on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ovarian cancer

Lynparza is indicated as monotherapy for the:

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

Lynparza in combination with bevacizumab is indicated for the:

- maintenance treatment of adult patients with advanced (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).

Adenocarcinoma of the pancreas

- Lynparza is indicated as monotherapy for the maintenance treatment of adult patients with deleterious or suspected deleterious germline BRCA1/2-mutations who have metastatic adenocarcinoma of the pancreas and have not progressed on at least 16 weeks of a first-line platinum based chemotherapy regimen.

Breast cancer

Lynparza is indicated as 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.

Prostate cancer

Lynparza tablets for the treatment of adult patients with metastatic castration-resistant prostate cancer and BRCA1/2-mutations (germline and/or somatic) who have progressed following a prior therapy that included new hormonal agent.

4.2 Posology and method of administration

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

Patients selection

Detection of *BRCA1/2* mutations

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.

Maintenance treatment of HRD positive advanced ovarian cancer in combination with bevacizumab:
Before Lynparza with bevacizumab treatment is initiated for the 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).

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

Maintenance treatment of g*BRCA-mutated metastatic adenocarcinoma of the pancreas*:
For 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.

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

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 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 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).

Duration of treatment

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.

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).

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.

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.

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

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.

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

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

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

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

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

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

Dose adjustments for co-administration with CYP3A inhibitors
Concomitant use of strong or moderate CYP3A inhibitors is not recommended and alternative agents should be considered. If a strong CYP3A inhibitor must be co-administered, the recommended Lynparza dose reduction is to 100 mg (one 100 mg tablet) taken twice daily (equivalent to a total daily dose of 200 mg). If a moderate CYP3A inhibitor must be co-administered, the recommended Lynparza dose reduction is to 150 mg (one 150 mg tablet) taken twice daily (equivalent to a total daily dose of 300 mg) (see sections 4.4 and 4.5).

Special populations

Elderly
No adjustment in starting dose is required for elderly patients.

Renal impairment
For patients with moderate renal impairment (creatinine clearance 31 to 50 ml/min) the recommended dose of Lynparza is 200 mg (two 100 mg tablets) twice daily (equivalent to a total daily dose of 400 mg) (see section 5.2).

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

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

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

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

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

Method of administration

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

4.3 Contraindications

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

4.4 Special warnings and special precautions for use

Haematological toxicity
Haematological toxicity has been reported in patients treated with Lynparza, including clinical diagnoses and/or laboratory findings of generally mild or moderate (CTCAE grade 1 or 2) anaemia, neutropenia, thrombocytopenia and lymphopenia. Patients should not start treatment with Lynparza until they have recovered from haematological toxicity caused by previous 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 Lynparza in patients who developed MDS/AML varied from < 6 months to > 4 years. All patients had potential contributing factors for the development of MDS/AML, having received previous chemotherapy with platinum agents. Many had also received other DNA damaging 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 (1.7% and 1.4%, respectively). Some of the patients had a history of previous cancer or of bone marrow dysplasia. If MDS and/or AML are confirmed while on treatment with Lynparza, it is recommended that Lynparza should be discontinued and the patient be treated appropriately.

Pneumonitis

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

Embryofoetal toxicity

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

Pregnancy/contraception

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

Interactions

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Clinical studies of olaparib in combination with other anticancer medicinal products, including DNA damaging agents, indicate a potentiation and prolongation of

myelosuppressive toxicity. The recommended Lynparza monotherapy dose is not suitable for combination with myelosuppressive anticancer medicinal products.

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

Pharmacokinetic interactions

Effect of other medicinal products on olaparib

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

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

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

Effect of olaparib on other medicinal products

Olaparib inhibits CYP3A4 *in vitro* and is predicted to be a mild CYP3A inhibitor *in vivo*. Therefore, caution should be exercised when sensitive CYP3A substrates or substrates with a narrow therapeutic margin (e.g. simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, 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 significant interaction was observed with anastrozole or letrozole,

whereas tamoxifen decreased exposure to olaparib by 27%. The clinical relevance of this effect is unknown. Olaparib does not affect the pharmacokinetics of tamoxifen.

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 1 month after receiving the last dose of Lynparza, unless abstinence is the chosen method of contraception (see section 4.4). Two highly effective and complementary forms of contraception are recommended.

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

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

Pregnancy
Studies in animals have shown reproductive toxicity including serious teratogenic effects and effects on embryofoetal survival in the rat at maternal systemic exposures lower than those in humans at therapeutic doses (see section 5.3). There are no data from the use of olaparib in pregnant women, however, based on the mode of action of olaparib, Lynparza should not be used during pregnancy and in women of childbearing potential not using reliable contraception during therapy and for 1 month 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, anaemia, vomiting, diarrhoea, decreased appetite, headache, dysgeusia, cough, neutropenia, dyspnoea, dizziness, dyspepsia, leukopenia and thrombocytopenia.

The Grade ≥ 3 adverse reactions occurring in > 2% of patients were anaemia (16%), neutropenia (5%), fatigue/asthenia (5%), thrombocytopenia (3%) and leukopenia (2%).

Adverse reactions that most commonly led to dose interruptions and/ or reductions in monotherapy were anaemia (17%), fatigue/asthenia (6.%), *vomiting (6%), nausea (6%)* and neutropenia (6%). Adverse reactions that most commonly led to permanent discontinuation were anaemia (1.8%), thrombocytopenia (0.8%), fatigue/asthenia (0.7%), nausea (0.6%) *neutropenia (0.5%) and vomiting (0.5%)*.

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

Adverse events led to dose interruption and/ or reduction of olaparib in 57.4% of patients when used in combination with bevacizumab and led to permanent discontinuation of treatment with olaparib/bevacizumab and placebo/bevacizumab in 20.4% and 5.6% of patients, respectively. The adverse reactions that most commonly led to dose interruption and/or reduction were anaemia (21.5%),nausea (9.5%) and fatigue/asthenia (5.2%). The adverse reactions that most commonly led to permanent discontinuation were anaemia (3.6%), nausea (3.4%) and fatigue/asthenia (1.5%).

Tabulated list of adverse reactions
The safety profile is based on pooled data from 3077 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	**Uncommon** Myelodysplastic syndrome/Acute myeloid leukaemia
Blood and lymphatic system disorders	**Very common** Anaemia[a], Neutropenia[a], Thrombocytopenia[a], Leukopenia[a] **Common** Lymphopenia[a]	**Very common** Anaemia[a] **Common** Neutropenia[a], Thrombocytopenia[a], Leukopenia[a] **Uncommon** Lymphopenia[a]
Immune system disorders	**Uncommon** Hypersensitivity[a], Angioderma[*]	**Rare** Hypersensitivity[a]
Metabolism and nutrition disorders	**Very common** Decreased appetite	**Uncommon** Decreased appetite
Nervous system disorders	**Very common** Dizziness, Headache, Dysgeusia[a]	**Uncommon** Dizziness, Headache
Respiratory, thoracic and mediastinal disorders	**Very common** Cough[a], Dyspnoea[a]	**Common** Dyspnoea[a] **Uncommon** Cough[a]

	Adverse reactions	
MedDRA System Organ Class	**Frequency of All CTCAE grades**	**Frequency of CTCAE grade 3 and above**
Gastrointestinal disorders	**Very common** Vomiting, Diarrhoea, Nausea, Dyspepsia **Common** Stomatitis[a], Upper abdominal pain	**Common** Vomiting, Diarrhoea, Nausea **Uncommon** Stomatitis[a], Upper abdominal pain **Rare** Dyspepsia
Skin and subcutaneous tissue disorders	**Common** Rash[a] **Uncommon** Dermatitis[a] **Rare** Erythema nodosum	**Uncommon** Rash[a]
General disorders and administration site conditions	**Very common** Fatigue (including asthenia)	**Common** Fatigue (including asthenia)
Investigations	**Common** Blood creatinine increased **Uncommon** Mean cell volume elevation	**Uncommon** Blood creatinine increased

[a] MDS/AML includes preferred terms (PTs) of acute myeloid leukaemia, myelodysplastic syndrome and myeloid leukaemia. Anaemia includes PTs of anaemia, anaemia macrocytic, erythropenia, haematocrit decreased, haemoglobin decreased, normocytic anaemia and red blood cell count decreased; Neutropenia includes PTs offebrile neutropenia, neutropenia, neutropenic infection, neutropenic sepsis and neutrophil count decreased. Leukopenia includes PTs of leukopenia and white blood cell count decreased.Thrombocytopenia includes PTs of platelet count decreased and thrombocytopenia. Lymphopenia includes PTs of lymphocyte count decreased and lymphopenia. Cough includes PTs of cough and productive cough. Dyspnoea includes PTs of dyspnoea and dyspnoea exertional. Stomatitis includes PTs of aphthous ulcer, mouth ulceration and stomatitis. Rash includes PTs of erythrema, exfoliative rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular and rash pruritic. Dermatitis includes PTs of dermatitis and dermatitis allergic.

* As observed in post-marketing setting

Description of selected adverse reactions

Myelodysplastic syndrome/Acute myeloid leukaemia
In clinical studies, across all indications, MDS/AML occurred uncommonly in patients on treatment and during the 30-day safety follow up, and <1.5% at any time after starting olaparib, including cases actively solicited during the long term follow up for overall survival. In patients with *BRCA*m platinum-sensitive relapsed ovarian cancer who had received at least two prior lines of platinum chemotherapy and received study treatment until disease progression (SOLO2 study, with olaparib treatment ≥ 2 years in 45% of patients), the incidence of MDS/AML was 8% in patients receiving olaparib and 4% in patients receiving placebo at a follow-up of 5 years. In the olaparib arm, 9 out of 16 MDS/AML cases occurred after discontinuation of olaparib during the survival follow-up. The incidence of MDS/AML was observed in the context of extended overall survival in the olaparib arm and late onset of MDS/AML. The risk of MDS/AML remains < 1.5% at 5 year follow up in the first-line setting when olaparib maintenance treatment is given after one line of platinum chemotherapy for a duration of 2 years.

Haematological toxicity
Anaemia and other haematological toxicities 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 39.2% (CTCAE grade ≥3 17.2%) and the incidences of dose interruptions, reductions and discontinuations for anaemia were 17.8%, 11.1% and 2.2%, respectively; 21.8% 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 20%, absolute neutrophils 20%, platelets 5%, lymphocytes 30% and leucocytes 20% (all % approximate).

