SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Lynparza 100 mg film-coated tablets
Lynparza 150 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

Excipient with known effect:
This medicinal product contains 0.24 mg sodium per 100 mg tablet and 0.35 mg sodium per 150 mg tablet.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablet (tablet).

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

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

4. CLINICAL PARTICULARS

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

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

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

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

Breast cancer

Germline BRCA-mutated HER2-negative Metastatic Breast Cancer
Lynparza is indicated in patients with deleterious or suspected deleterious *gBRCAm*, HER2-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor (HR)- positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy.

Adjuvant Treatment of Germline BRCA-mutated HER2-negative High Risk Early Breast Cancer
Lynparza is indicated for the adjuvant treatment of adult patients with deleterious or suspected deleterious gBRCAm human epidermal growth factor receptor 2 (HER2)-negative high risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy.

Adenocarcinoma of the pancreas
First-Line Maintenance Treatment of Germline BRCA-mutated Metastatic Pancreatic Adenocarcinoma
Lynparza is indicated for the maintenance treatment of adult patients with deleterious or suspected deleterious gBRCAm metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen.

Prostate cancer
- Germline or somatic BRCA1/2 or ATM- Gene-mutated Metastatic Castration-Resistant Prostate Cancer

  Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA1/2 or ATM Gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone.
- in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with deleterious or suspected deleterious HRR-mutated (HRRm) metastatic castration-resistant prostate cancer (mCRPC). Select patients for therapy based on an approved companion diagnostic for Lynparza.

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

Detection of BRCA1/2 mutations
Before Lynparza treatment is initiated for first-line maintenance treatment of high-grade epithelial ovarian cancer (EOC), fallopian tube cancer (FTC) or primary peritoneal cancer (PPC), patients must have confirmation of deleterious or suspected deleterious germline and/or somatic mutations in the breast cancer susceptibility genes (BRCA) 1 or 2 using a validated test.

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

For germline breast cancer susceptibility genes (gBRCA1/2) mutated human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer and BRCA1/2 or ATM Gene-mutated Metastatic Castration-Resistant Prostate Cancer and Metastatic Pancreatic Adenocarcinoma 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.

Patients receiving Lynparza for mCRPC should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.

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

Treatment of mCRPC in combination with abiraterone and prednisone or prednisolone:
Select patients for treatment with Lynparza based on the presence of deleterious or suspected deleterious HRR gene mutations.
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For First-Line Maintenance Treatment of HRD Positive Advanced Ovarian Cancer in Combination with Bevacizumab Select patients with advanced ovarian cancer who are in complete or partial response to first-line platinum-based chemotherapy for maintenance treatment with Lynparza in combination with bevacizumab associated with HRD positive status based on either deleterious or suspected deleterious BRCA mutation and/or genomic instability.

Posology
Lynparza is available as 100 mg and 150 mg tablets.

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

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

Lynparza in combination with abiraterone and prednisone or prednisolone:
When Lynparza is used in combination with abiraterone for the treatment of patients with mCRPC, the dose of abiraterone is 1000 mg orally once daily (see section 5.1). Abiraterone should be given with prednisone or prednisolone 5 mg orally twice daily. Please refer to the full product information for abiraterone.

Duration of treatment
First-line maintenance treatment of BRCA-mutated advanced ovarian cancer:
Patients can continue treatment until radiological disease progression, unacceptable toxicity or for up to 2 years if there is no radiological evidence of disease after 2 years of treatment. Patients with evidence of disease at 2 years, who in the opinion of the treating physician can derive further benefit from continuous treatment, can be treated beyond 2 years.

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

Monotherapy treatment of gBRCA1/2-mutated HER2-negative metastatic breast cancer:
It is recommended that treatment be continued until progression of the underlying disease or unacceptable toxicity.

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

Adjuvant Treatment of Germline BRCA-mutated HER2-negative High Risk Early Breast Cancer
Continue treatment for a total of 1 year, or until disease recurrence, or unacceptable toxicity, whichever occurs first. Patients receiving Lynparza for hormone receptor

positive HER2-negative breast cancer should continue concurrent treatment with endocrine therapy as per current clinical practice guidelines.

First-line maintenance treatment of germline BRCA-mutated metastatic pancreatic adenocarcinoma
Continue treatment until disease progression or unacceptable toxicity.

First-Line Maintenance Treatment of Advanced Ovarian Cancer in Combination with Bevacizumab
Continue Lynparza treatment until disease progression, unacceptable toxicity, or completion of 2 years of treatment. Patients with a complete response (no radiological evidence of disease) at 2 years should stop treatment. Patients with evidence of disease at 2 years, who in the opinion of the treating healthcare provider can derive further benefit from continuous Lynparza treatment, can be treated beyond 2 years. When used with Lynparza, the recommended dose of bevacizumab is 15 mg/kg every three weeks. Bevacizumab should be given for a total of 15 months including the period given with chemotherapy and given as maintenance. Refer to the Prescribing Information for bevacizumab when used in combination with Lynparza for more information.

Monotherapy treatment of BRCA1/2 or ATM Gene-mutated Metastatic Castration-Resistant Prostate Cancer
Continue treatment until disease progression or unacceptable toxicity**.**

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

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

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

Dose adjustments for adverse reactions
Treatment may be interrupted to manage adverse reactions such as nausea, vomiting, diarrhoea, and anaemia and dose reduction can be considered (see section 4.8).
The recommended dose reduction is to 250 mg (one 150 mg tablet and one 100 mg tablet) twice daily (equivalent to a total daily dose of 500 mg).
If a further dose reduction is required, then reduction to 200 mg (two 100 mg tablets) twice daily (equivalent to a total daily dose of 400 mg) is recommended.

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

<u>Special populations</u>
Elderly

No adjustment in starting dose is required for elderly patients. There are limited clinical data in patients aged 75 years and over.

Renal impairment
For patients with moderate renal impairment (creatinine clearance 31 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 ≤ 30 ml/min), as safety and pharmacokinetics have not been studied in these patients. Lynparza may only be used in patients with severe renal impairment if the benefit outweighs the potential risk, and the patient should be carefully monitored for renal function and adverse events.

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

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

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

Method of administration
Lynparza is for oral use.

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

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

4.4 Special warnings and precautions for use
Haematological toxicity
Haematological toxicity has been reported in patients treated with Lynparza, including clinical diagnoses and/or laboratory findings of generally mild or moderate (CTCAE grade 1 or 2) anaemia, neutropenia, thrombocytopenia and lymphopenia. Patients should not start treatment with Lynparza until they have recovered from haematological toxicity caused by previous anticancer therapy (haemoglobin, platelet and neutrophil levels should be ≤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

Myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML) has occurred in patients treated with Lynparza (see section 4.8). The majority of events had a fatal outcome. Patients with *BRCA*m platinum-sensitive relapsed ovarian cancer who had received at least two prior lines of platinum chemotherapy were at higher risk to experience MDS/AML. The duration of therapy with olaparib in patients who developed MDS/AML varied from <6 months to >4 years. If MDS/AML is suspected, the patient should be referred to a haematologist for further investigations, including bone marrow analysis and blood sampling for cytogenetics. If, following investigation for prolonged haematological toxicity, MDS/ AML is confirmed, Lynparza should be discontinued and the patient treated appropriately.

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

Pneumonitis
Pneumonitis, including events with a fatal outcome, has been reported in patients treated with Lynparza in clinical studies (see section 4.8). If patients present with new or worsening respiratory symptoms such as dyspnoea, cough and fever, or an abnormal chest radiologic finding is observed, Lynparza treatment should be interrupted and prompt investigation initiated. If pneumonitis is confirmed, Lynparza treatment should be discontinued and the patient treated appropriately.

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

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

Pregnancy/contraception
Lynparza should not be used during pregnancy. Women of childbearing potential must use two forms of reliable contraception before starting Lynparza treatment, during therapy and for 6 months after receiving the last dose of Lynparza. Two highly effective and complementary forms of contraception are recommended. Male patients and their female partners of childbearing potential should use reliable contraception during therapy and for 3 months after receiving the last dose of Lynparza (see section 4.6).

Interactions
Lynparza co-administration with strong or moderate CYP3A inhibitors is not recommended (see section 4.5). If a strong or moderate CYP3A inhibitor must be co-administered, the dose of Lynparza should be reduced (see sections 4.2 and 4.5).
Lynparza co-administration with strong or moderate CYP3A inducers is not recommended. In the event that a patient already receiving Lynparza requires treatment with a strong or moderate CYP3A inducer, the prescriber should be aware that the efficacy of Lynparza may be substantially reduced (see section 4.5).

Sodium

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

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

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

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

Pharmacokinetic interactions

Effect of other medicinal products on olaparib

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

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

Effect of olaparib on other medicinal products

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

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

In vitro, olaparib inhibits the efflux transporter P-gp (IC50 = 76 µM), therefore it cannot be excluded that olaparib may cause clinically relevant drug interactions with substrates of P-gp (e.g. simvastatin, pravastatin, dabigatran, digoxin and colchicine). Appropriate clinical monitoring is recommended for patients receiving this type of medicinal product concomitantly.

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

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

4.6 Fertility, pregnancy and lactation
Women of childbearing potential/contraception in females
Women of childbearing potential should not become pregnant while on Lynparza and not be pregnant at the beginning of treatment. A pregnancy test should be performed on all women of childbearing potential prior to treatment and considered regularly throughout treatment.
Women of childbearing potential must use two forms of reliable contraception before starting Lynparza therapy, during therapy and for 6 months after receiving the last dose of Lynparza, unless abstinence is the chosen method of contraception (see section 4.4). Two highly effective and complementary forms of contraception are recommended.
Since it cannot be excluded that olaparib may reduce exposure to substrates of CYP2C9 through enzyme induction, the efficacy of some hormonal contraceptives may be reduced if co-administered with olaparib. Therefore, an additional non-hormonal contraceptive method should be considered during treatment (see section 4.5). For women with hormone dependent cancer, two non-hormonal contraceptive methods should be considered.

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

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

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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

The Grade ≥ 3 adverse reactions occurring in > 2% of patients were anaemia (14%), neutropenia (5%), fatigue/asthenia (4%), leukopenia (2%) and thrombocytopenia (2%)

Adverse reactions that most commonly led to dose interruptions and/ or reductions in monotherapy were anaemia (16%), nausea (7%), fatigue/asthenia (6%), neutropenia (6%) and vomiting (6%).

Adverse reactions that most commonly led to permanent discontinuation were anaemia (1.7%), nausea (0.9%), fatigue/asthenia (0.8%), thrombocytopenia (0.7%), neutropenia (0.6%) and vomiting (0.5%).

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

Adverse events led to dose interruption and/ or reduction of olaparib in 57% of patients when used in combination with bevacizumab and led to permanent discontinuation of treatment with olaparib/bevacizumab and placebo/bevacizumab in 21% and 6% of patients, respectively. The adverse reactions that most commonly led to dose interruption and/or reduction were anaemia (21.7%), nausea (9.5%), fatigue/asthenia (5.4%), vomiting (3.7%), neutropenia (3.6%), thrombocytopenia (3.0%) and diarrhoea (2.6%). The adverse reactions that most commonly led to permanent discontinuation were anaemia (3.7%), nausea (3.6%) and fatigue/asthenia (1.5%).
Adverse events led to dose interruption and/or reduction of olaparib in 50.7% of patients when used in combination with abiraterone and led to permanent discontinuation of treatment with olaparib/abiraterone and placebo/abiraterone in 19.0% and 8.8% of patients, respectively. The adverse reactions that most commonly led to dose interruption and/or reduction were anaemia (17.1%), fatigue/asthenia (5.5%), nausea (4.1%), neutropenia (3.4%), vomiting (2.3%), diarrhoea (2.1%) and venous thrombotic events (2.1%). The adverse reactions that most commonly led to permanent discontinuation were anaemia (4.5%) and fatigue/asthenia (1.3%).

Tabulated list of adverse reactions

The safety profile is based on pooled data from 4499 patients with solid tumours treated with Lynparza monotherapy in clinical trials at the recommended dose.

The following adverse reactions have been identified in clinical trials with patients receiving Lynparza monotherapy where patient exposure is known. Adverse drug reactions are listed by MedDRA System Organ Class (SOC) and then by MedDRA preferred term in Table 1. Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common (≥ 1/10); common (≥1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); very rare (< 1/10,000); not known (cannot be estimated from available data).