The incidence of elevations in mean corpuscular volume from low or normal at baseline to above the ULN was approximately 68%. Levels appeared to return to normal after treatment discontinuation and did not appear to have any clinical consequences.

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

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 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.

4.9 Overdose

There is limited experience of overdose with olaparib. No unexpected adverse reactions were reported in a small number of patients who took a daily dose of up to 900 mg of olaparib tablets over two days. Symptoms of overdose are not established and there is no specific treatment in the event of Lynparza overdose. In the event of an overdose, physicians should follow general supportive measures and should treat the patient symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action and pharmacodynamic effects

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

PARPs are required for the efficient repair of DNA single strand breaks and an important aspect of PARP-induced repair requires that after chromatin modification, PARP auto-modifies itself and dissociates from the DNA to facilitate access for base excision repair (BER) enzymes. When olaparib is bound to the active site of DNA-associated PARP it prevents the dissociation of PARP and traps it on the DNA, thus blocking repair. In replicating cells this also leads to the formation of DNA double-strand breaks (DSBs) when replication forks meet the PARP-DNA adducts. In normal cells, homologous recombination repair (HRR) pathway is effective at repairing these DNA DSBs. In cancers cell 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.

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.

Clinical efficacy and safety

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.

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

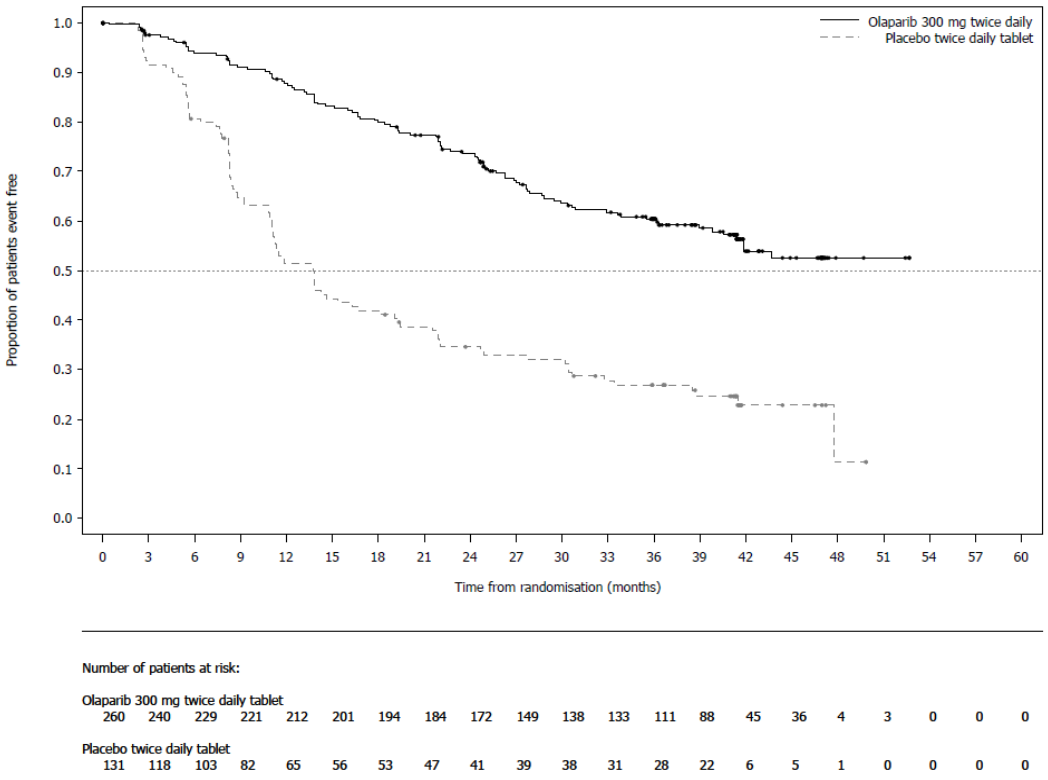
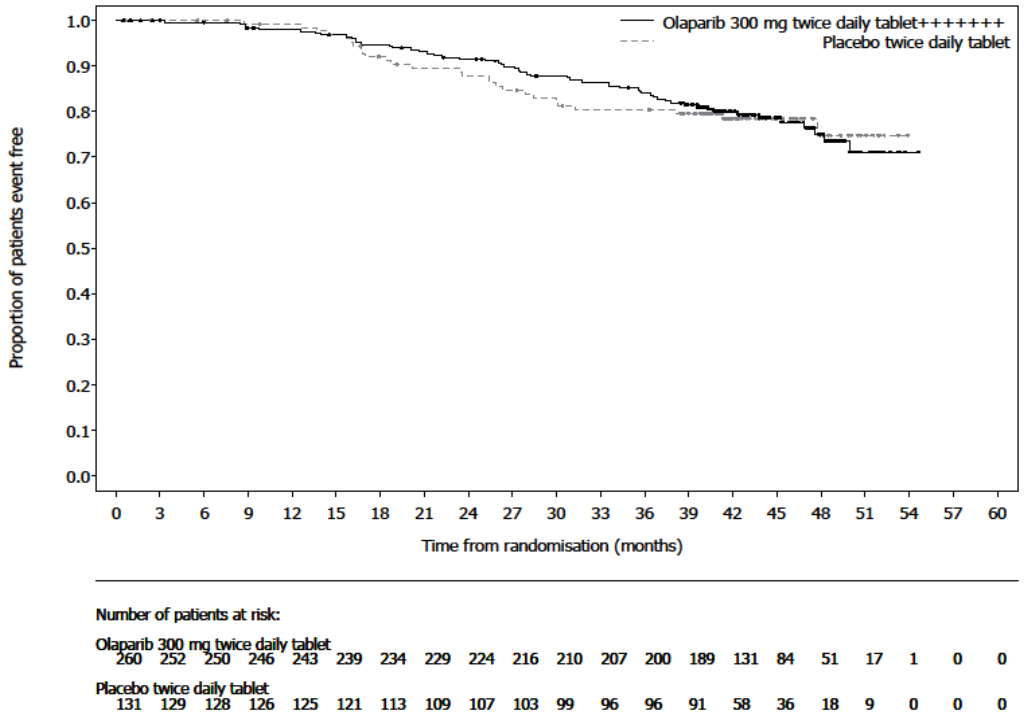


Figure 2 SOLO1: Kaplan-Meier plot of OS in newly diagnosed patients with *BRCA1/2m* advanced ovarian cancer (21% maturity)



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

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

SOLO2 Study

The safety and efficacy of olaparib as maintenance therapy were studied in a Phase III randomised, double-blind, placebo-controlled trial in patients with germline *BRCA1/2*-mutated PSR ovarian, fallopian tube or primary peritoneal cancer. The study compared the efficacy of Lynparza maintenance treatment (300 mg [2 x 150 mg tablets] twice daily) taken until progression with placebo treatment in 295 patients with high-grade serous or endometrioid PSR ovarian cancer (2:1 randomisation: 196 olaparib and 99 placebo) who were in response (CR or PR) following completion of platinum-containing chemotherapy.

Patients who have received two or more platinum-containing regimens and whose disease had recurred >6 months after completion of penultimate platinum-based chemotherapy were enrolled. Patients could not have received prior olaparib or other PARP inhibitor treatment. Patients could have received prior bevacizumab, except in the regimen immediately prior to randomisation.

All patients had evidence of 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. 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.

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

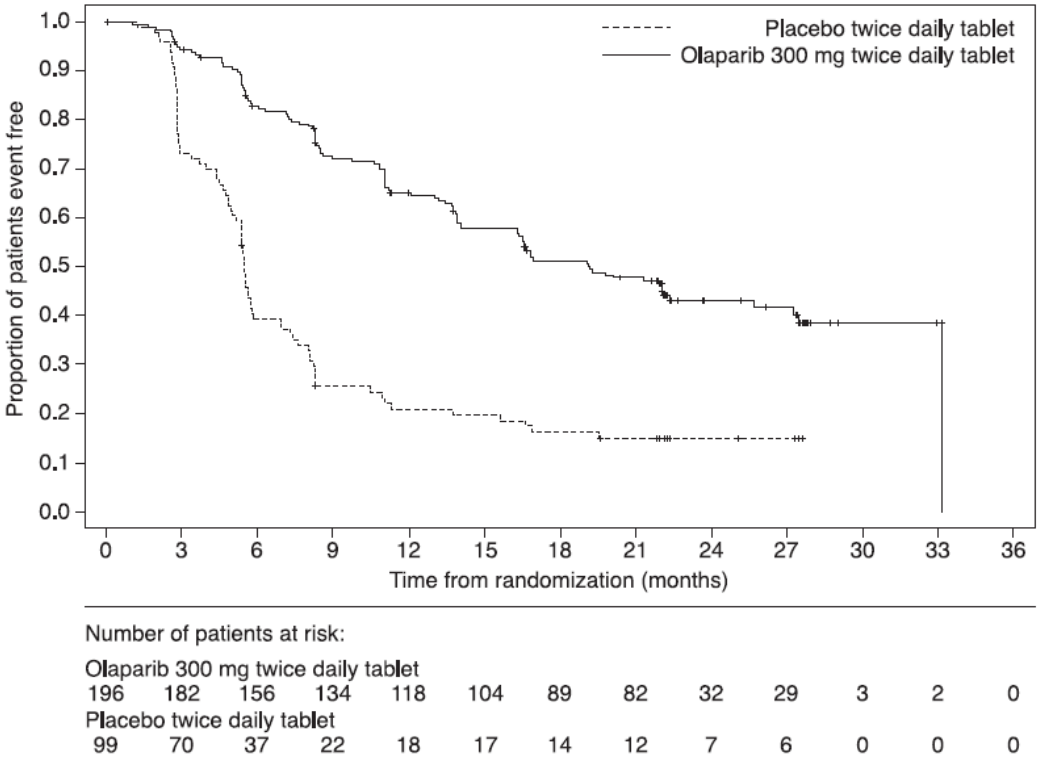
	Olaparib 300 mg tablet bd	**Placebo**
PFS (63% maturity)		
Number of events: Total number of patients (%)	107:196 (55)	80:99 (81)
Median time (months) (95% CI)	19.1 (16.3-25.7)	5.5 (5.2-5.8)

	Olaparib 300 mg tablet bd	Placebo
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.