Table 1 Tabulated list of adverse reactions:

	Adverse reactions	
MedDRA System Organ Class	**Frequency of All CTCAE grades**	**Frequency of CTCAE grade 3 and above**
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**Uncommon** Myelodysplastic syndrome/ Acute myeloid leukaemia[a]	**Uncommon** Myelodysplastic syndrome/ Acute myeloid leukaemia
Blood and lymphatic system disorders[b]	**Very common** Anaemia[a] Neutropenia[a], Leukopenia[a] **Common** Lymphopenia[a], Thrombocytopenia[a]	**Very common** Anaemia[a] **Common** Neutropenia[a], Thrombocytopenia[a], Leukopenia[a], Lymphopenia[a]
Immune system disorders	**Uncommon** Hypersensitivity[a] **Rare** Angioedema[*]	**Rare** Hypersensitivity[a]
Hepatobiliary disorders	**Common** Transaminases increased[a] **Not known** Drug-induced liver injury[*]	
Metabolism and nutrition disorders	**Very common** Decreased appetite	**Uncommon** Decreased appetite
Nervous system disorders	**Very common** Dizziness, Headache, Dysgeusia[a]	**Uncommon** Dizziness, Headache
Respiratory, thoracic and mediastinal disorders	**Very common** Cough[a], Dyspnoea[a] **Uncommon** Pneumonitis[a]	**Common** Dyspnoea[a] **Uncommon** Cough[a], Pneumonitis[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, Nausea **Uncommon** Stomatitis[a], Diarrhoea, **Rare** Dyspepsia, Upper abdominal pain
Skin and subcutaneous tissue disorders	**Common** Rash[a] **Uncommon** Dermatitis[a] **Rare** Erythema nodosum	**Uncommon** Rash[a] **Rare** Dermatitis[a]
General disorders and administration site conditions	**Very common** Fatigue (including asthenia)	**Common** Fatigue (including asthenia)
Investigations[b]	**Common** Blood creatinine increased **Uncommon** Mean cell volume increased	**Rare** Blood creatinine increased
Vascular disorders	**Common** Venous thromboembolism[a]	**Common** Venous thromboembolism[a]

[a] MDS/AML includes preferred terms (PTs) of acute myeloid leukaemia, myelodysplastic syndrome and myeloid leukaemia.
Anaemia includes PTs of anaemia, anaemia macrocytic, erythropenia, haematocrit decreased, haemoglobin decreased, normocytic anaemia and red blood cell count decreased.
Neutropenia includes PTs of febrile neutropenia, neutropenia, neutropenic infection, neutropenic sepsis and neutrophil count decreased.
Thrombocytopenia includes PTs of platelet count decreased, and thrombocytopenia; Leukopenia includes PTs of leukopenia and white blood cell count decreased.
Lymphopenia includes PTs of lymphocyte count decreased and lymphopenia.
Hypersensitivityincludes PTs of drug hypersensitivity and hypersensitivity
Transaminases increased includes PTs of alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, and hypertransaminasaemia.
Dysgeusia includes PTs of dysgeusia and taste disorder.
Cough includes PTs of cough and productive cough.
Dyspnoea includes PTs of dyspnoea and dyspnoea exertional;
Pneumonitis includes PTs of pneumonitis, interstitial lung disease, acute interstitial pneumonitis, eosinophilic pneumonia, eosinophilic pneumonia acute and hypersensitivity pneumonitis.
Stomatitis includes PTs of aphthous ulcer, mouth ulceration and stomatitis.
Rash includes PTs of erythema, exfoliative rash, rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular and rash pruritic;
Dermatitis includes PTs of dermatitis, and dermatitis allergic.
Venous thromboembolism includes PTs of embolism, pulmonary embolism, thrombosis, deep vein thrombosis, vena cava thrombosis and venous thrombosis.

[b]Registered laboratory data are presented below under Haematological toxicity and Other laboratory findings.

*As observed in the post-marketing setting

Description of selected adverse reactions

Haematological toxicity

Anaemia and other haematological toxicities were generally low grade (CTCAE grade 1 or 2), however, there were reports of CTCAE grade 3 and higher events. Anaemia was the most common CTCAE grade ≥3 adverse reaction reported in clinical studies. Median time to first onset of anaemia was approximately 4 weeks (approximately 7 weeks for CTCAE grade ≥3 events). Anaemia was managed with dose interruptions and dose reductions (see section 4.2), and where appropriate with blood transfusions. In clinical studies with the tablet formulation, the incidence of anaemia adverse reactions was 35.2% (CTCAE grade ≥3 14.8%) and the incidences of dose interruptions, reductions and discontinuations for anaemia were 16.4%, 11.1% and 2.1%, respectively; 15.6% of patients treated with olaparib needed one or more blood transfusions. An exposure-response relationship between olaparib and decreases in haemoglobin has been demonstrated. In clinical studies with Lynparza the incidence of CTCAE grade ≥ 2 shifts (decreases) from baseline in haemoglobin was 21%, absolute neutrophils 17%, platelets 5%, lymphocytes 26% and leucocytes 19% (all % approximate).

The incidence of elevations in mean corpuscular volume from low or normal at baseline to above the ULN was approximately 51%. Levels appeared to return to normal after treatment discontinuation and did not appear to have any clinical consequences.

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

Myelodysplastic syndrome/Acute myeloid leukaemia

MDS/AML are serious adverse reactions that occurred uncommonly in monotherapy clinical studies at the therapeutic dose, across all indications (0.9%). The incidence was 0.5% including events reported during the long term safety follow up (rate calculated based on overall safety population of 18576 patients exposed to at least one dose of oral olaparib in clinical studies). All patients had potential contributing factors for the development of MDS/AML, having received previous chemotherapy with platinum agents. Many had also received other DNA damaging agents and radiotherapy. The majority of reports were in germline breast cancer susceptibility gene 1 or 2 (gBRCA1/2) mutation carriers. The incidence of MDS/AML cases was similar among gBRCA1m and gBRCA2m patients (1.6% and 1.2%, respectively). Some of the patients had a history of previous cancer or of bone marrow dysplasia.

In patients with BRCAm platinum-sensitive relapsed ovarian cancer who had received at least two prior lines of platinum chemotherapy and received study treatment until disease progression (SOLO2 study, with olaparib treatment ≥ 2 years in 45% of patients), the incidence of MDS/AML was 8% inpatients 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 low in the first-line setting when olaparib maintenance treatment is given after one line of platinum chemotherapy for a duration of 2 years (1.5%) in SOLO1 study at 7 year follow up and 1.1% in PAOLA-1 study at 5 year follow-up. For risk mitigation and management (see section 4.4).

Venous Thromboembolic Events

In men who received olaparib plus abiraterone as first line therapy for mCRPC (PROpel study), the incidence of venous thromboembolic events was 8% in the olaparib plus abiraterone arm, and 3.3% in the placebo plus abiraterone arm. The median time to onset in this study was 170

days (range: 12 to 906 days). The majority of patients recovered from the event and were able to continue olaparib with standard medical treatment.

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

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

Gastrointestinal toxicities
Nausea was generally reported very early, with first onset within the first month of Lynparza treatment in the majority of patients. Vomiting was reported early, with first onset within the first two months of Lynparza treatment in the majority of patients. Both nausea and vomiting were reported to be intermittent for the majority of patients and can be managed by dose interruption, dose reduction and/or antiemetic therapy. Antiemetic prophylaxis is not required.

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

Paediatric population
No studies have been conducted in paediatric patients.

Other special populations
Limited safety data are available in non-Caucasian patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, ATC code: L01XK01

Mechanism of action and pharmacodynamic effects

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

PARPs are required for the efficient repair of DNA single strand breaks and an important aspect of PARP-induced repair requires that after chromatin modification, PARP auto-modifies itself and dissociates from the DNA to facilitate access for base excision repair (BER) enzymes. When olaparib is bound to the active site of DNA-associated PARP it prevents the dissociation of PARP and traps it on the DNA, thus blocking repair. In replicating cells this also leads to the formation of DNA double-strand breaks (DSBs) when replication forks meet the PARP-DNA adducts. In normal cells, homologous recombination repair (HRR) pathway is effective at repairing these DNA DSBs. In cancer cells lacking critical functional components for efficient HRR such as BRCA1 or 2, DNA DSBs cannot be repaired accurately or effectively, leading to substantial homologous recombination deficiency (HRD). Instead, alternative and error-prone pathways are activated, such as the classical non-homologous end joining (NHEJ) pathway, leading to a high degree of genomic instability. After a number of rounds of replication, genomic instability can reach insupportable levels and result in cancer cell death, as cancer cells already have a high DNA damage load relative to normal cells. HRR pathway may be compromised by other mechanisms, although the causative aberrancy and penetrance are not fully elucidated. Absence of fully functional HRR pathway is one of the key determinants of platinum sensitivity in ovarian and possibly other cancers.

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

Combined anti-tumour effect with NHAs

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

Detection of *BRCA1/2* mutations

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

Detection of genomic instability

HR deficiency-associated genomic alterations that have been investigated in Paola-1 include genome-wide loss of heterozygosity, telomeric allelic imbalance and large scale transition, which are continuous measures with pre-defined criteria and score. Composite

genomic instability score (GIS, also called HRD score) is determined when the combined measures and respective scores are used to assess the extent of specific genomic aberrations accumulated in tumour cells. Lower score defines lower likelihood of HR deficiency of tumour cells and higher score determines higher likelihood of HR deficiency of tumour cells at the time of the sample collection relative to exposure to DNA damaging agents. Validated cut-offs should be used to determine GIS positive status.
HRD positive status can be defined by a composite GIS score for HR deficiency-associated genomicalterations tested by an experienced laboratory using a validated test.

Clinical efficacy and safety

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

The safety and efficacy of olaparib as maintenance therapy were studied in patients with newly diagnosed advanced (FIGO Stage III-IV) high-grade serous or endometrioid BRCA1/2 mutated (BRCA1/2m) ovarian cancer following completion of first-line platinum-based chemotherapy in a Phase III randomised, double-blind, placebo-controlled, multicentre trial. In this study 391 patients were randomised 2:1 to receive either Lynparza (300 mg [2 x 150 mg tablets] twice daily) or placebo. Patients were stratified by response to first-line platinum chemotherapy; complete response (CR) or partial response (PR). Treatment was continued until radiological progression of the underlying disease, unacceptable toxicity or for up to 2 years. For patients who remained in complete clinical response (i.e. no radiological evidence of disease), the maximum duration of treatment was 2 years; however, patients who had evidence of disease that remained stable (i.e. no evidence of disease progression) could continue to receive Lynparza beyond 2 years.

Patients with germline or somatic BRCA1/2 mutations were identified prospectively either from germline testing in blood via a local test (n=208) or central test (n=181) or from testing a tumour sample using a local test (n=2). By central germline testing, deleterious or suspected deleterious mutations were identified in 95.3% (365/383) and 4.7% (18/383) of patients, respectively. Large rearrangements in the BRCA1/2 genes were detected in 5.5% (21/383) of the randomised patients. The gBRCAm status of patients enrolled via local testing was confirmed retrospectively by central testing. Retrospective testing of patients with available tumour samples was performed using central testing and generated successful results in 341 patients, of which 95% had an eligible mutation (known [n=47] or likely pathogenic [n=277]) and 2 gBRCAwt patients were confirmed to have sBRCAm only. There were 389 patients who were germline BRCA1/2m and 2 who were somatic BRCA1/2m in SOLO1.

Demographic and baseline characteristics were generally well balanced between the olaparib and placebo treatment arms. Median age was 53 years in both arms. Ovarian cancer was the primary tumour in 85% of the patients. The most common histological type was serous (96%), endometrioid histology was reported in 2% of the patients. Most patients were ECOG performance status 0 (78%), there are no data in patients with performance status 2 to 4. Sixty-three percent (63%) of the patients had upfront debulking surgery and of these the majority (75%) had no macroscopic residual disease. Interval debulking surgery was performed in 35% of the patients and of these 82% had no macroscopic residual disease reported. Seven patients, all stage IV, had no cytoreductive surgery. All patients had received first-line platinum-based therapy. There was no evidence of disease at study entry (CR), defined by the investigator as no radiological evidence of disease and cancer antigen 125 (CA-125) within normal range, in 73% and 77% of patients in the olaparib and placebo arms, respectively. PR, defined as the presence of any measurable or non-measurable lesions at baseline or elevated CA-125, was reported in 27% and 23% of patients in the olaparib and placebo arms, respectively. Ninety three percent (93%) of patients were randomised within 8 weeks of their last dose of platinum-based chemotherapy. Patients who had been treated with bevacizumab were excluded from the study, therefore there are no safety and efficacy data on olaparib patients who had previously received bevacizumab. There are very limited data in patients with a somatic *BRCA* mutation.

The primary endpoint was progression-free survival (PFS) defined as time from randomisation to progression determined by investigator assessment using modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, or death. Secondary efficacy endpoints included time from randomisation to second progression or death (PFS2), overall survival (OS), time from randomisation to discontinuation of treatment or death (TDT), time from randomisation to first subsequent anti- cancer therapy or death (TFST) and health related quality of life (HRQoL). Patients had tumour assessments at baseline and every 12 weeks for 3 years, and then every 24 weeks relative to date of randomisation, until objective radiological disease progression.

The study demonstrated a clinically relevant and statistically significant improvement in investigator assessed PFS for olaparib compared to placebo. The investigator assessment of PFS was supported with a blinded independent central radiological (BICR) review of PFS. A descriptive analysis performed at seven years after the last patient was randomized demonstrated a clinically meaningful benefit in OS that numerically favoured the olaparib arm. 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	
OS (38% maturity)[d]		
Number of events: Total number of patients (%)	84:260 (32)	65:131 (50)
Median time (months)	NR	75.2
HR (95% CI)[b]	0.55 (0.40-0.76)	
TFST (60% maturity)		
Number of events: Total number of patients (%)	135:260 (52)	98:131 (75)
Median time (months)	64.0	15.1
HR (95% CI) [c]	0.37 (0.28-0.48)	

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

[d] Based on Kaplan-Meier estimates, the proportion of patients that were alive 84 months was 67% for olaparib versus 47% for placebo.