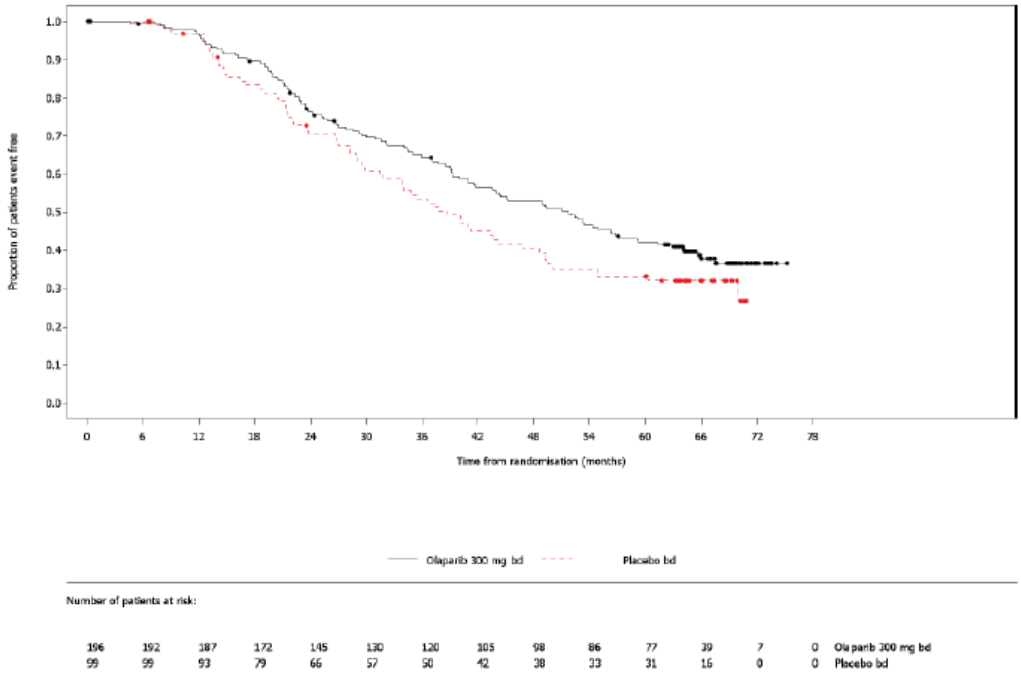
bd Twice daily; PFS progression-free survival; CI confidence interval

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

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



DCO 03 February 2020.

bd = twice daily; CSR = clinical study report; DCO = data cut-off; FAS = full analysis set.

Data derived from Figure 14.2.3.1, SOLO2 CSR Addendum, Module 5.3.5.1.

The secondary endpoints TFST and PFS2 demonstrated a persistent and statistically significant improvement for olaparib compared with placebo (Table 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**
TFST (58% maturity)		
Number of events: Total number of patients (%)	92:196 (47)	79:99 (80)
Median time (months) (95% CI)	27.9 (22.6-NR)	7.1 (6.3-8.3)
HR (95% CI) [a]	0.28 (0.21-0.38)	
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.

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

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

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

Study 19 (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 capsule maintenance treatment (400 mg [8 x 50 mg capsules] twice daily) taken until progression with placebo treatment in 265 (136 olaparib and 129 placebo) PSR high grade serous ovarian cancer patients who were in response (CR or PR) following completion of platinum-containing chemotherapy. The primary endpoint was PFS based on investigator assessment using RECIST 1.0. Secondary efficacy endpoints included OS, disease control rate (DCR) defined as confirmed CR/PR + SD (stable disease), HRQoL and disease related symptoms. Exploratory analyses of TFST and TSST were also performed.

Patients whose disease had recurred >6 months after completion of penultimate platinum-based chemotherapy were enrolled. Enrolment did not require evidence of *BRCA1/2* mutation (*BRCA* mutation status for some patients was determined retrospectively). Patients could not have received prior olaparib or other PARP inhibitor treatment. Patients could have received prior bevacizumab, except in the regimen immediately prior to randomisation. Retreatment with olaparib was not permitted following progression on olaparib.

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

Demographic and baseline characteristics were generally well balanced between the olaparib and placebo arms. Median age was 59 years in both arms. Ovarian cancer was the primary tumour in 86% of the patients. In the olaparib arm 44% of the patients had only 2 prior lines of treatment with 56% receiving 3 or more prior lines of treatment. In the placebo arm 49% of patients had received only 2

prior lines with 51% receiving 3 or more prior lines of treatment. Most patients were ECOG performance status 0 (77%), there are no data in patients with performance status 2 to 4. Platinum free interval was > 12 months in 60% and 6-12 months in 40% of the patients. Response to prior platinum chemotherapy was complete in 45% and partial in 55% of the patients. In the olaparib and placebo arms, 6% and 5% of patients had prior bevacizumab, respectively.

The study met its primary objective demonstrating a statistically significant improvement in PFS for olaparib compared with placebo in the overall population with a HR of 0.35 (95% CI 0.25-0.49; p<0.00001; median 8.4 months olaparib vs 4.8 months placebo). At the final OS analysis (data cut off [DCO] 9 May 2016) at 79% maturity, the hazard ratio comparing olaparib with placebo was 0.73 (95% CI 0.55-0.95; p=0.02138 [did not meet pre-specified significance level of <0.0095]; median 29.8 months olaparib versus 27.8 months placebo). In the olaparib-treated group, 23.5% (n=32/136) of patients remained on treatment for ≥2 years as compared with 3.9% (n=5/128) of the patients on placebo. Although patient numbers were limited, 13.2% (n=18/136) of the patients in the olaparib-treated group remained on treatment for ≥5 years as compared with 0.8% (n=1/128) in the placebo group.

Preplanned subgroup analysis identified patients with *BRCA1/2*-mutated ovarian cancer (n=136, 51.3%; including 20 patients identified with a somatic tumour *BRCA1/2* mutation) as the subgroup that derived the greatest clinical benefit from olaparib maintenance monotherapy. A benefit was also observed in patients with *BRCA1/2* wild-type/variants of uncertain significance (*BRCA1/2 wt*/VUS), although of a lesser magnitude. There was no strategy for multiple testing in place for the sub-group analyses.
A summary of the primary objective outcome for patients with *BRCA1/2*-mutated and *BRCA1/2 wt*/VUS PSR ovarian cancer in Study 19 is presented in Table 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

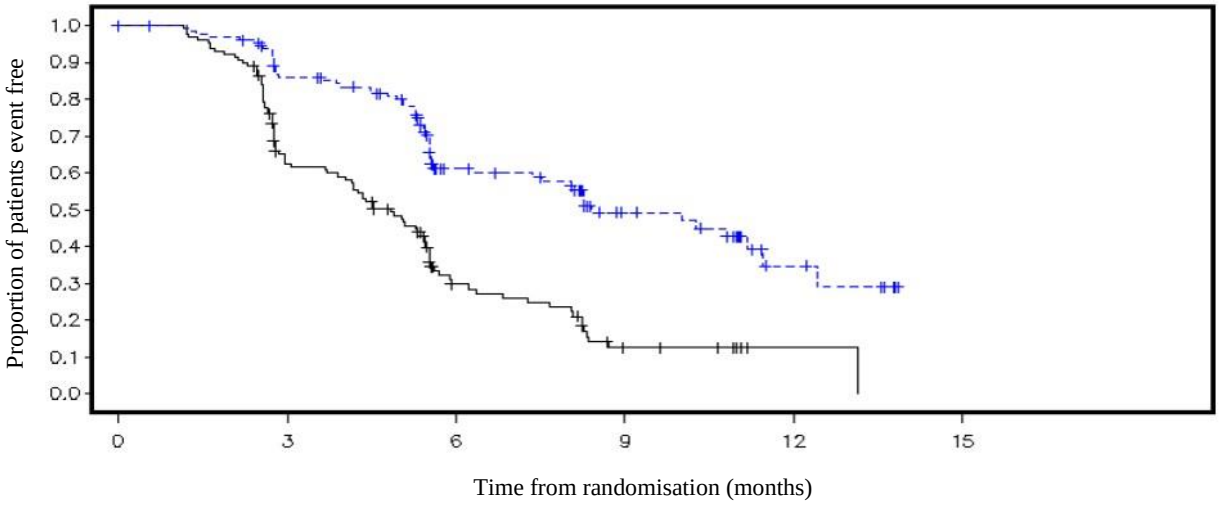
	All patients[a]		***BRCA1/2*-mutated**		***BRCA1/2 wt*/VUS**	
	Olaparib 400 mg capsule bd	**Placebo**	**Olaparib 400 mg capsule bd**	**Placebo**	**Olaparib 400 mg capsule bd**	**Placebo**
PFS – DCO 30 June 2010						
Number of events: Total number of patients (%)	60:136 (44)	94:129 (73)	26:74 (35)	46:62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

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

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

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

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



Number of patients at risk:

136	106	53	24	7	0	Olaparib 400 mg bd
129	72	24	7	1	0	Placebo

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

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

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

	All patients[a]		***BRCA1/2*-mutated**		***BRCA1/2 wt*/VUS**	
	Olaparib 400 mg capsule bd	**Placebo**	**Olaparib 400 mg capsule bd**	**Placebo**	**Olaparib 400 mg capsule bd**	**Placebo**
OS - DCO 09 May 2016						
Number of events: Total 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)	

	All patients[a]		***BRCA1/2*-mutated**		***BRCA1/2 wt*/VUS**	
	Olaparib 400 mg capsule bd	**Placebo**	**Olaparib 400 mg capsule bd**	**Placebo**	**Olaparib 400 mg capsule bd**	**Placebo**
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.

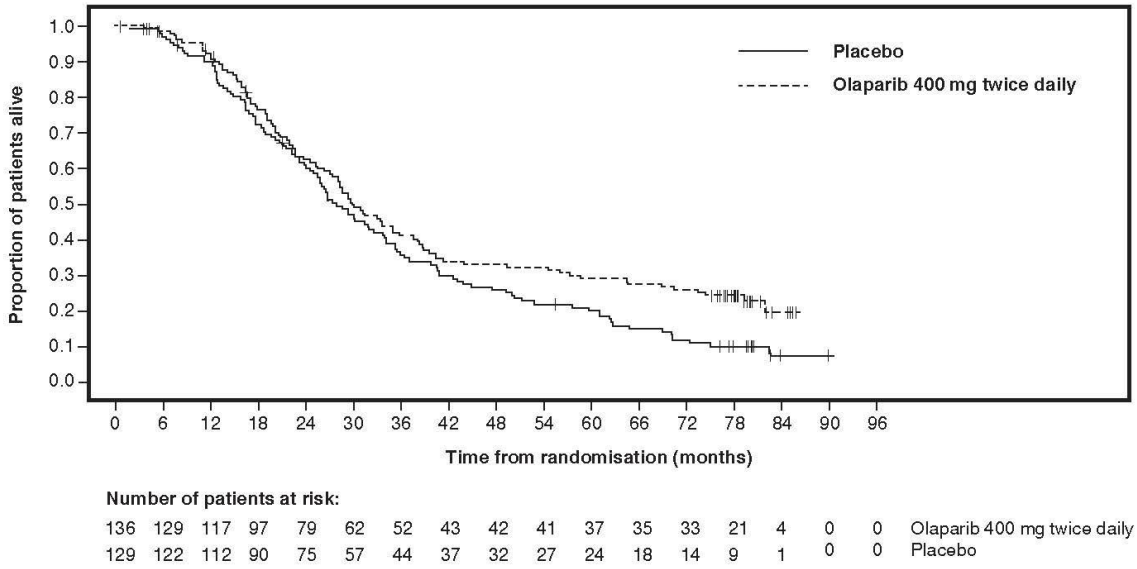
[a] All patients comprises of the following subgroups: *BRCA1/2*-mutated, *BRCA1/2 wt*/VUS and *BRCA1/2* status unknown (11 patients with status unknown, not shown as a separate subgroup in table).

[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.

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

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



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

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

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

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

Final analysis of PFS2 (DCO 22 March 2020, 53% maturity) in the overall population was statistically significant (HR 0.78, 95% CI 0.64-0.95, p=0.0125 with a median of 36.5 months for olaparib/ bevacizumab vs 32.6 months for placebo/bevacizumab). Overall survival data were immature in the overall population and biomarker subgroups. Sixty percent (60%) of patients in the olaparib/ bevacizumab arm and 74% in the placebo/bevacizumab arm received subsequent therapy and of these patients, 20% and 47% in the olaparib/bevacizumab and placebo/bevacizumab arms, respectively, received a PARP inhibitor.

In the 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 7.

Table 7 **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)	
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.

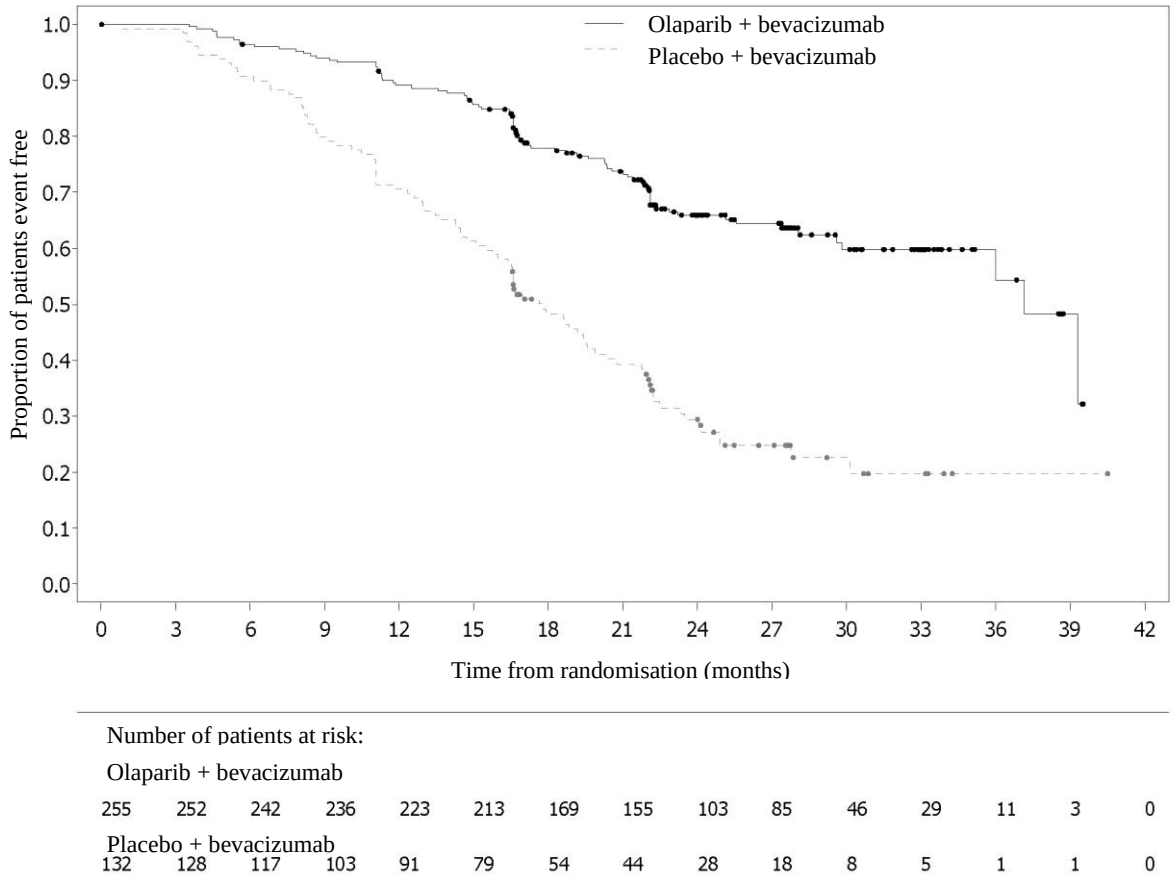
[b] A value <1 favours olaparib. The analysis was performed using a Cox proportional hazards model stratified by first line treatment outcome at screening and screening laboratory t*BRCA* status.

[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)



gBRCA1/2-mutated HER2-negative metastatic breast cancer

OlympiAD (Study D0819C00003)

The safety and efficacy of olaparib in patients with *gBRCA1/2*-mutations who had HER2-negative metastatic breast cancer were studied in a Phase III randomised, open-label, controlled trial (OlympiAD). In this study 302 patients with a documented deleterious or suspected deleterious 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 8).

Table 8 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.

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 9 and Figure 7).

Table 9 Summary of key efficacy findings for patients with *gBRCA1/2*-mutated HER2-negative metastatic breast cancer in OlympiAD

	Olaparib 300 mg bd	Chemotherapy
PFS (77% maturity) – DCO 09 December 2016		
Number of events: Total number of patients (%)	163:205 (80)	71:97 (73)
Median time (months) (95% CI)	7.0 (5.7-8.3)	4.2 (2.8-4.3)
HR (95% CI)	0.58 (0.43-0.80)	
P value (2-sided)[a]	p=0.0009	
PFS2 (65% maturity) - DCO 25 September 2017[b]		
Number of events: Total number of patients (%)	130:205 (63)	65:97 (67)
Median time (months) (95% CI)	12.8 (10.9-14.3)	9.4 (7.4-10.3)
HR (95% CI)	0.55 (0.39-0.77)	
P value (2-sided)[a]	p=0.0005	
OS (64% maturity) – DCO 25 September 2017		
Number of events: Total number of patients (%)	130:205 (63)	62:97 (64)
Median time (months) (95% CI)	19.3 (17.2-21.6)[c]	17.1 (13.9-21.9)
HR (95% CI)	0.90 (0.66-1.23)	
P value (2-sided)[a]	p=0.5131	
Confirmed ORR – DCO 09 December 2016		
Number of objective responders: Total number of patients with measurable disease (%)	87: 167 (52)[d]	15:66 (23)
95% CI	44.2-59.9	13.3-35.7
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.

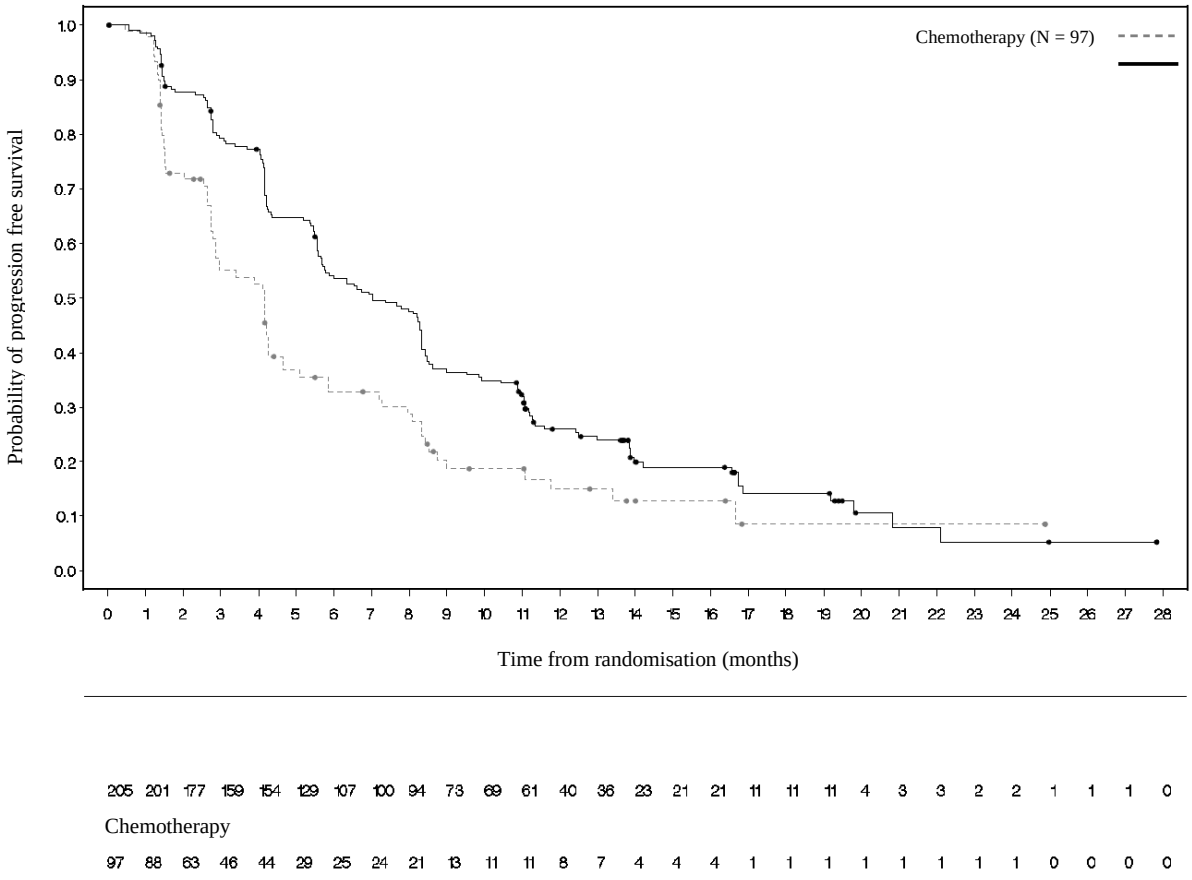
[b] Post-hoc analysis.