[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)

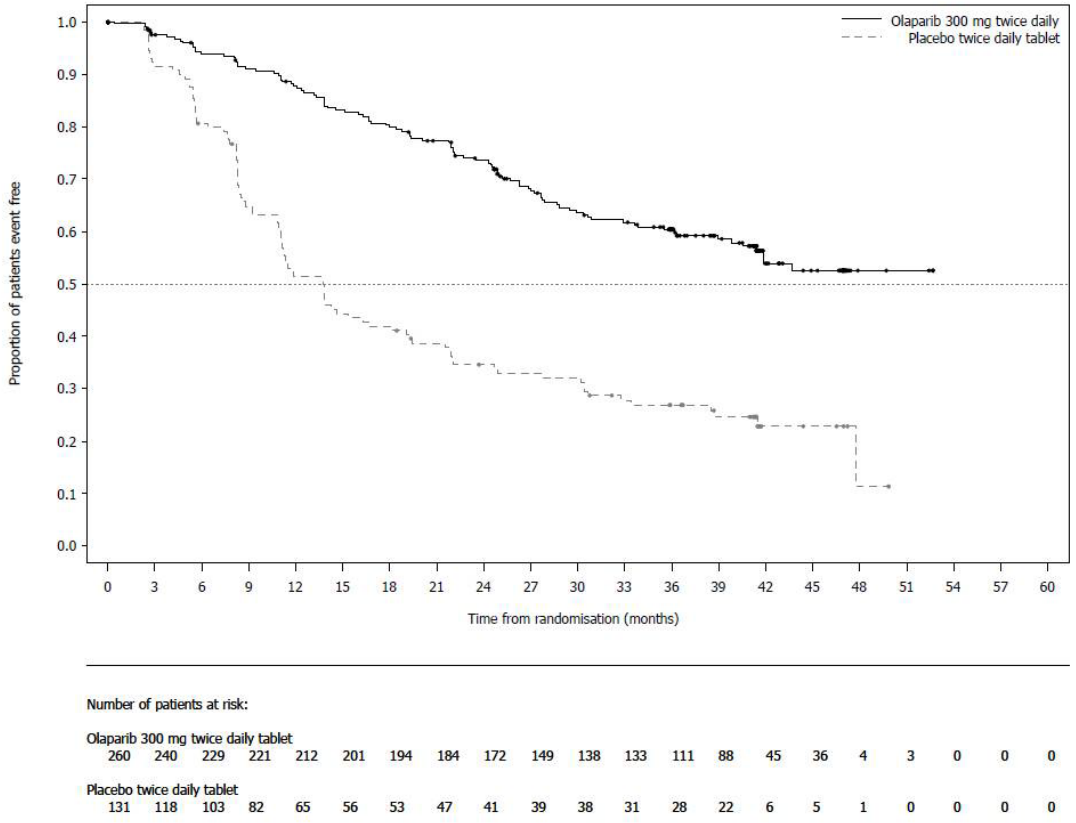
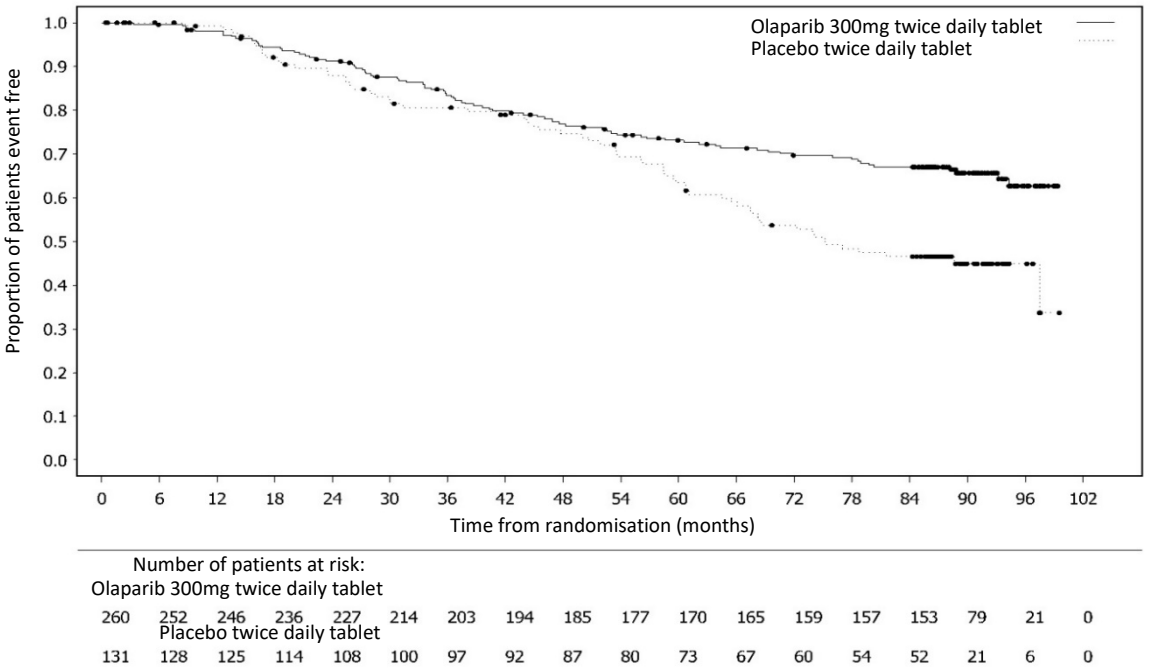


Figure 2 SOLO1: Kaplan-Meier plot of OS in newly diagnosed patients with *BRCA1/2m* advanced ovarian cancer (38% maturity)



Consistent results were observed in the subgroups of patients by evidence of the disease at study entry. Patients with CR defined by the investigator had HR 0.34 (95% CI 0.24–0.47); median PFS not reached on olaparib vs 15.3 months on placebo. At 24 and 36 months,

respectively, 68% and 45% patients remained in CR in the olaparib arm, and 34% and 22% of patients in the placebo arm. Patients with PR at study entry had PFS HR 0.31 (95% CI 0.18, 0.52; median PFS 30.9 months on olaparib vs 8.4 months on placebo). Patients with PR at study entry either achieved CR (15% in olaparib arm and 4% in the placebo arm at 24 months, remained in CR at 36 months) or had further PR/stable disease (43% in olaparib arm and 15% in the placebo arm at 24 months; 17% in olaparib arm and 15% in placebo arm at 36 months). The proportion of patients who progressed within 6 months of the last dose of platinum-based chemotherapy was 3.5% for olaparib and 8.4% for placebo.

Maintenance treatment of platinum-sensitive relapsed (PSR) ovarian cancer
SOLO2 Study
The safety and efficacy of olaparib as maintenance therapy were studied in a Phase III randomised, double-blind, placebo-controlled trial in patients with germline *BRCA1/2*-mutated PSR ovarian, fallopian tube or primary peritoneal cancer. The study compared the efficacy of Lynparza maintenance treatment (300 mg [2 x 150 mg tablets] twice daily) taken until progression with placebo treatment in 295 patients with high-grade serous or endometrioid PSR ovarian cancer (2:1 randomisation: 196 olaparib and 99 placebo) who were in response (CR or PR) following completion of platinum-containing chemotherapy.

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

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

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

The primary endpoint was PFS determined by investigator assessment using RECIST 1.1. Secondary efficacy endpoints included PFS2; OS TDT, TFST, TSST; and HRQoL.

The study met its primary objective demonstrating a statistically significant improvement in investigator assessed PFS for olaparib compared with placebo with a HR of 0.30 (95% CI 0.22-0.41; p<0.0001; median 19.1 months olaparib vs 5.5 months placebo). The investigator assessment of PFS was supported with a blinded independent central radiological review of PFS (HR 0.25; 95% CI 0.18-0.35; p<0.0001; median 30.2 months for olaparib and 5.5 months placebo). At 2 years, 43% olaparib-treated patients remained progression free compared with only 15% placebo-treated patients.

A summary of the primary objective outcome for patients with g*BRCA1/2m* PSR ovarian cancer in SOLO2 is presented in Table 3 and Figure 3.

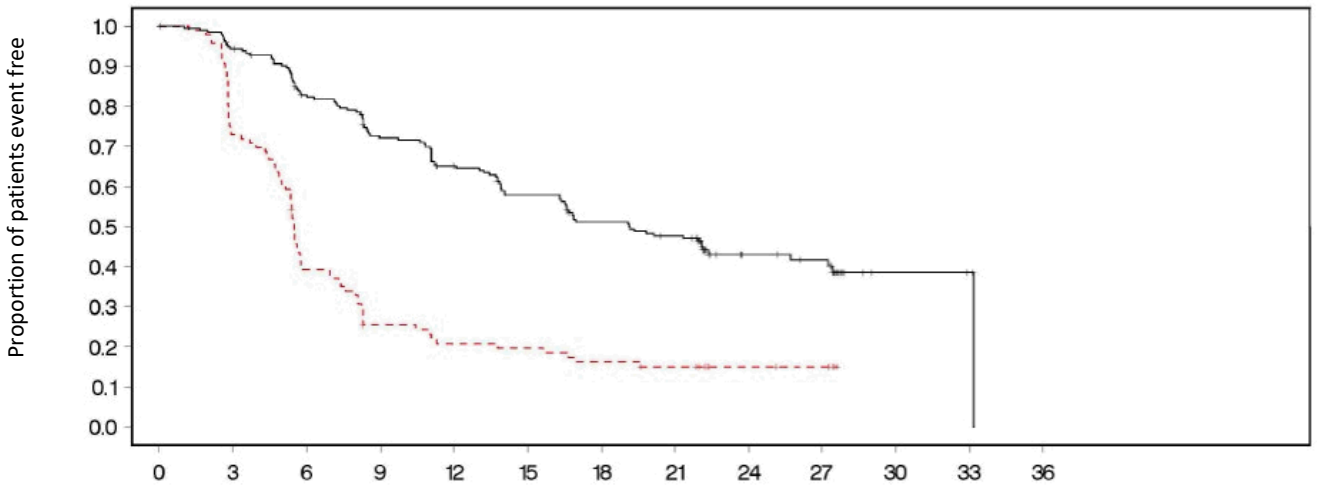
Table 3 Summary of primary objective outcome for patients with g*BRCA1/2m* PSR ovarian cancer in SOLO2

	Olaparib 300 mg tablet bd	Placebo
PFS (63% maturity)		
Number of events: Total number of patients (%)	107:196 (55)	80:99 (81)
Median time (months) (95% CI)	19.1 (16.3-25.7)	5.5 (5.2-5.8)
HR (95% CI) [a]	0.30 (0.22-0.41)	
P value (2-sided)	p<0.0001	

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

Figure 3 SOLO2: Kaplan-Meier plot of PFS in patients with g*BRCA1/2m* PSR ovarian cancer

(63% maturity - investigator assessment)



Number of patients at risk:

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

bd Twice daily; PFS Progression free survival

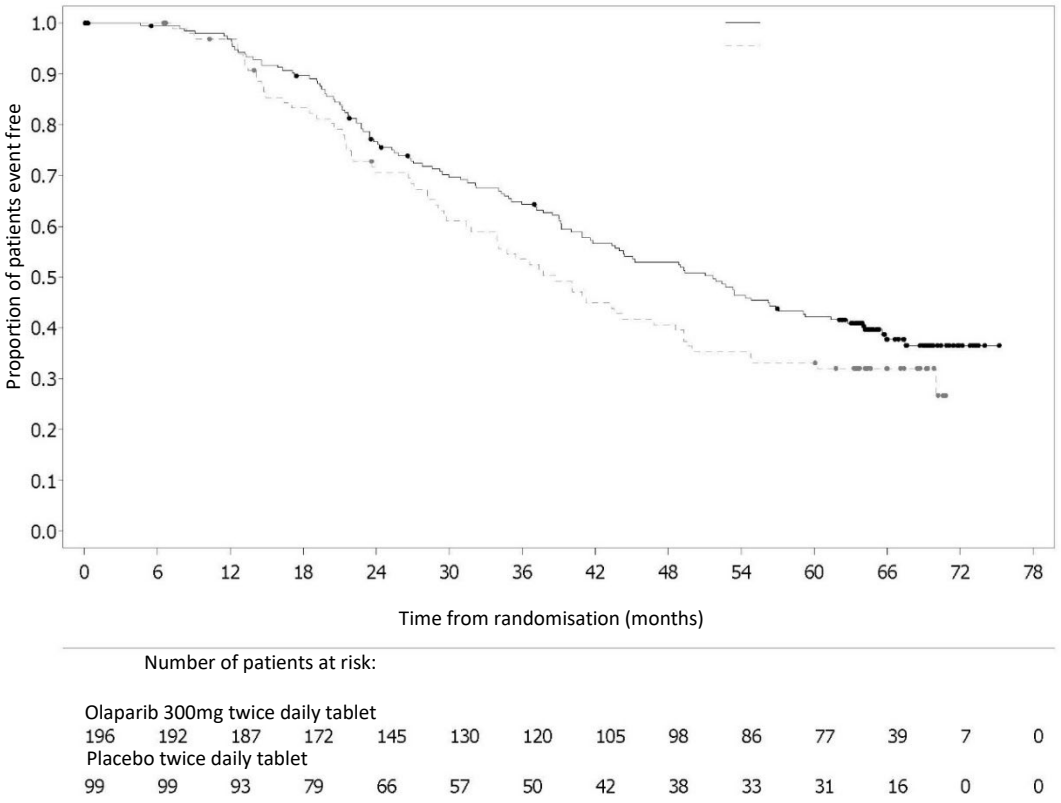
At the final analysis of OS (61% maturity) the HR was 0.74 (95% CI 0.54-1.00; p=0.0537; median
51.7 months for olaparib vs 38.8 months for placebo) which did not reach statistical significance. The secondary endpoints TFST and PFS2 demonstrated a persistent and statistically significant improvement for olaparib compared with placebo. Results for OS, TFST and PFS2 are presented in Table 4 and Figure 4.