[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.

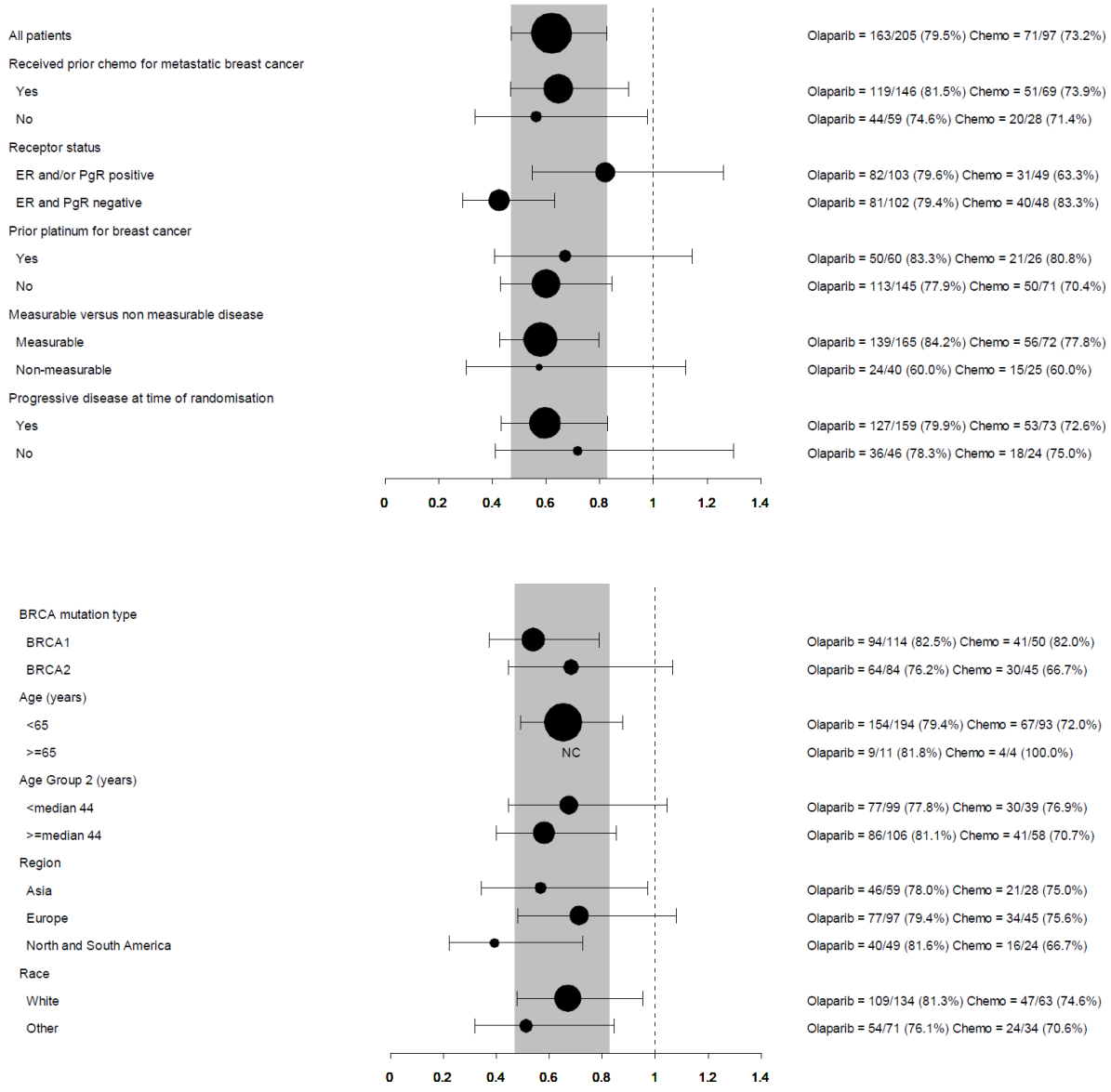
bd Twice daily; CI Confidence interval; DOR Duration of response; DCO Data cut off; HR Hazard ratio; HR+ Hormone receptor positive, ORR Objective response rate; OS overall survival; PFS progression-free survival; PFS2 Time to second progression or death, TNBC triple negative breast cancer.

Figure 8 OlympiAD: Kaplan-Meier plot of BICR PFS in patients with *gBRCA1/2*-mutated HER2-negative metastatic breast cancer (77% maturity) DCO 09 December 2016



Consistent results were observed in all predefined patient subgroups (see Figure 8). Subgroup analysis indicated PFS benefit of olaparib versus comparator in TNBC (HR 0.43; 95% CI: 0.29-0.63, n=152) and HR+ (HR 0.82; 95% CI: 0.55-1.26, n=150) patient subgroups.

Figure 9 PFS (BICR), Forest plot, by subgroup (FAS)



[a] Patients in the 'BRCA1/2 (both)' category were excluded from the analysis in accordance with the SAP as there were <20 events.

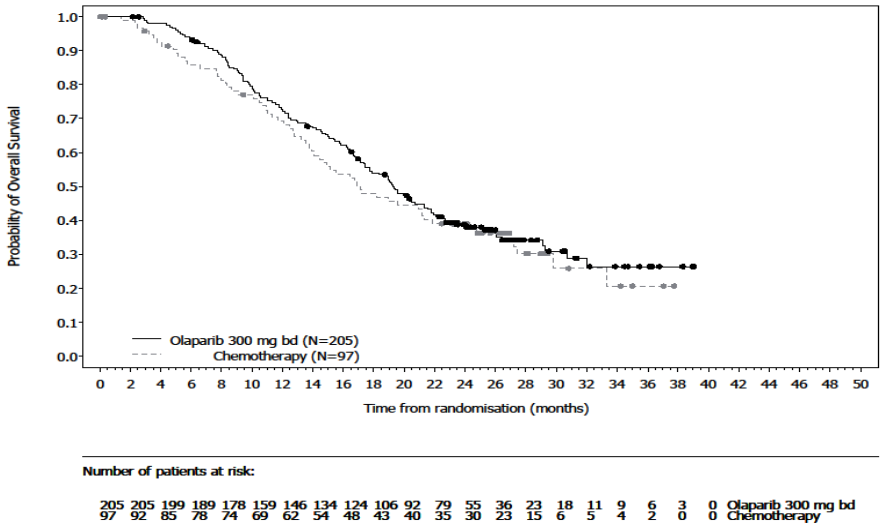
Note: Hazard ratio (HR) (olaparib 300 mg bd: physician's choice of chemotherapy) and 95% CI. A HR <1 favours olaparib 300 mg bd. Each subgroup analysis was performed using a single Cox proportional hazards model containing the treatment term, the subgroup covariate of interest and the treatment by subgroup interaction. Size of circle is proportional to the number of events. Grey band represents the 95% CI for the overall (all patients) HR. This analysis is based on independent central review of radiological scans. RECIST version 1.1.

bd Twice daily; BICR Blinded Independent Central Review; *BRCA* Breast cancer susceptibility gene;Chemo Chemotherapy; CI Confidence interval; CSR Clinical study report; ER Estrogen receptor; HR Hazard ratio; NC Not calculated; PFS Progression-free survival; PgR Progesterone receptor; RECIST Response Evaluation Criteria in Solid Tumours; SAP Statistical analysis plan.

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

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

Figure 10 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 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 10). 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 10 Efficacy results for patients with g*BRCAm* metastatic adenocarcinoma of the pancreas in POLO (BICR, DCO 15 January 2019)

	Olaparib 300 mg bd	**Placebo**
PFS (68% maturity)		
Number of events: Total number of patients (%)	60:92 (65)	44:62 (71)
Median time (months)	7.4	3.8
HR (95% CI)[a,b]	0.53 (0.35-0.82)	
P value (2-sided)	p=0.0038	
OS (70% maturity)		
Number of events: Total number of patients (%)	61:92 (66)	47:62 (76)[c]
Median time (months)	19.0	19.2
HR (95% CI)[b,c]	0.83 (0.56-1.22)	
P value (2-sided)	p=0.3487	

[a] A value <1 favours olaparib.

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

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

[*] Not controlled for multiplicity.

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

Figure 11 POLO: Kaplan-Meier plot of PFS for patients with g*BRCAm* metastatic adenocarcinoma of the pancreas (68% maturity – BICR, DCO 15 January 2019)