Table 4 Summary of key secondary objective outcomes for patients with g*BRCA1/2m* PSR ovarian cancer in SOLO2

	Olaparib 300 mg tablet bd	**Placebo**
OS (61% maturity)		
Number of events: Total number of patients (%)	116:196 (59)	65:99 (66)
Median time (95% CI), months	51.7 (41.5, 59.1)	38.8 (31.4, 48.6)
HR (95% CI) [a]	0.74 (0.54-1.00)	
P value (2-sided)	p=0.0537	
TFST (71% maturity)		
Number of events: Total number of patients (%)	139:196 (71)	86:99 (87)
Median time (months) (95% CI)	27.4 (22.6-31.1)	7.2 (6.3-8.5)
HR (95% CI) [a]	0.37 (0.28-0.48)	
P value* (2-sided)	P<0.0001	
PFS2 (40% maturity)		
Number of events: Total number of patients (%)	70:196 (36)	49:99 (50)
Median time (months) (95% CI)	NR (24.1-NR)	18.4 (15.4-22.8)
HR (95% CI) [a]	0.50 (0.34-0.72)	
P value (2-sided)	p=0.0002	

Not controlled for multiplicity
[a] HR= Hazard Ratio. A value <1 favours olaparib. The analysis was performed using a Cox proportional hazard model including response to previous platinum chemotherapy (CR or PR), and time to disease progression (>6-12 months and >12 months) in the penultimate platinum-based chemotherapy as covariates.
[bd] Twice daily; NR not reached; CI confidence interval; PFS2 time from randomisation to second progression or death; TFST Time from randomisation to start of first subsequent therapy or death.

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



Among the patients entering the trial with measurable disease (target lesions at baseline), an objective response rate of 41% was achieved in the Lynparza arm versus 17% on placebo. Of patients treated with Lynparza, who entered the study with evidence of disease (target or non-target lesions at baseline), 15.0% experienced complete response compared with 9.1% of patients on placebo.
At the time of the analysis of PFS the median duration of treatment was 19.4 months for olaparib and 5.6 months for placebo. The majority of patients remained on the 300 mg bd starting dose of olaparib. The incidence of dose interruptions, reductions, discontinuations due to an adverse event was 45.1%, 25.1% and 10.8%, respectively. Dose interruptions occurred most frequently in the first 3 months and dose reductions in the first 3-6 months of treatment. The most frequent adverse reactions leading to dose interruption or dose reduction were anaemia, nausea and vomiting.
Patient-reported outcome (PRO) data indicate no difference for the olaparib-treated patients as compared to placebo as assessed by the change from baseline in the TOI of the FACT-O.

Study 19 (D0810C00019)
The safety and efficacy of olaparib as a maintenance therapy in the treatment of PSR ovarian, including fallopian tube or primary peritoneal cancer patients, following treatment with two or more platinum containing regimens, were studied in a large Phase II randomised, double-blind, placebo-controlled trial (study 19). The study compared the efficacy of Lynparza maintenance treatment taken until progression with placebo treatment in 265 (136 olaparib and 129 placebo) PSR high grade serous ovarian cancer patients who were in response (CR or PR) following completion of platinum-containing chemotherapy. The primary endpoint was PFS based on investigator assessment using RECIST 1.0. Secondary efficacy endpoints included OS, disease control rate (DCR) defined as confirmed CR/PR + SD (stable disease), HRQoL and disease related symptoms. Exploratory analyses of TFST and TSST were also performed.
Patients whose disease had recurred >6 months after completion of penultimate platinum-based chemotherapy were enrolled. Enrolment did not require evidence of *BRCA1/2*

mutation (*BRCA* mutation status for some patients was determined retrospectively). Patients could not have received prior olaparib or other PARP inhibitor treatment. Patients could have received prior bevacizumab, except in the regimen immediately prior to randomisation. Retreatment with olaparib was not permitted following progression on olaparib.
Patients with *BRCA1/2* mutations were identified either from germline testing in blood via a local test or by central testing at Myriad or from testing a tumour sample using a test performed by Foundation Medicine. Large rearrangements in the *BRCA1/2* genes were detected in 7.4% (10/136) of the randomised patients.
Demographic and baseline characteristics were generally well balanced between the olaparib and placebo arms. Median age was 59 years in both arms. Ovarian cancer was the primary tumour in 86% of the patients. In the olaparib arm 44% of the patients had only 2 prior lines of treatment with 56% receiving 3 or more prior lines of treatment. In the placebo arm 49% of patients had received only 2 prior lines with 51% receiving 3 or more prior lines of treatment. Most patients were ECOG performance status 0 (77%), there are no data in patients with performance status 2 to 4. Platinum free interval was > 12 months in 60% and 6-12 months in 40% of the patients. Response to prior platinum chemotherapy was complete in 45% and partial in 55% of the patients. In the olaparib and placebo arms, 6% and 5% of patients had prior bevacizumab, respectively.

The study met its primary objective demonstrating a statistically significant improvement in PFS for olaparib compared with placebo in the overall population with a HR of 0.35 (95% CI 0.25-0.49; p<0.00001; median 8.4 months olaparib vs 4.8 months placebo). At the final OS analysis (data cut off [DCO] 9 May 2016) at 79% maturity, the hazard ratio comparing olaparib with placebo was 0.73 (95% CI 0.55-0.95; p=0.02138 [did not meet pre-specified significance level of < 0.0095]; median 29.8 months olaparib versus 27.8 months placebo). In the olaparib-treated group, 23.5% (n=32/136) of patients remained on treatment for ≥2 years as compared with 3.9% (n=5/128) of the patients on placebo. Although patient numbers were limited, 13.2% (n=18/136) of the patients in the olaparib-treated group remained on treatment for ≥5 years as compared with 0.8% (n=1/128) in the placebo group. Preplanned subgroup analysis identified patients with *BRCA1/2*-mutated ovarian cancer (n=136, 51.3%; including 20 patients identified with a somatic tumour *BRCA1/2* mutation) as the subgroup that derived the greatest clinical benefit from olaparib maintenance monotherapy. A benefit was also observed in patients with *BRCA1/2* wild-type/variants of uncertain significance (*BRCA1/2 wt*/VUS), although of a lesser magnitude. There was no strategy for multiple testing in place for the sub-group analyses.

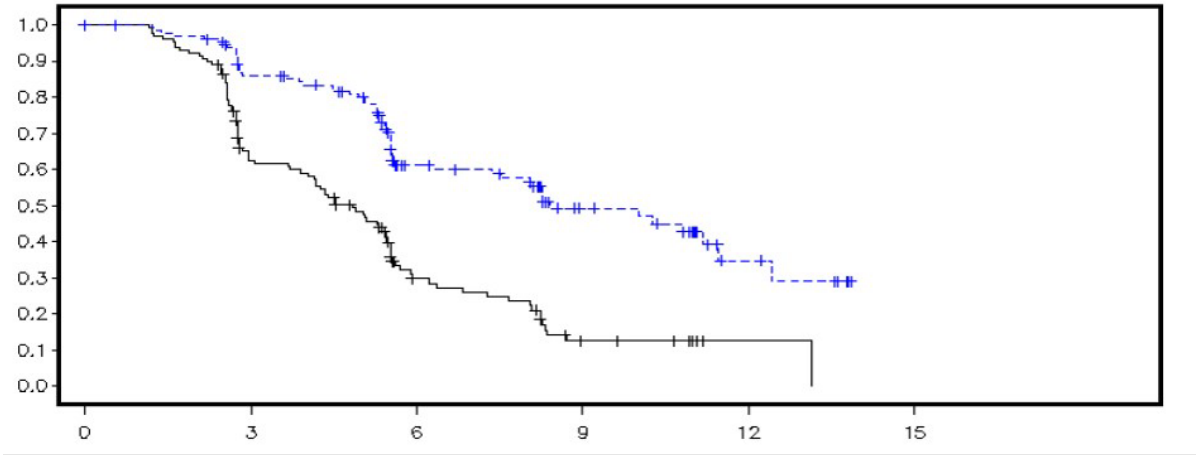
A summary of the primary objective outcome for patients with *BRCA1/2*-mutated and *BRCA1/2 wt*/VUS PSR ovarian cancer in study 19 is presented in Table 5 and for all patients in Study 19 in Table 5 and Figure 5.

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

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

[a] All patients comprises of the following subgroups: *BRCA1/2*-mutated, *BRCA1/2 wt*/VUS and *BRCA1/2* status unknown (11 patients with status unknown, not shown as a separate subgroup in table).
[b] HR= Hazard Ratio. A value <1 favours olaparib. The analysis was performed using a Cox proportional hazards model with factors for treatment, ethnic descent, platinum sensitivity and response to final platinum therapy.
PFS progression-free survival; DCO data cut off; CI confidence interval; NR not reached.

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



Time from randomisation (months)

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

Number of patients at risk:

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

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.

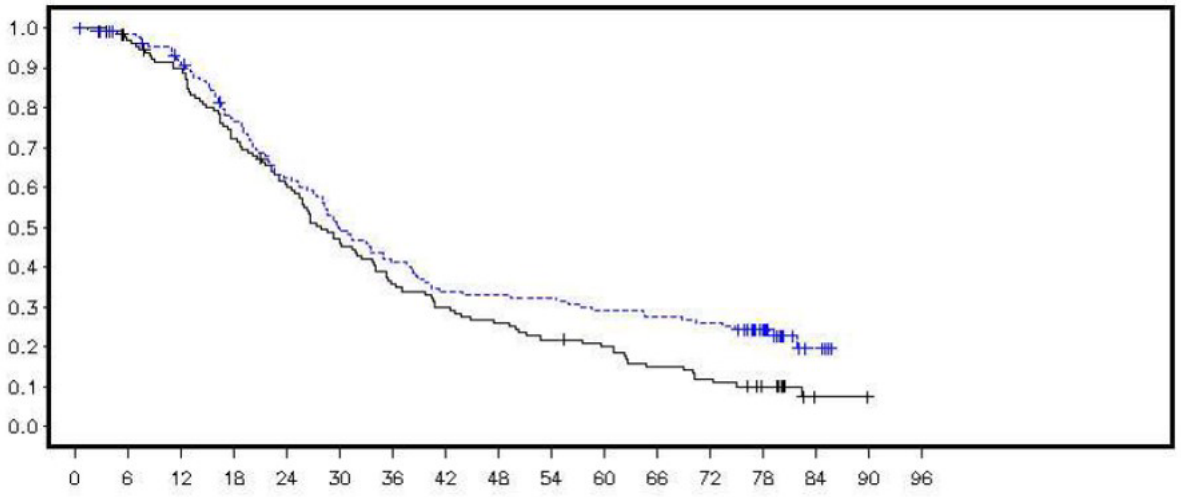
Table 6 Summary of key secondary objective outcomes for all patients and patients with *BRCA1*/2-mutated and *BRCA1/2* wt/VUS PSR ovarian cancer in study 19

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

* There was no strategy for multiple testing in place for the sub-group analyses or for the all patients TFST.
[a] All patients comprises of the following subgroups: *BRCA1/2*-mutated, *BRCA1/2 wt*/VUS and *BRCA1/2* status unknown (11 patients with status unknown, not shown as a separate subgroup in table).
[b] HR= Hazard Ratio. A value <1 favours olaparib. The analysis was performed using a Cox proportional hazards model with factors for treatment, ethnic descent, platinum sensitivity and response to final platinum therapy.

[c] Approximately a quarter of placebo-treated patients in the *BRCA*-mutated subgroup (14/62; 22.6%) received a subsequent PARP inhibitor.
OS Overall survival; DCO data cut off; CI confidence interval; TFST time from randomisation to start of first subsequent therapy or death.

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



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

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

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

OPINION Study

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

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

Olaparib, when used as maintenance therapy, demonstrated clinical activity in patients with non-g*BRCA*m PSR ovarian cancer. At the final overall survival analysis (DCO 17 September 2021), the OS data were 52.3% mature.

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

Table 7 Summary of key objective outcome for non-gBRCAm patients with PSR ovarian cancer in OPINION

	Olaparib tablets 300 mg bd
PFS (75% maturity) (DCO 2 October 2020)	
Number of events: total number of patients (%)	210: 279 (75.3)
Median PFS (95% CI), months[a]	9.2 (7.6, 10.9)
OS (52.3% maturity) (DCO 17 September 2021)	
Number of events: total number of patients (%)	146: 279 (52.3)
Median OS (95% CI), months[a]	32.7 (29.5, 35.3)

[a] Calculated using the Kaplan-Meier technique.

Confidence intervals for median PFS and OS were derived based on Brookmeyer Crowley method.

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

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

OlympiA

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

Dose interruptions due to an adverse reaction of any grade occurred in 31% of patients receiving Lynparza; dose reductions due to an adverse reaction occurred in 23% of patients receiving Lynparza. The most frequent adverse reactions leading to dose interruption of Lynparza were anemia (11%), neutropenia (6%), nausea (5%), leukopenia (3.5%), fatigue (3%), and vomiting (2.9%) and the most frequent adverse reactions leading to dose reduction of Lynparza were anemia (8%), nausea (4.7%), neutropenia (4.2%), fatigue (3.3%), leukopenia (1.8%), and vomiting (1.5%). Discontinuation due to adverse reactions occurred in 10% of patients receiving Lynparza. The adverse reactions that most frequently led to discontinuation of Lynparza were nausea (2%), anemia (1.8%), and fatigue (1.3%).
Tables 7 and 8 summarize the adverse reactions and laboratory abnormalities, respectively, in patients in OlympiA.