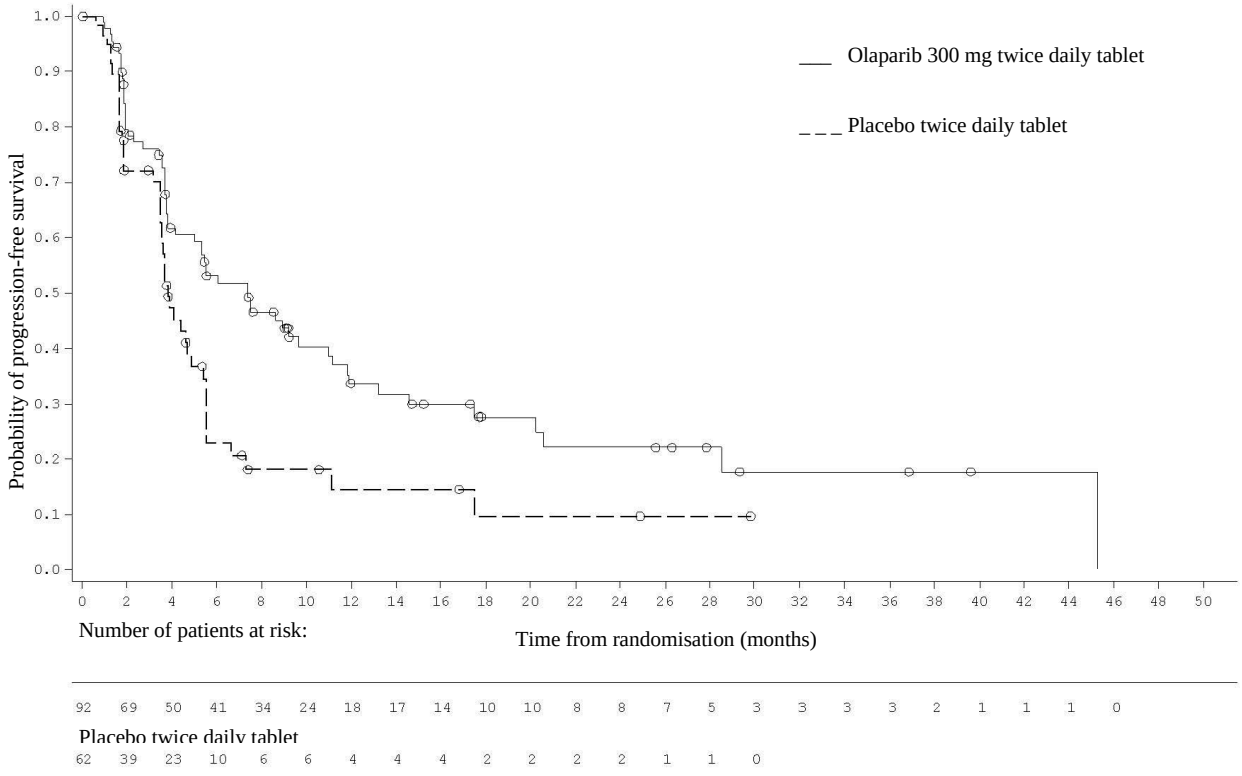
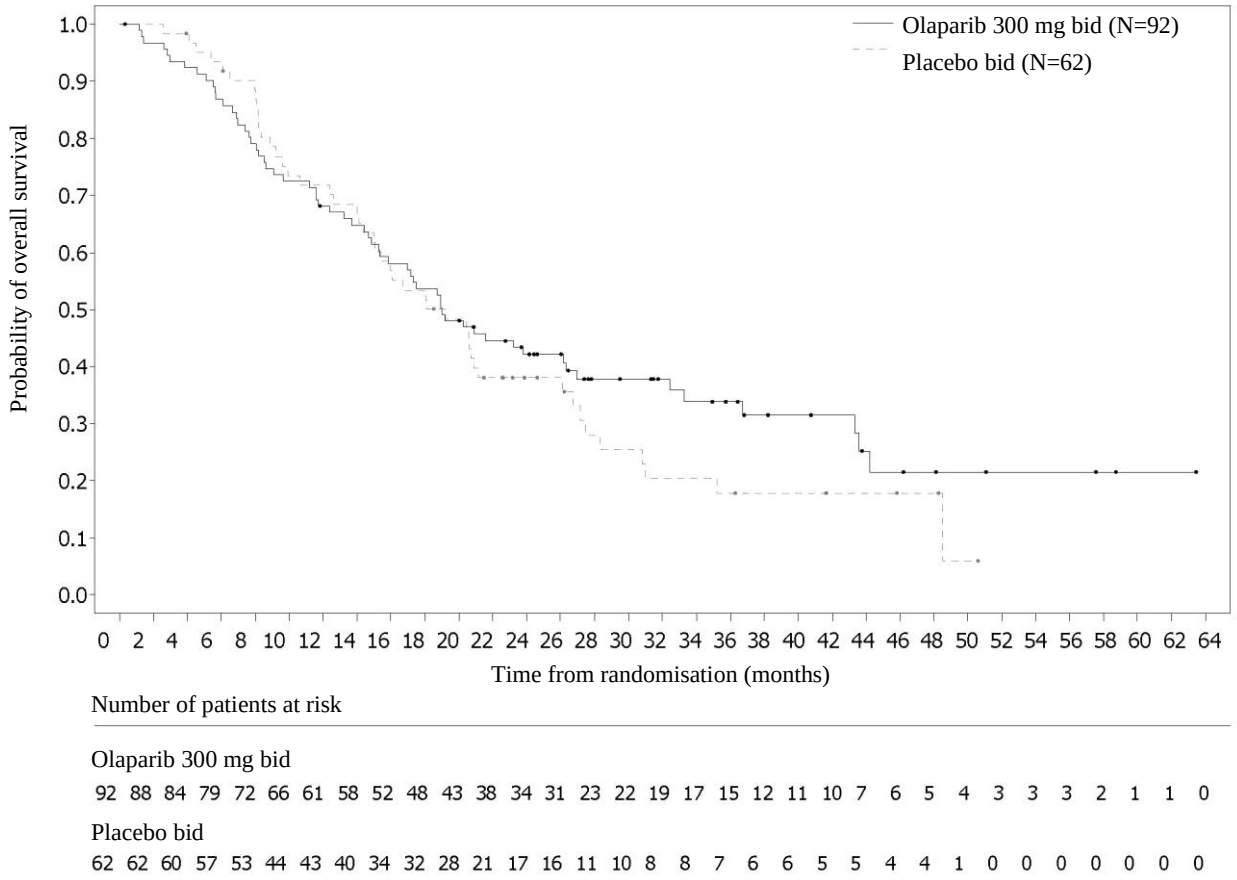


Figure 12 POLO: Kaplan-Meier plot of OS for patients with g*BRCAm* metastatic adenocarcinoma of the pancreas (70% maturity)



<u>BRCA1/2-mutated metastatic castration-resistant prostate cancer:</u>
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 for olaparib vs comparator in Cohort A..

Results for patients with *BRCA1/2* mutations are presented in Table 11. 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 demonstrated a nominally statistically significant improvement in OS *BRCA1/2*m patients randomised to Lynparza vs comparator .

Table 11 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

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

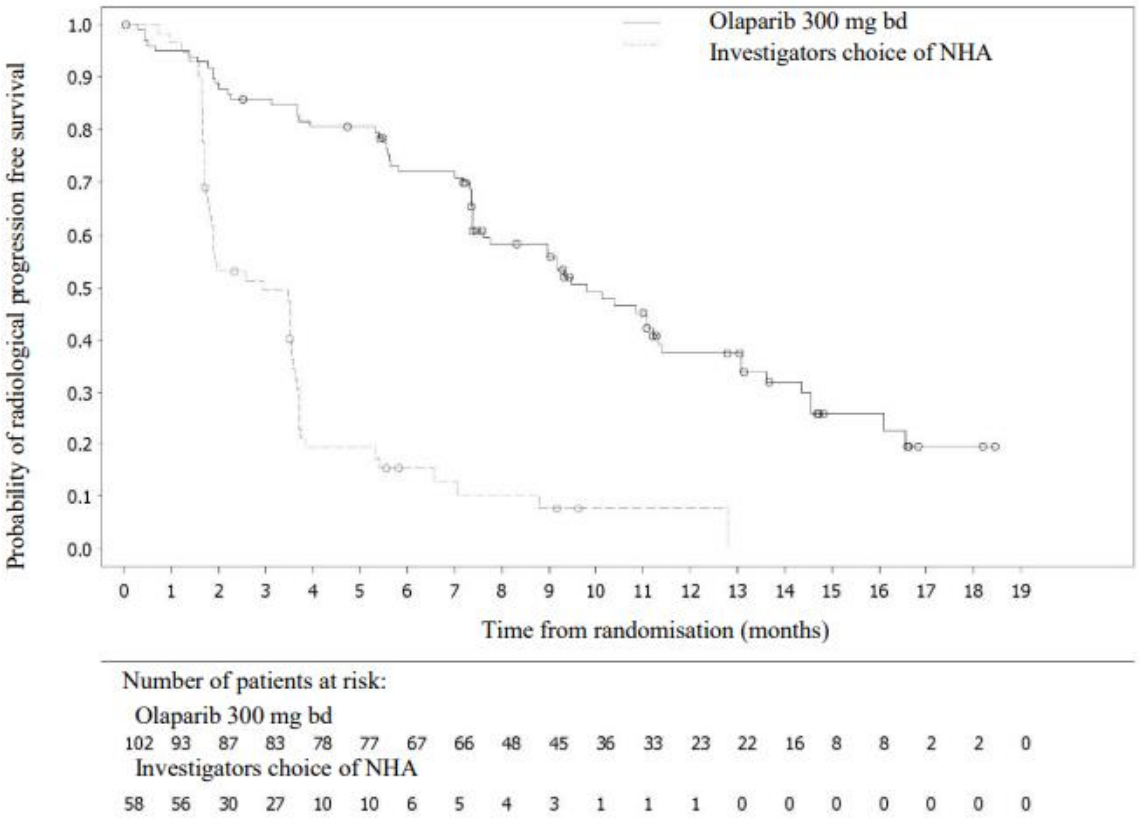
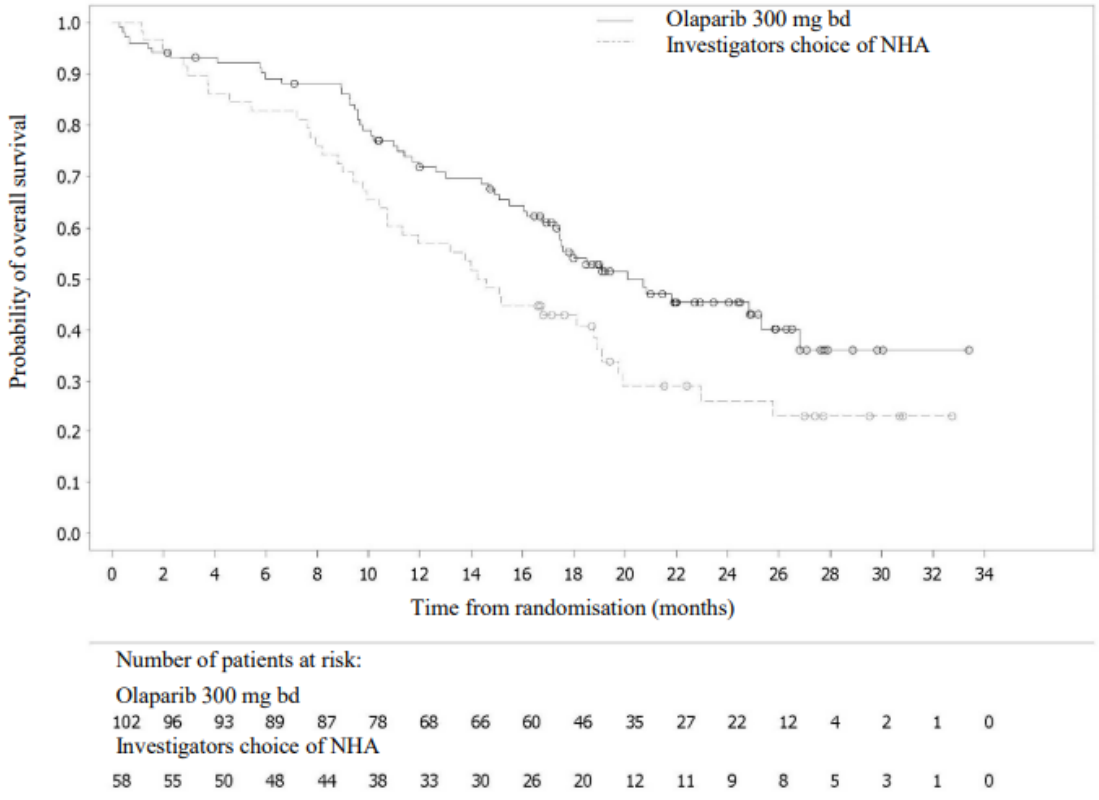


Figure 14 ***BRCA1/2*m patients: Kaplan-Meier plot of OS**

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



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

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

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

Reproductive toxicology

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

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

Carcinogenicity
Carcinogenicity studies have not been conducted with olaparib.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Copovidone
Silica, colloidal anhydrous
Mannitol
Sodium stearyl fumarate

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

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

36 months.

6.4 Special precautions for storage

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

Do not store above 30°C.

6.5 Nature and contents of container

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

6.6 Instructions for use, handling and disposal

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

7. PACK SIZE

100 mg: Box, 7 blisters @ 8 film-coated tablets, Reg No: DKI2159602717A1
150 mg: Box, 7 blisters @ 8 film-coated tablets, Reg No: DKI2159602717B1

HARUS DENGAN RESEP DOKTER

Manufactured by:

AbbVie Limited KM 58.0
Caretera 2, Cruce Davila, Barceloneta
Puerto Rico (PR) 00617
United States

Released by:

AstraZeneca UK Limited
Silk Road Business Park, Macclesfield
SK10 2NA
United Kingdom

Imported by:

PT AstraZeneca Indonesia
Cikarang, Bekasi
Indonesia

DATE OF FIRST AUTHORISATION

22 February 2021

DATE OF REVISION OF THE TEXT

30 Sep 2022
ANGEL Doc ID: Doc ID-004579966

Proposed packaging material		
Code	LYNPARZA 100 150 (56s) TAB-PIL-01.02	
Submission	☐NDA ☐Renewal ☑Variation change detail no.: MU-104953-135498	
Code of previous version	N/A	
Changes	Additional Indication of POLO and PAOLA	
Reference	☐CDS version: ☑CPIL version:	☐SmPC country/version/date: EU SmPC/ Feb 2021/ Doc ID-004086888 v11. ☐GRL approval: 24 May 2021
Name & Date	MMN – 2 June 2022	

Leaflet Informasi Pasien
LYNPARZA 100 mg tablet salut selaput
LYNPARZA 150 mg tablet salut selaput
Olaparib

Bacalah seluruh isi leaflet ini dengan seksama sebelum Anda mulai menggunakan obat ini karena leaflet ini berisi hal-hal penting untuk Anda.

- Simpanlah leaflet ini. Anda mungkin perlu membacanya di kemudian hari
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakanlah dokter, apoteker, atau perawat Anda
- Obat ini diresepkan khusus hanya untuk Anda. Jangan berikan pada orang lain. Obat ini dapat membahayakan mereka walaupun tanda-tanda penyakit yang mereka miliki sama dengan anda.
- Jika Anda mengalami efek samping, beritahu dokter, apoteker, ataupun perawat Anda. Hal ini termasuk efek samping yang mungkin terjadi terdapat pada leaflet ini. Lihat bagian 4.

Leaflet ini berisi informasi mengenai:

1. LYNPARZA dan kegunaannya

Lynparza mengandung zat aktif olaparib. Olaparib adalah jenis obat kanker yang disebut PARP inhibitor (inhibitor polimerase poli [adenosin difosfat-ribosa]).

Inhibitor PARP dapat menghancurkan sel kanker yang tidak bagus memperbaiki kerusakan DNA. Sel-sel kanker spesifik ini dapat diidentifikasi dengan:
- respons terhadap kemoterapi platinum, atau
- mencari gen perbaikan DNA yang salah, seperti gen BRCA (BReast CAncer).

1.1 Kegunaan Lynparza
Lynparza digunakan untuk pengobatan:

- Jenis kanker ovarium (bermutasi BRCA) yang merespons pengobatan pertama standar kemoterapi berbasis platinum standar.
    - Tes digunakan untuk mengetahui apakah Anda menderita kanker ovarium bermutasi BRCA.

- Kanker ovarium yang telah kembali (kambuh). Ini dapat digunakan setelah kanker merespon pengobatan sebelumnya dengan standar kemoterapi berbasis platinum.

- Jenis kanker ovarium (HRD positif seperti yang didefinisikan dengan adanya mutasi BRCA dan/atau ketidakstabilan genom) yang memberikan respon pada pengobatan pertama menggunakan kemoterapi berbasis platinum standar dan bevacizumab. Pada kondisi ini, penggunaan Lynparza dikombinasikan dengan bevacizumab.

- Jenis kanker payudara tertentu (bermutasi BRCA, negatif HER2) yang telah menyebar di luar tumor asli. Anda harus menerima obat kemoterapi sebelum atau setelah kanker Anda menyebar.
    - Tes digunakan untuk mengetahui apakah Anda menderita kanker payudara bermutasi BRCA

- Jenis kanker pankreas (bermutasi BRCA) yang telah memberikan respon pada pengobatan pertama menggunakan kemoterapi standar berbasis platinum.
    - Tes digunakan untuk mengetahui apakah Anda menderita kanker pankreas bermutasi BRCA.

- Kanker prostat (bermutasi BRCA) yang telah menyebar di luar tumor asli dan tidak lagi memberikan respon terhadap pengobatan sebelumnya, termasuk pengobatan hormonal. Pengujian diperlukan untuk menentukan apakah Anda memiliki jenis kanker prostat ini.

Apabila Anda menggunakan Lynparza yang dikombinasikan dengan obat anti kanker lainnya, penting untuk Anda membaca pula brosur dan informasi obat-obatan lainnya. Jika Anda memiliki pertanyaan tentang obat-obatan ini, tanyakan kepada dokter Anda

2. Hal yang perlu diketahui sebelum menggunakan LYNPARZA.

Jangan gunakan LYNPARZA, jika:
- Anda alergi (hipersensitif) terhadap olaparib atau bahan lain yang terkandung dalam obat ini (baca bagian 6).
- Anda sedang menyusui (baca bagian 2 untuk informasi lebih lanjut)

Jika Anda tidak yakin, beritahu dokter, apoteker ataupun perawat Anda sebelum menggunakan LYNPARZA.

Peringatan dan perhatian
Beritahu dokter, apoteker ataupun perawat Anda, Jika:
- Jika Anda memiliki jumlah sel darah rendah pada pengujian. Ini mungkin jumlah rendah untuk darah merah atau putih sel, atau jumlah trombosit yang rendah. Lihat bagian 4 untuk informasi lebih lanjut tentang efek samping ini, termasuk tanda dan gejala yang perlu diwaspadai (misalnya, demam atau infeksi, memar atau berdarah). Jarang, ini mungkin merupakan tanda masalah yang lebih serius pada tulang sumsum seperti 'myelodysplastic syndrome' (MDS) atau 'akut myeloid leukemia' (AML).

- Jika Anda mengalami gejala sesak napas, batuk, atau mengi. Sejumlah kecil pasien yang diobati dengan Lynparza melaporkan peradangan paru-paru (pneumonitis). Pneumonitis adalah kondisi serius yang seringkali memerlukan perawatan di rumah sakit.

Jika Anda mengalami salah satu hal di atas (atau jika Anda tidak yakin), beritau dokter, apoteker, ataupun perawat Anda sebelum menggunakan obat ini.

Tes dan pengecekan

Dokter Anda akan melakukan pengecekan pada darah Anda sebelum dan pada saat pengobatan dengan Lynparza.

Anda akan melakukan tes darah :

- Sebelum dilakukan pengobatan
- Setiap bulan pada tahun pertama pengobatan
- Jangka waktu yang ditentukan oleh dokter Anda setelah tahun pertama pengobatan

Jika tekanan darah Anda berubah menjadi rendah, Anda mungkin memerlukan transfuse darah (dimana kamu berada diberikan darah baru atau produk berbasis darah dari donor)

Obat-obatan lain dan LYNPARZA
Beritau dokter Anda jika Anda sedang menggunakan atau mungkin menggunakan obat-obatan lain termasuk obat herbal, dan obat yang Anda beli tanpa resep dokter. Hal ini karena LYNPARZA dapat mempengaruhi kerja beberapa obat lainnya dan obat lain juga dapat mempengaruhi cara kerja LYNPARZA.

Beritau dengan dokter Anda sebelum menggunakan LYNPARZA, jika Anda sedang menggunakan obat-obatan berikut:

- Obat antikanker lainnya
- Vaksin atau obat yang menekan sistem kekebalan tubuh, karena Anda mungkin harus selalu dipantau
- Itraconazole, fluconazole - digunakan untuk infeksi jamur
- Telithromycin, clarithromycin, erythromycin - digunakan untuk infeksi bakteri
- Protease inhibitor yang dikuatkan dengan ritonavir atau cobicistat, boceprevir, telaprevir, nevirapine, efavirenz - digunakan untuk infeksi virus, termasuk HIV
- Rifampicin, rifapentine, rifabutin - digunakan untuk infeksi bakteri, termasuk tuberkulosis (TB)
- Fenitoin, karbamazepin, fenobarbital - digunakan sebagai obat penenang atau untuk mengobati kejang (kejang) dan epilepsi
- Obat herbal yang mengandung St John Wort (Hypericum perforatum) - digunakan terutama untuk depresi
- Digoxin, diltiazem, furosemide, verapamil, valsartan - digunakan untuk mengobati penyakit jantung atau tinggi tekanan darah
- Bosentan - digunakan untuk mengobati hipertensi arteri pulmonalis
- Statin, misalnya simvastatin, pravastatin, rosuvastatin - digunakan untuk menurunkan level kolesterol pada darah
- Dabigatran - digunakan untuk mengencerkan darah
- Glibenclamide, metformin, repaglinide - digunakan untuk mengobati diabetes
- Alkaloid ergot - digunakan untuk mengobati migrain dan sakit kepala
- Fentanyl - digunakan untuk mengobati nyeri kanker
- Pimozide, quetiapine - digunakan untuk mengobati masalah kesehatan mental
- Cisapride - digunakan untuk mengobati masalah perut
- Colchicine - digunakan untuk mengobati asam urat
- Siklosporin, sirolimus, tacrolimus - digunakan untuk menekan sistem kekebalan tubuh
- Metotreksat - digunakan untuk mengobati kanker, rheumatoid arthritis dan psoriasis.