Table 7 Adverse Reactions* in OlympiA (≥ 10% of Patients Who Received Lynparza)

Adverse Reactions	**Lynparza tablets n=911**	**Placebo n=904**

	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Gastrointestinal Disorders				
Nausea	57	0.8	23	0
Vomiting	23	0.7	8	0
Diarrhea	18	0.3	14	0.3
Stomatitis†	10	0.1	4.5	0
General Disorders and Administration Site Conditions				
Fatigue (including asthenia)	42	1.8	28	0.7
Blood and Lymphatic Disorders				
Anemia‡	24	9	3.9	0.3
Leukopenia§	17	3	6	0.3
Neutropenia¶	16	5	7	0.8
Nervous System Disorders				
Headache	20	0.2	17	0.1
Dysgeusia#	12	0	4.8	0
Dizziness	11	0.1	7	0.1
Metabolism and Nutrition Disorders				
Decreased appetite	13	0.2	6	0

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

† Includes aphthous ulcer, mouth ulceration, stomatitis.

‡ Includes anemia, anemia macrocytic, erythropenia, hematocrit decreased, hemoglobin decreased, normochromic anemia, normochromic normocytic anemia, normocytic anemia, red blood cell count decreased.

§ Includes leukopenia, white blood cell count decreased.

¶ Includes agranulocytosis, febrile neutropenia, granulocyte count decreased, granulocytopenia, idiopathic neutropenia, neutropenia, neutropenic infection, neutropenic sepsis, neutrophil count decreased.

Includes dysgeusia, taste disorder.

Clinically relevant adverse reactions that occurred in <10% of patients receiving Lynparza were cough (%9.2), lymphopenia (7%), dyspepsia (6%), upper abdominal pain (4.9%), rash (4.9%), dyspnea,(%4.2) thrombocytopenia (4.2%), increase in creatinine (2%), hypersensitivity (0.9%), pneumonitis (0.8%), VTE (0.5%), dermatitis (0.5%), increase in mean corpuscular volume (0.2%), and MDS/AML (0.2%).**Table 8 Laboratory Abnormalities Reported in ≥25% of Patients in OlympiA**

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

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

† This number represents the safety population. The derived values in the table are based on

the total number of evaluable patients for each laboratory parameter.
‡ Represents the proportion of subjects whose mean corpuscular volume was > ULN.

The efficacy of Lynparza was evaluated in OlympiA (NCT02032823), a randomized (1:1), double-blind, placebo-controlled, international study in patients with g*BRCA*m HER2-negative high risk early breast cancer who had completed definitive local treatment and neoadjuvant or adjuvant chemotherapy. Patients were randomized to receive Lynparza tablets 300 mg orally twice daily or placebo. Treatment was continued for up to 1 year, or until disease recurrence, or unacceptable toxicity. Patients were required to have completed at least 6 cycles of neoadjuvant or adjuvant chemotherapy containing anthracyclines, taxanes or both. Prior platinum for previous cancer (e.g. ovarian) or as adjuvant or neoadjuvant treatment for breast cancer was allowed. Patients with high risk early breast cancer were defined as follows:

- patients who received prior neoadjuvant chemotherapy: patients with either triple negative breast cancer (TNBC) or hormone receptor positive breast cancer must have had residual invasive cancer in the breast and/or the resected lymph nodes (non-pathologic complete response) at the time of surgery. Additionally, patients with hormone receptor positive breast cancer must have had a score of ≥3 based on pre-treatment clinical and post-treatment pathologic stage (CPS), estrogen receptor (ER) status, and histologic grade as shown in Table 9.

Table 9 Early Breast Cancer Stage, Receptor Status, and Grade Scoring Requirements for Study Enrollment*

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

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

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

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

The major efficacy outcome measure was invasive disease free survival (IDFS), defined as the time from randomization to date of first recurrence, where recurrence is defined as invasive loco-regional, distant recurrence, contralateral invasive breast cancer, new cancer or death from any cause. An additional efficacy outcome measure was OS.

A total of 1836 patients were randomized, 921 to Lynparza and 915 to placebo. Demographic and baseline characteristics were well balanced between arms. The median age was 42 years. Sixty-seven percent (67%) of patients were White, 29% were Asian, and 3% were Black. Three percent (3%) of patients were Hispanic or Latino. Two patients (0.2%) in the Lynparza arm and four patients (0.4%) in the placebo arm were male. Sixty-one percent (61%) of patients were pre-menopausal. Eighty-nine percent (89%) of patients were ECOG performance status 0 and 11% ECOG PS 1. Eighty-two percent (82%) of patients had TNBC and 18% had hormone receptor-positive disease. Fifty percent (50%) of patients had received prior neoadjuvant and 50% received prior adjuvant chemotherapy. Ninety-four percent (94%) of patients received anthracycline and taxane chemotherapy. Twenty-six (26%) of patients overall had received prior platinum for breast cancer. Ninety percent (90%) of patients with hormone receptor positive breast cancer received concurrent endocrine therapy.

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

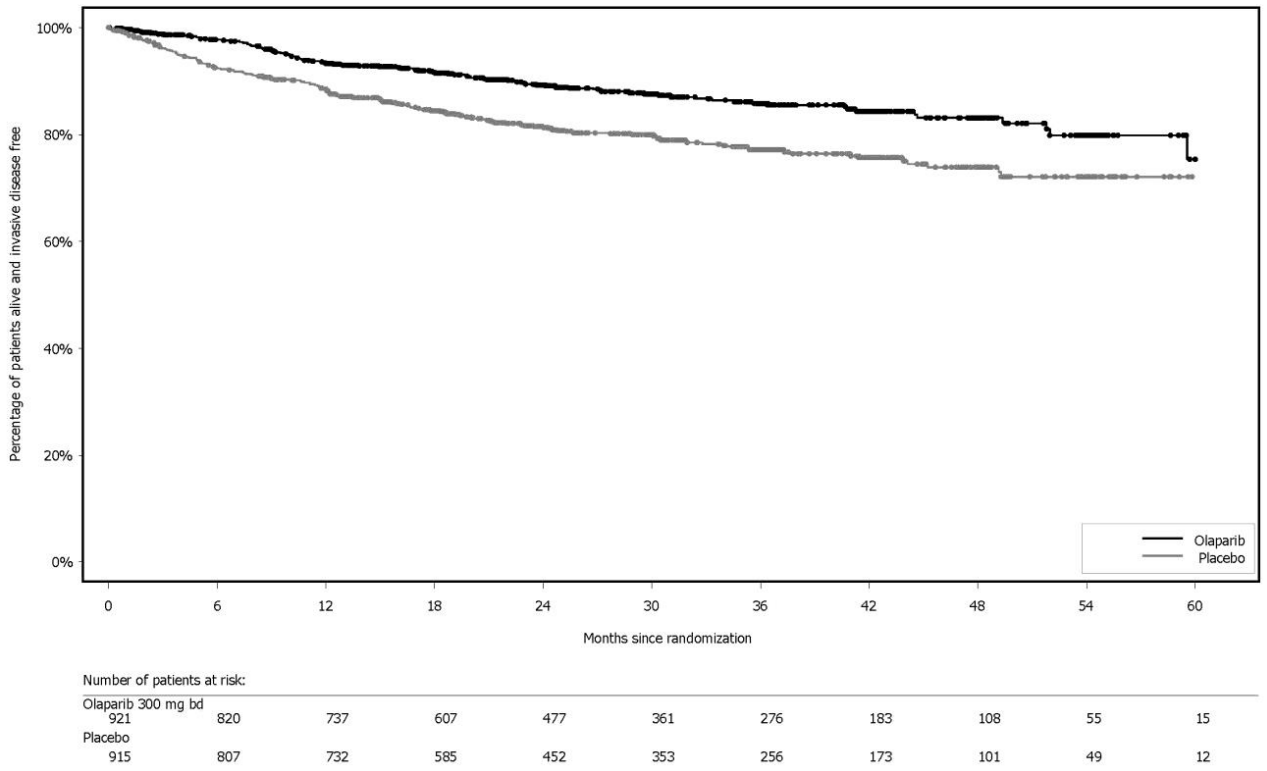
A statistically significant improvement in IDFS and OS was demonstrated in patients in the Lynparza arm compared with the placebo arm. Efficacy data for OlympiA (FAS) are presented in Table 10 and Figures 7 and 8.

Table 10 Efficacy Results – OlympiA

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

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

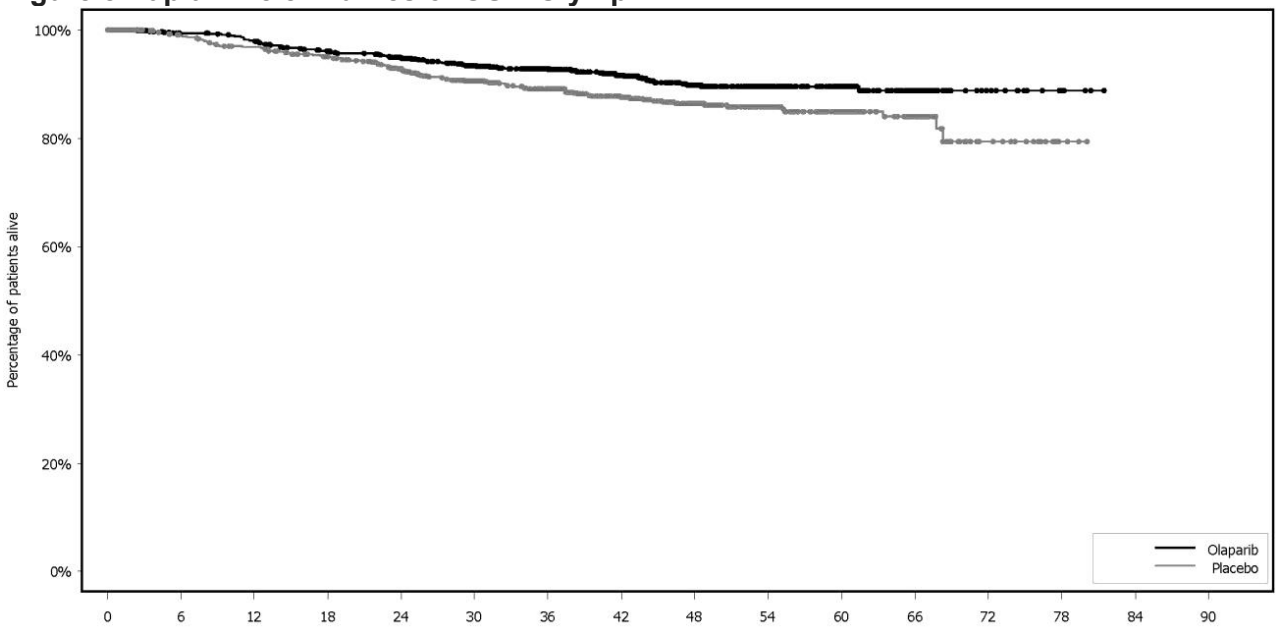
Figure 7 Kaplan-Meier Curves of IDFS – OlympiA



Number of patients at risk:

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

Figure 8 Kaplan-Meier Curves of OS – OlympiA



Number of patients at risk:

Olaparib 300 mg bd															
921	862	844	809	773	672	560	437	335	228	151	70	16	6	0	0
Placebo															
915	868	843	808	752	647	530	423	333	218	141	74	17	4	0	0

gBRCA1/2-mutated HER2-negative Metastatic Breast Cancer

<u>OlympiAD *(Study D0819C00003)*</u>

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 11).

Table 11 Patient demographic and baseline characteristics in OlympiAD

	Olaparib 300 mg bd n=205	**Chemotherapy n=97**
Age - year (median)	44	45
Gender (%)		
Female	200 (98)	95 (98)
Male	5 (2)	2 (2)
Race (%)		
White	134 (65)	63 (65)
Asian	66 (33)	28 (29)
Other	5 (2)	6 (6)
ECOG performance status (%)		
0	148 (72)	62 (64)
1	57 (28)	35 (36)
Overall disease classification		
Metastatic	205 (100)	97 (100)
Locally advanced	0	0
New metastatic breast cancer (%)	26 (13)	12 (12)
Hormone receptor status (%)		
HR+	103 (50)	49 (51)
TNBC	102 (50)	48 (49)
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 (%)	167 (82)	66 (68)
Progressive disease at time of randomization (%)	159 (78)	73 (75)
Tumour grade at diagnosis		
Well differentiated (G1)	5 (2)	2 (2)
Moderately differentiated (G2)	52 (25)	23 (24)
Poorly differentiated (G3)	108 (53)	55 (57)
Undifferentiated (G4)	4 (2)	0
Unassessable (GX)	27 (13)	15 (16)
Missing	9 (4)	2 (2)
Number of prior lines of chemotherapy for metastatic breast cancer (%)		
0	68 (33)	31 (32)
1	80 (39)	42 (43)
2	57 (28)	24 (25)
Previous platinum-based therapy(%)	60 (29)	26 (27)
in (neo)adjuvant setting	15 (7)	7 (7)
metastatic setting	43 (21)	14 (14)
in (neo)adjuvant and metastatic setting	1 (1)	3 (1)
Previous anthracycline treatment		
in (neo) adjuvant setting	169 (82)	76 (78)
metastatic setting	41 (20)	16 (17)
Previous taxane treatment		
in (neo)adjuvant setting	146 (71)	66 (68)
metastatic setting	107 (52)	41 (42)
Previous anthracycline and taxane treatment	204 (99.5)	96 (99)

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

A statistically significant improvement in PFS, the primary efficacy outcome, was demonstrated for olaparib-treated patients compared with those in the comparator arm (see Table 12 and Figure 9).