Jika Anda menggunakan salah satu obat di atas, beritau dokter anda sebelum menggunakan LYNPARZA.
Dokter Anda akan mendiskusikan pengobatan yang sesuai untuk Anda.

Lynparza dengan minuman

Jangan minum jus jeruk bali saat Anda sedang melakukan pengobatan dengan Lynparza. Ini dapat mempengaruhi cara obat bekerja.

Kontrasepsi, Kehamilan, dan Menyusui
Informasi untuk pasien wanita

- Anda tidak boleh menggunakan Lynparza jika Anda hamil atau berkemungkinan hamil. Ini karena itu dapat membahayakan bayi yang belum lahir.
- Anda tidak boleh hamil saat minum obat ini. Anda harus menggunakan metode yang efektif kontrasepsi saat mengambil obat ini dan selama 1 bulan setelah mengambil dosis terakhir Lynparza. Tidak diketahui apakah Lynparza dapat memengaruhi efektivitas beberapa hormon kontrasepsi. Tolong beritahu dokter Anda jika Anda menggunakan kontrasepsi hormonal, seperti Anda dokter dapat merekomendasikan penambahan metode kontrasepsi non-hormonal.
- Anda harus menjalani tes kehamilan sebelum memulai Lynparza, secara teratur selama perawatan dan 1 bulan setelah mengambil dosis terakhir Lynparza. Jika Anda menjadi hamil selama ini, Anda harus segera berbicara dengan dokter Anda.
- Tidak diketahui apakah Lynparza masuk ke ASI. Jangan menyusui jika Anda meminumnya Lynparza dan selama 1 bulan setelah mengambil dosis terakhir Lynparza. Jika Anda berencana untuk melakukannya menyusui, beri tahu dokter Anda.

Informasi untuk pasien pria

- Anda harus menggunakan kondom saat berhubungan seks dengan pasangan wanita, bahkan jika pasangan Anda hamil, saat menggunakan Lynparza dan selama 3 bulan setelah mengambil dosis terakhir. Tidak diketahui apakah Lynparza masuk ke air mani.

- Pasangan wanita Anda juga harus menggunakan metode kontrasepsi yang sesuai.

- Anda tidak boleh menyumbangkan sperma saat menggunakan Lynparza dan selama 3 bulan setelah mengambil dosis terakhir.

Mengemudi dan menjalankan mesin
Lynparza dapat memengaruhi kemampuan Anda untuk mengemudi dan menggunakan mesin. Jika Anda merasa pusing, lemah atau lelah saat menggunakan Lynparza, jangan mengemudi atau menggunakan alat atau mesin.

Informasi terkait zat tambahan lain yang terdapat didalam obat
Obat ini mengandung kurang dari 1 mmol natrium (23 mg) per 100 mg atau 150 mg tablet, artinya pada dasarnya "bebas natrium".

3. Cara penggunaan LYNPARZA

Selalu gunakan obat ini sesuai dengan petunjuk dari dokter Anda. Periksa kembali dengan dokter atau apoteker Anda jika Anda tidak yakin.

Berapa banyak yang digunakan

- Dokter Anda akan memberi tahu Anda berapa banyak tablet Lynparza yang harus diminum. Penting bahwa Anda mengambil dosis total yang disarankan setiap hari. Terus melakukannya selama dokter, apoteker, atau perawat Anda memberi tahu Anda.
- Dosis yang dianjurkan adalah 300 mg (2 x 150 mg tablet) dua kali sehari, total 4 tablet setiap hari.

Bagaimana cara menggunakannya

- Telan tablet Lynparza utuh, dengan atau tanpa makanan.
- Ambil Lynparza sekali di pagi hari dan sekali di malam hari.

- Jangan mengunyah, menghancurkan, melarutkan, atau membagi tablet karena ini dapat mempengaruhi seberapa cepat obat masuk ke tubuh Anda.

Dokter Anda mungkin meresepkan dengan dosis yang berbeda jika:
- Anda memiliki masalah dengan ginjal Anda. Anda akan diminta untuk minum 200 mg (2 x 100 mg tablet) dua kali sehari - total 4 tablet setiap hari.
- Anda meminum obat-obatan tertentu yang dapat memengaruhi Lynparza (lihat bagian 2).
- Anda memiliki efek samping tertentu saat menggunakan Lynparza (lihat bagian 4). Dokter Anda dapat menurunkan dosis Anda atau menghentikan perawatan, baik untuk waktu yang singkat atau secara permanen.

Jika Anda menggunakan LYNPARZA lebih dari yang seharusnya
Jika Anda menggunakan lebih dari dosis normal, segera hubungi dokter Anda atau pergilah ke rumah sakit terdekat.

Jika Anda lupa menggunakan LYNPARZA
Jika Anda lupa minum Lynparza, gunakan dosis normal berikutnya sesuai jadwal. Jangan minum dosis ganda (dua dosis sekaligus) untuk mengganti dosis yang terlupakan.

Jika Anda memiliki pertanyaan lebih lanjut mengenai pemakaian obat ini, tanyakanlah pada dokter, apoteker, ataupun perawat Anda.

4. Efek samping yang mungkin terjadi

Seperti obat lainnya, Obat ini dapat menimbulkan efek samping, walaupun tidak setiap orang dapat mengalaminya.

Beri tahu dokter Anda segera jika Anda melihat salah satu dari yang berikut:

Sangat umum (dapat mempengaruhi lebih dari 1 dari 10 orang):
- merasa sesak napas, merasa sangat lelah, kulit pucat atau jantung berdetak cepat - ini mungkin merupakan gejala dari penurunan jumlah sel darah merah (anemia).

Tidak sering (dapat mempengaruhi hingga 1 dari 100 orang):
- reaksi alergi (mis. bengkak pada wajah, bibir, lidah atau tenggorokan, gatal-gatal, sulit bernapas atau menelan, pusing yang merupakan tanda dan gejala reaksi hipersensitivitas).

Jarang (dapat mempengaruhi 1 dari 1000 orang)
- Peradangan yang disertai dengan nyeri pada jaringan lemak di bawah kulit.

Efek samping lain termasuk:

Sangat umum (dapat mempengaruhi lebih dari 1 dalam 10 orang):
- merasa mual (mual)
- muntah
- merasa lelah atau lemah
- gangguan pencernaan atau mulas (dispepsia)
- rasa sakit di daerah perut di bawah tulang rusuk (nyeri perut bagian atas)
- kehilangan selera makan
- sakit kepala
- perubahan rasa makanan (dysgeusia)
- merasa pusing
- batuk
- sesak napas

- diare jika menjadi parah, beri tahu dokter Anda segera.

Efek samping yang sangat umum yang mungkin muncul dalam tes darah:
- penurunan jumlah trombosit dalam darah (trombositopenia) Anda mungkin melihat gejala-gejala berikut:
    - Memar atau berdarah lebih lama dari biasanya jika Anda melukai diri sendiri
- jumlah sel darah putih yang rendah (leukopenia atau neutropenia) yang dapat menurunkan kemampuan Anda untuk melawan infeksi dan mungkin berhubungan dengan demam.

Umum (dapat memengaruhi hingga 1 dari 10 orang):
- ruam atau ruam gatal pada kulit yang bengkak dan memerah (dermatitis)
- sakit mulut (stomatitis).
- rasa sakit di daerah perut di bawah tulang rusuk (nyeri perut bagian atas)

Efek samping umum yang mungkin muncul dalam tes darah:
- jumlah sel darah putih yang rendah (limfopenia) yang dapat menurunkan kemampuan Anda untuk melawan infeksi dan mungkin berhubungan dengan demam
- peningkatan kreatinin darah tes ini digunakan untuk memeriksa cara kerja ginjal Anda**.**

Efek samping yang tidak biasa yang mungkin muncul dalam tes darah:
- peningkatan ukuran sel darah merah (tidak terkait dengan gejala apa pun).

Dokter Anda akan menguji darah Anda setiap bulan untuk tahun pertama perawatan dan secara berkala setelah itu. Dokter Anda akan memberi tahu Anda jika ada perubahan dalam tes darah Anda yang mungkin memerlukan perawatan.

Pelaporan efek samping
Jika Anda mengalami efek samping, hubungi dokter, apoteker, atau perawat Anda, termasuk efek samping yang tidak tertera pada leaflet ini. Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi mengenai keamanan obat ini.

5. Cara Penyimpanan LYNPARZA

- Jauhkan obat ini dari pandangan dan jangkauan anak-anak.
- Jangan gunakan obat ini setelah tanggal kedaluwarsa yang tertera di karton dan blister setelah EXP. Tanggal kedaluwarsa mengacu pada hari terakhir bulan itu.
- Jangan simpan pada suhu diatas 30°C.
- Simpan dalam paket asli untuk melindungi dari kelembaban.
- Jangan membuang obat apa pun melalui air limbah atau limbah rumah tangga. Tanyakan apoteker Anda cara membuang obat yang tidak lagi Anda gunakan. Langkah-langkah ini akan membantu melindungi lingkungan.

Hubungi apoteker Anda bagaimana cara membuang obat yang sudah tidak dikonsumsi lagi. Ini akan membantu menjaga lingkungan.

6. Isi kemasan dan informasi lainnya

LYNPARZA mengandung:
- Zat aktif olaparib. Setiap tablet salut selaput 100 mg mengandung 100 mg olaparib. Setiap tablet salut selaput 150 mg mengandung 150 mg olaparib.
- Bahan lainnya adalah Copovidone, Silica, colloidal anhidrat, Mannitol, Sodium stearyl fumarate, Hypromellose, Macrogol 400, Titanium dioksida (E171), *Iron oxide yellow* (E172), *Iron oxide black* (E172) (hanya 150 mg tablet)

Isi kemasan

LYNPARZA 100 mg adalah tablet kuning hingga kuning tua, oval, bi-cembung dengan tanda 'OP100' di satu sisi dan polos di bagian belakang.

LYNPARZA 150 mg adalah tablet hijau hingga hijau keabu-abuan, oval, bi-cembung dengan tanda 'OP150' di satu sisi dan polos di bagian belakang.

LYNPARZA dikemas dalam karton berisi 7 blister, masing-masing 8 tablet salut selaput.

HARUS DENGAN RESEP DOKTER

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