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

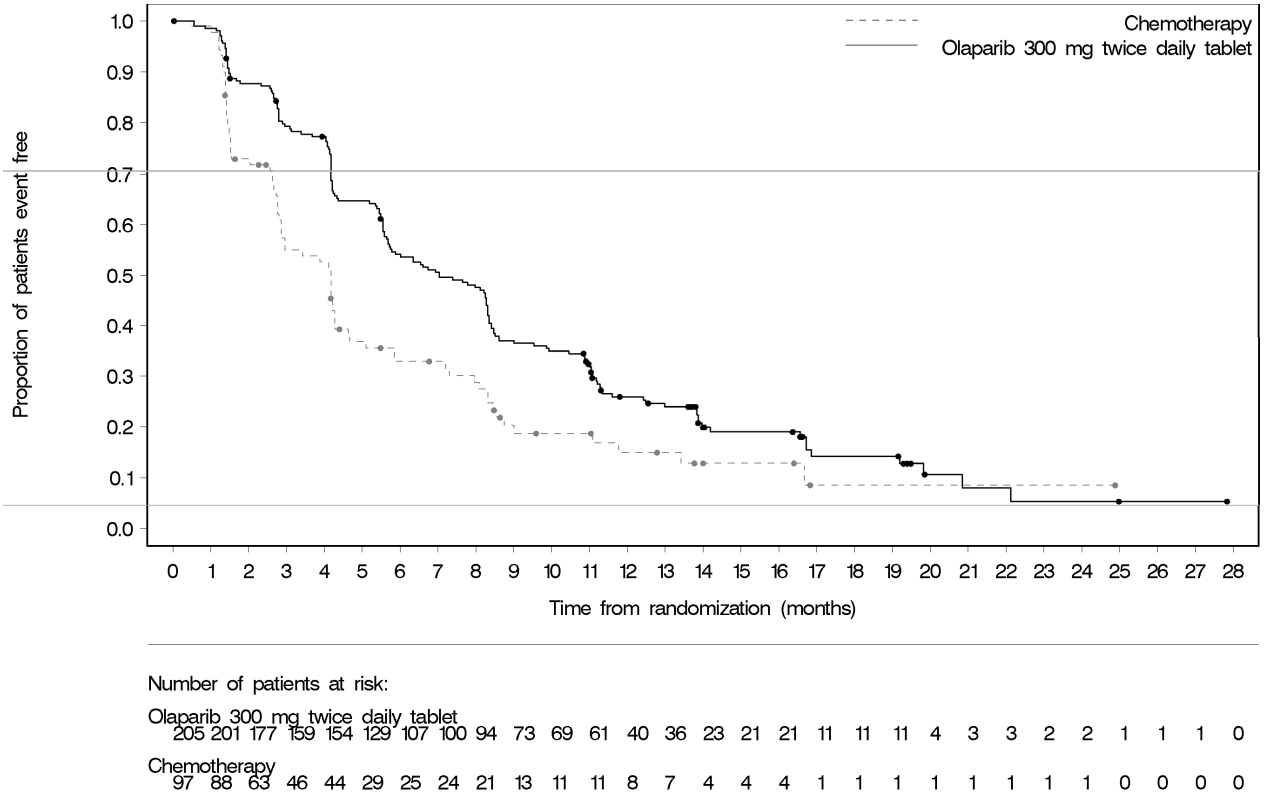
	Olaparib 300 mg bd	Chemotherapy
PFS (77% maturity) – DCO 09 December 2016		
Number of events: Total number of patients (%)	163:205 (80)	71:97 (73)
Median time (months) (95% CI)	7.0 (5.7-8.3)	4.2 (2.8-
4.3) HR (95% CI)	0.58 (0.43-0.80)	
P value (2-sided)[a]	p=0.0009	
PFS2 (65% maturity) - DCO 25 September 2017[b]		
Number of events: Total number of patients (%)		
130:205 (63)	65:97 (67)	
Median time (months) (95% CI)	12.8 (10.9-14.3)	9.4 (7.4-
10.3) HR (95% CI)	0.55 (0.39-0.77)	
P value (2-sided)[a]	p=0.0005	
OS (64% maturity) – DCO 25 September 2017		

Number of events: Total number of patients (%)		
	130:205 (63)	62:97 (64)
Median time (months) (95% CI)	19.3 (17.2-21.6)[c]	17.1 (13.9-
21.9) HR (95% CI)	0.90 (0.66-1.23)	
P value (2-sided)[a]	p=0.5131	
Confirmed ORR – DCO 09 December 2016		
Number of objective responders: Total number of patients with measurable disease (%)		
	87: 167 (52)[d]	15:66 (23)
95% CI	44.2-59.9	13.3-34.7
DOR – DCO 09 December 2016		
Median, months (95% CI)	6.9 (4.2, 10.2)	7.9 (4.5, 12.2)

[a] Based on stratified log-rank test.
[b] Post-hoc analysis.
[c] The median follow-up time in censored patients was 25.3 months for olaparib versus 26.3 months for comparator.
[d] Confirmed responses (by BICR) were defined as a recorded response of either CR/PR, confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed. In the olaparib arm 8% with measurable disease had a complete response versus 1.5% of patients in the comparator arm; 74/167 (44%) of patients in the olaparib arm had a partial response versus 14/66 (21%) of patients in the chemotherapy arm. In the TNBC patient subgroup the confirmed ORR was 48% (41/86) in the olaparib arm and 12% (4/33) in the comparator arm. In the HR+ patient subgroup the confirmed ORR was 57% (46/81) in the olaparib arm and 33% (11/33) in the comparator arm.

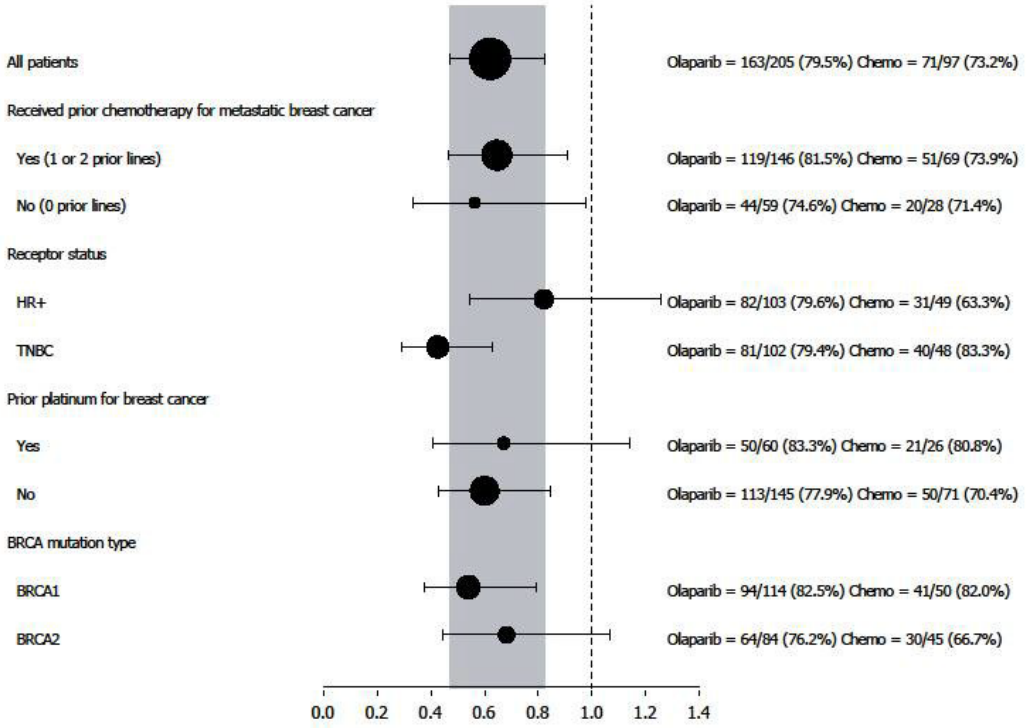
bd Twice daily; CI Confidence interval; DOR Duration of response; DCO Data cut off; HR Hazard ratio; HR+ Hormone receptor positive, ORR Objective response rate; OS overall survival; PFS progression-free survival; PFS2 Time to second progression or death, TNBC triple negative breast cancer.

Figure 9 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.

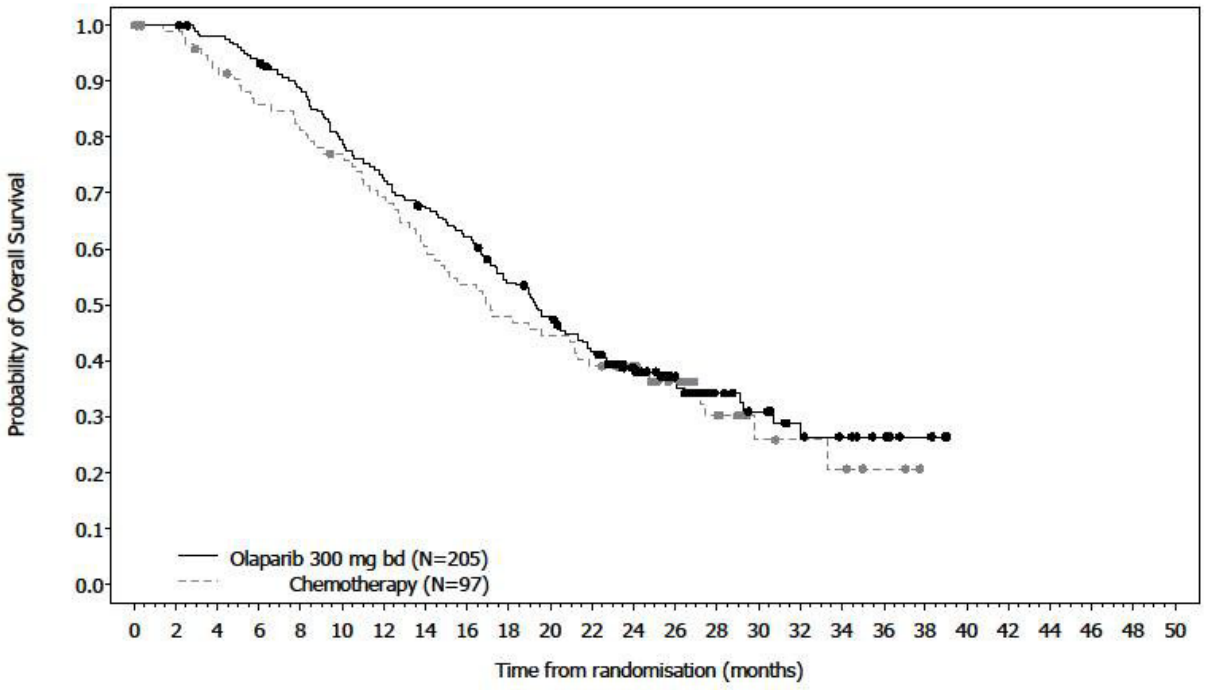
Figure 10 PFS (BICR), Forest plot, by prespecified subgroup



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

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

Figure 11 OlympiAD: Kaplan-Meier plot of OS in patients with g*BRCA1/2*-mutated HER2-negative metastatic breast cancer (64% maturity) DCO 25 September 2017



Number of patients at risk:

205	205	199	189	178	159	146	134	124	106	92	79	55	36	23	18	11	9	6	3	0	Olaparib 300 mg bd
97	92	85	78	74	69	62	54	48	43	40	35	30	23	15	6	5	4	2	0	0	Chemotherapy

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.

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

POLO

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

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

Tables 13 and 14 summarize the adverse reactions and laboratory abnormalities in patients in POLO.

Table 13 Adverse Reactions[*] in POLO (Occurring in ≥10% of Patients who Received Lynparza)

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

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

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

Clinically relevant adverse reactions that occurred in <10% of patients receiving Lynparza were cough (9%), abdominal pain upper (7%), blood creatinine increased (7%), dizziness (7%), headache (7%), dyspepsia (5%), leukopenia (5%), hypersensitivity (2%) and lymphopenia (2%) and pneumonitis (1.1%).

Table 14 Laboratory Abnormalities Reported in ≥25% of Patients in POLO

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

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

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

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

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

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

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

A total of 154 patients were randomized, 92 to Lynparza and 62 to placebo. The median age was 57 years (range 36 to 84); 54% were male; 92% were White, 4% were Asian and 3% were Black; baseline ECOG PS was 0 (67%) or 1 (31%). The median time from initiation of first-line platinum-based chemotherapy to randomization was 5.8 months (range 3.4 to 33.4 months). Seventy-five percent (75%) of patients received FOLFIRINOX with a median of 9 cycles (range 4-61), 8% received FOLFOX or XELOX, 4% received GEMOX, and 3% received gemcitabine plus cisplatin; 49% achieved a complete or partial response to platinum-based chemotherapy.

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

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

Efficacy results of POLO are provided in Table 15 and Figure 12.

Table 15 Efficacy Results - POLO (BICR-assessed)

	Lynparza tablets (n=92)	**Placebo (n=62)**
Progression-Free Survival		

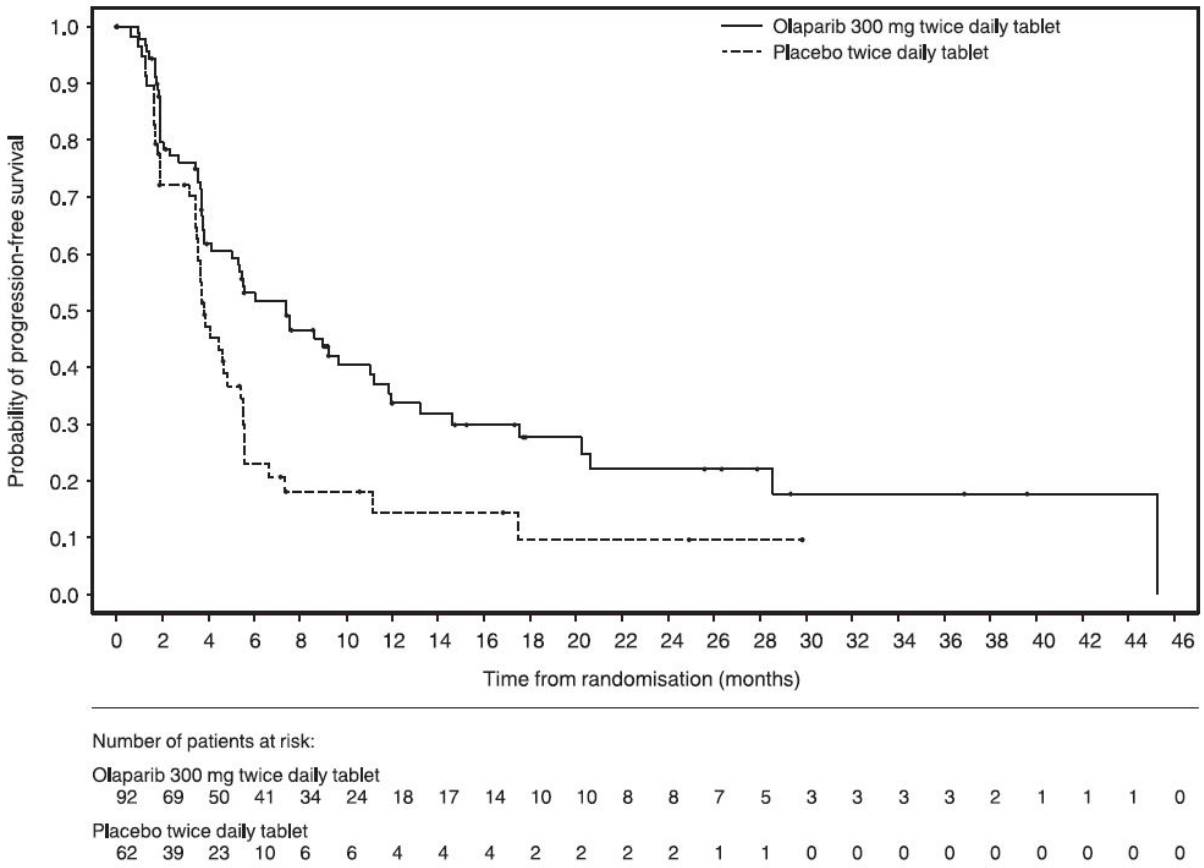
Number of events (%)*	60 (65%)	44 (71%)
Median, months (95% CI)	7.4 (4.1, 11.0)	3.8 (3.5, 4.9)
Hazard ratio** (95% CI)	0.53 (0.35, 0.81)	
p-value	0.0035	
Overall Survival		
Number of events (%)	61 (66)	47 (76)
Median, months (95% CI)	19.0 (15.3, 26.3)	19.2 (14.3, 26.1)
Hazard ratio† (95% CI)	0.83 (0.56, 1.22)	
p-value	0.3487	
Patients with Measurable Disease	n=78	n=52
Objective Response Rate (95% CI)	23% (14, 34)	12% (4, 23)
Complete response (%)	2 (2.6)	0
Partial response (%)	16 (21)	6 (12)
Duration of Response (DOR)		
Median time in months (95% CI)	25 (15, NC)	4 (2, NC)

* Number of events: Progression – Lynparza 55, placebo 44; death before BICR-documented progression – Lynparza 5, placebo 0

** Hazard ratio, 95% CI, and p-value calculated from a log-rank test. A hazard ratio <1 favors Lynparza.

NC Not calculable

Figure12 Kaplan-Meier Curves of BICR-Assessed Progression-Free Survival - POLO



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

PAOLA-1

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

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

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

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

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

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

Tables 16 and 17 summarize adverse reactions and laboratory abnormalities in PAOLA-1, respectively.

Table 16 Adverse Reactions* Occurring in ≥10% of Patients Treated with Lynparza/bevacizumab in PAOLA-1 and at ≥5% Frequency Compared to the Placebo/bevacizumab Arm

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

* Graded according to the National Cancer Institute Common T erminology Criteria for Adverse Events (NCI CTCAE), version 4.0.
† Includes asthenia, and fatigue.
‡ Includes anemia, anemia macrocytic, erythropenia, haematocrit decreased, haemoglobin decreased, normochromic anemia, normochromic normocytic anemia, normocytic anemia, and red blood cell count decreased.
§ Includes B-lymphocyte count decreased, lymphocyte count decreased, lymphopenia, and T-lymphocyte count decreased.
‖ Includes leukopenia, and white blood cell count decreased.

Clinically relevant adverse reactions that occurred in <10% of patients receiving Lynparza/bevacizumab were dysgeusia (8%), dyspnea (8%), stomatitis (5%), dyspepsia

(4.3%), erythema (3%), dizziness (2.6%), hypersensitivity (1.7%) pneumonitis (0.9%), and MDS/AML (0.7%).

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

Table 17 Laboratory Abnormalities Reported in ≥25% of Patients in PAOLA-1*

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

* Reported within 30 days of the last dose.

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

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

PAOLA-1 (NCT03737643) was a randomized, double-blind, placebo-controlled, multi-center trial that compared the efficacy of Lynparza in combination with bevacizumab versus placebo/bevacizumab for the maintenance treatment of advanced high-grade epithelial ovarian cancer, fallopian tube or primary peritoneal cancer following first-line platinum-based chemotherapy and bevacizumab. Randomization was stratified by first-line treatment outcome (timing and outcome of cytoreductive surgery and response to platinum-based chemotherapy) and tBRCAm status, determined by prospective local testing. All available clinical samples were retrospectively tested with Myriad myChoice® CDx. Patients were required to have no evidence of disease (NED) due to complete surgical resection, or who were in complete response (CR), or partial response (PR) following completion of first-line platinum-containing chemotherapy and bevacizumab. Patients were randomized (2:1) to receive Lynparza tablets 300 mg orally twice daily in combination with bevacizumab (n=537) 15 mg/kg every three weeks or placebo/bevacizumab (n=269) Patients continued bevacizumab in the maintenance setting and started treatment with Lynparza after a minimum of 3 weeks and up to a maximum of 9 weeks following completion of their last dose of chemotherapy. Lynparza treatment was continued for up to 2 years or until progression of the underlying disease or unacceptable toxicity. Patients who in the opinion of the treating physician could derive further benefit from continuous treatment could be treated beyond 2 years. Treatment with bevacizumab was for a total of up to 15 months, including the period given with chemotherapy and given as maintenance.

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

A statistically significant difference in PFS was observed in the intent-to-treat (ITT) population. Planned exploratory analyses of PFS and OS were conducted in patients

with known HRD status. The PFS hazard ratio (HR) for patients with HRD-negative tumors (277/806; 34%) was 1.00 (95% CI: 0.75, 1.34) and the OS HR was 1.18 (95% CI: 0.87, 1.60) indicating that the clinical benefit was primarily attributed to the results seen in the HRD-positive population. Efficacy results in patients with HRD-positive tumors are summarized in Table 19, Figure 13, and Figure 14.

Among the 387 patients (48%) with HRD-positive tumors identified post-randomization using the Myriad myChoice® HRD Plus tumor test the median age was 58 years in both arms (range 32-82). Ovarian cancer was the primary tumor type in 87% of patients in both arms. Ninety five percent (95%) were serous histological type. The ECOG performance score was 0 in 75% of patients and 1 in 24% of patients. All patients had received first-line platinum-based therapy and bevacizumab. First-line treatment outcomes at screening indicated that patients had no evidence of disease with complete macroscopic resection at initial debulking surgery (36%), no evidence of disease/ CR with complete macroscopic resection at interval debulking surgery (29%, both arms), no evidence of disease/ CR in patients who had either incomplete resection (at initial or interval debulking surgery) or no debulking surgery (16%, both arms) and patients with a partial response (19%, both arms). Sixty-two (62%) of patients in Lynparza/bevacizumab arm and 58% of patients in placebo/bevacizumab armhad tumors with a deleterious BRCA mutation. Patients were not restricted by the surgical outcome with 67% having complete cytoreduction at initial or interval debulking surgery and 33% having residual macroscopic disease.

Table 18 EfficacyResults - PAOLA-1 (HRD positive status*, Investigator Assessment)

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

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

Figure 13 Kaplan-Meier Curves of Investigator-Assessed Progression-Free Survival – PAOLA-1 (HRD positive status)

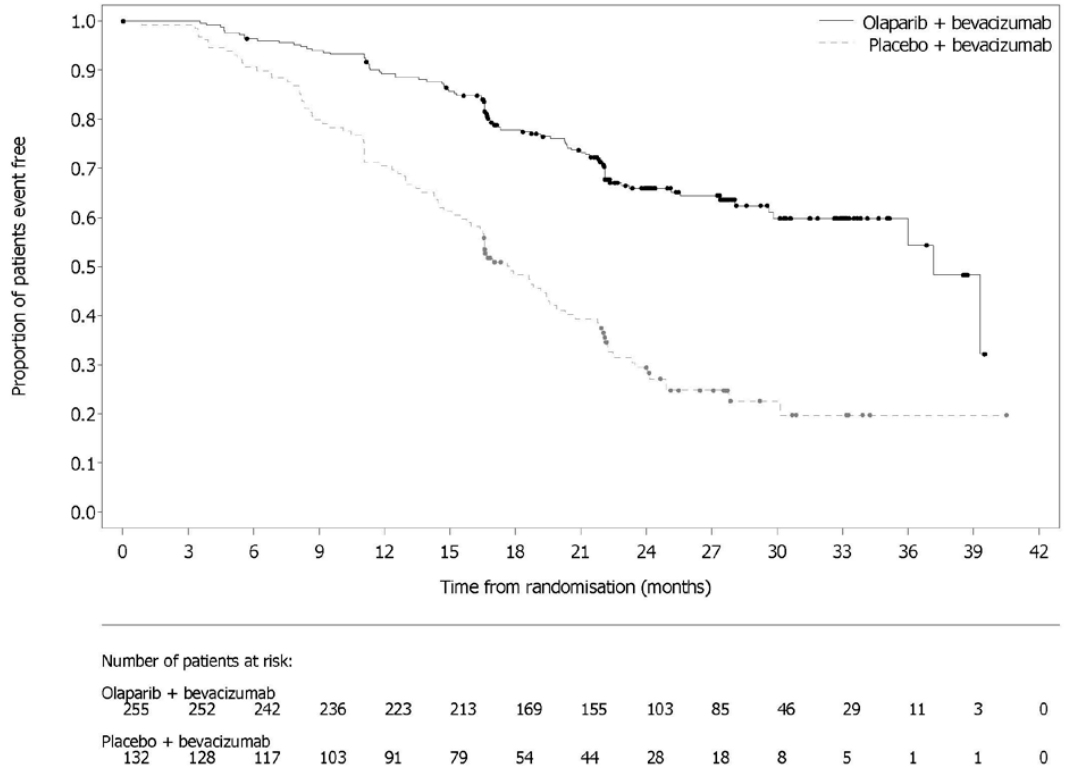
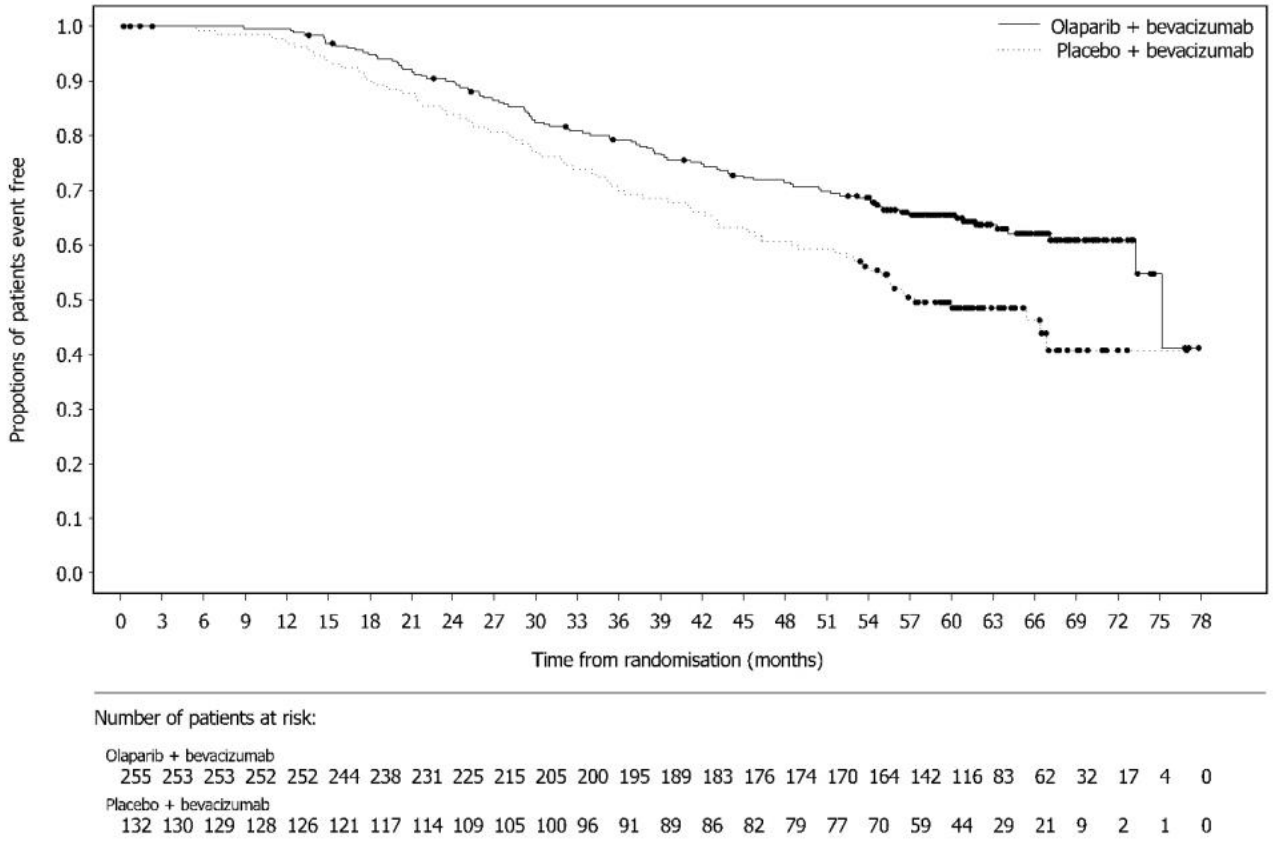


Figure 14 Kaplan-Meier Curves of Overall Survival – PAOLA-1 (HRD-positive status)*



* Based on final OS subgroup analysis.

BRCA1/2 or ATM Gene-mutated Metastatic Castration-Resistant Prostate Cancer

PROfound

The safety of Lynparza as monotherapy was evaluated in patients with mCRPC and BRCA1/2 or ATM gene mutations who have progressed following prior treatment with enzalutamide or abiraterone in PROfound . This study was a randomized, open-label, multi-center study in which 386 patients received either Lynparza tablets 300 mg orally twice daily (n=256) or investigator's choice of enzalutamide or abiraterone acetate (n=130) until disease progression or unacceptable toxicity. Among patients receiving Lynparza, 62% were exposed for 6 months or longer and 20% were exposed for greater than one year.

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

Serious adverse reactions occurred in 36% of patients receiving Lynparza. The most frequent serious adverse reactions (≥2%) were anemia (9%), pneumonia (4%), pulmonary embolism (2%), fatigue/asthenia (2%), and urinary tract infection (2%). Dose interruptions due to an adverse reaction of any grade occurred in 45% of patients receiving Lynparza; dose reductions due to an adverse reaction occurred in 22% of Lynparza patients. The most frequent adverse reactions leading to dose interruption of Lynparza were anemia (25%) and thrombocytopenia (6%) and the most frequent adverse reaction leading to reduction of Lynparza was anemia (16%). Discontinuation due to adverse reactions occurred in 18% of Lynparza. The adverse reaction that most frequently led to discontinuation of Lynparza was anemia (7%).

Tables 19 and 20 summarize the adverse reactions and laboratory abnormalities, respectively, in patients in PROfound.

Table 19 Adverse Reactions* Reported in ≥10% of Patients in PROfound

Adverse Reactions	**Lynparza tablets n=256**		**Enzalutamide or abiraterone n=130**	
	Grades 1-4 (%)	**Grades 3-4 (%)**	**Grades 1-4 (%)**	**Grades 3-4 (%)**
Blood and lymphatic disorders				
Anemia†	46	21	15	5
Thrombocytopenia‡	12	4	3	0
Gastrointestinal disorders				
Nausea	41	1	19	0
Diarrhea	21	1	7	0
Vomiting	18	2	12	1

General disorders and administration site conditions				
Fatigue (including asthenia)	41	3	32	5
Metabolism and nutrition disorders				
Decreased appetite	30	1	18	1
Respiratory, thoracic, and mediastinal disorders				
Cough	11	0	2	0
Dyspnea	10	2	3	0

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

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

Table 20 Laboratory Abnormalities Reported in ≥25% of Patients in PROfound

Laboratory Parameter*	**Lynparza tablets $n_{\dagger}$= 256**		**Enzalutamide or abiraterone $n_{\dagger}$=130**	
	Grades 1-4 (%)	**Grades 3-4 (%)**	**Grades 1-4 (%)**	**Grades 3-4 (%)**
Decrease in hemoglobin	98	13	73	4
Decrease in lymphocytes	62	23	34	13
Decrease in leukocytes	53	4	21	0
Decrease in absolute neutrophil count	34	3	9	0

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

BRCA1/2 or ATM Gene-mutated Metastatic Castration-Resistant Prostate Cancer

The efficacy of Lynparza was evaluated in PROfound (NCT02987543), randomized, open-label, multi-center trial that evaluated the efficacy of Lynparza 300 mg twice daily versus a comparator arm of investigator's choice of enzalutamide or abiraterone acetate in men with metastatic castration-resistant prostate cancer (mCRPC). All patients received a GnRH analog or had prior bilateral orchiectomy. Patients needed to have progressed on prior enzalutamide or abiraterone for the treatment of metastatic prostate cancer and/or CRPC and have a tumor mutation in one of 15 genes involved in the homologous recombination repair (HRR) pathway.

Patients were divided into two cohorts based on HRR gene mutation status. Patients with mutations in either BRCA1, BRCA2, or ATM were randomized in Cohort A; patients with mutations among 12 other genes involved in the HRR pathway (BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C,

RAD51D, or RAD54L) were randomized in Cohort B; patients with co-mutations (BRCA1, BRCA2, or ATM plus a Cohort B gene) were assigned to Cohort A. Although patients with PPP2R2A gene mutations were enrolled in the trial, Lynparza is not indicated for the treatment of patients with this gene mutation due to unfavorable risk-benefit. Patients were randomized (2:1), 256 to Lynparza arm and 131 to enzalutamide or abiraterone acetate arm; in Cohort A there were 245 (162 Lynparza arm and 83 in enzalutamide or abiraterone acetate arm) and in Cohort B there were 142 patients (94 in Lynparza arm and 48 in enzalutamide or abiraterone acetate arm). Randomization was stratified by prior receipt of taxane chemotherapy and presence of measurable disease by RECIST 1.1. Treatment was continued until objective radiological disease progression determined by BICR. Upon radiological progression confirmed by BICR, patients randomized to enzalutamide or abiraterone acetate were given the option to switch to olaparib. Patients with HRR gene mutations were identified by tissue-based testing using the Foundation Medicine FoundationOne® clinical trial HRR assay performed at a central laboratory.

Determination of deleterious or suspected deleterious somatic or germline HRR mutation status in line with the FDA approved mutation classification and testing criteria for the Foundation Medicine F1CDx tissue-based assay and assessment of the germline-BRCA status using the Myriad BRAC Analysis CDx blood-based assay was performed retrospectively. Representation of individual gene mutations by cohort is provided in Table 17. No patients were enrolled who had mutations in two of the 15 pre-specified HRR genes: FANCL and RAD51C.

Table 21 Frequency of Patients with HRR Mutations Enrolled in PROfound

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

* Three patients with single *BRCA2* or *ATM* gene mutations and 1 patient with co-occurring *BRCA2*+*CDK12* gene mutations were incorrectly assigned to Cohort B.
# Lynparza is not indicated for patients with *PPP2R2A* mutations.
** Patients with co-occurring mutations (*BRCA1*, *BRCA2*, or *ATM* plus a Cohort B gene) were assigned to Cohort A.

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

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

PROfound demonstrated a statistically significant improvement in BICR-assessed rPFS for Lynparza compared to investigator's choice of enzalutamide or abiraterone acetate in Cohort A and Cohort A+B. In an exploratory analysis for patients in Cohort B, the median rPFS was 4.8 months for Lynparza vs 3.3 months for comparator with a HR of 0.88 (95% CI 0.58, 1.36). The major efficacy outcome was supported by a statistically significant improvement in ORR by BICR for patients with measurable disease at baseline in Cohort A. In Cohort B, ORR by BICR was 3.7% (95% CI 0.5, 12.7) in Lynparza treated patients and 8.3% (95% CI 1.0, 27.0) in patients treated with enzalutamide or abiraterone acetate.

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

Efficacy results of PROfound are provided in Tables 22 and 23 and Figures 14 and 15.

Table 22 Efficacy Results -PROfound (BICR-assessed)

	Cohort A		Cohort A+B*	
	Lynparza tablets (n=162)	Enzalutamide or Abiraterone acetate (n=83)	Lynparza tablets (n=256)	Enzalutamide or Abiraterone acetate (n=131)
Radiological Progression-Free Survival (rPFS)				
Number of events (%)	106 (65)	68 (82)	180 (70)	99 (76)
Median (95% CI), in months	7.4 (6.2, 9.3)	3.6 (1.9, 3.7)	5.8 (5.5, 7.4)	3.5 (2.2, 3.7)
Hazard ratio (95% CI)‖	0.34 (0.25, 0.47)		0.49 (0.38, 0.63)	
p-value¶	<0.0001		<0.0001	
Confirmed ORR				
Patients with measurable disease at baseline	n=84	n=43	-	-
ORR, n (%)	28 (33)	1 (2)	-	-
(95% CI)	(23, 45)	(0, 12)	-	-
p-value	<0.0001		-	
Overall Survival	n=162	n=83	-	-
Number of events (%)	91 (56)	57 (69)	-	-
Median (95% CI), in months	19.1 (17.4, 23.4)	14.7 (11.9, 18.8)	-	-
Hazard ratio (95% CI)‖	0.69 (0.50, 0.97)		-	
p-value¶	0.0175		-	

* Although 10 patients with *PPP2R2A* mutation were included in all analyses of Cohort A+B, Lynparza is not indicated for this population due to unfavorable risk-benefit.

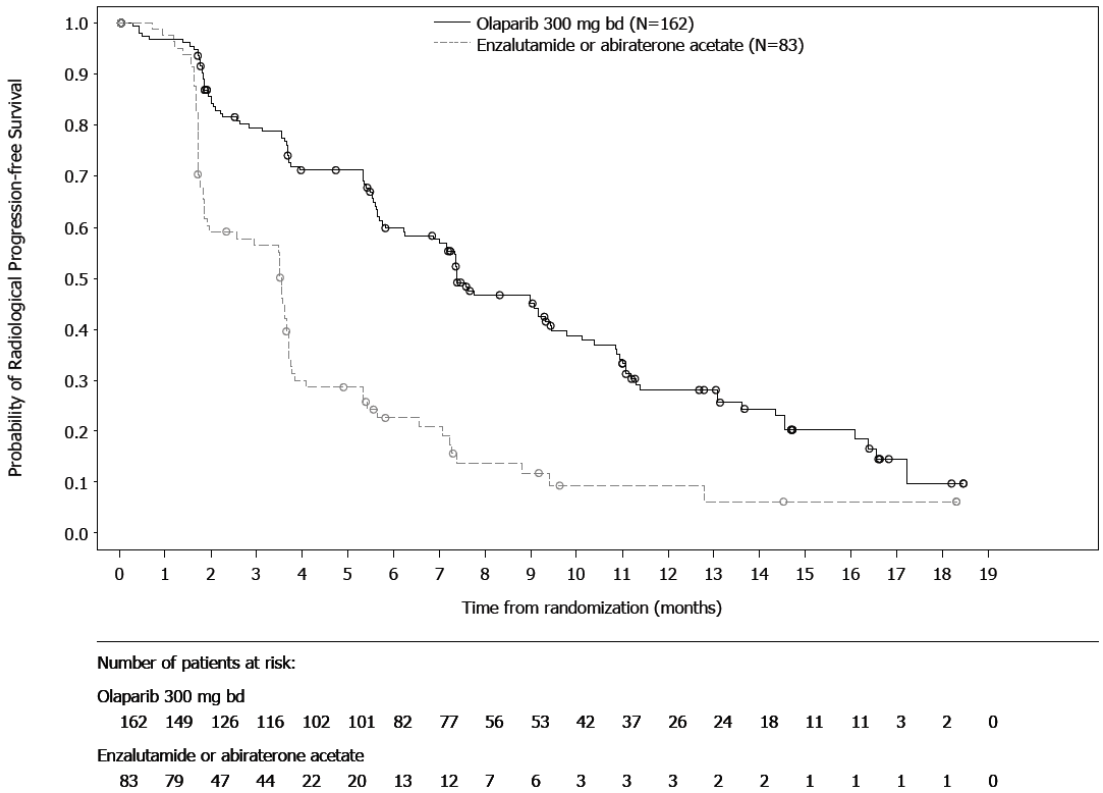
‖ The HR and CI were calculated using a Cox proportional hazards model adjusted for prior taxane use and measurable disease.

An HR <1 favors Lynparza 300 mg bd.

¶ The analysis was performed using the log-rank test stratified by prior taxane use and measurable disease.

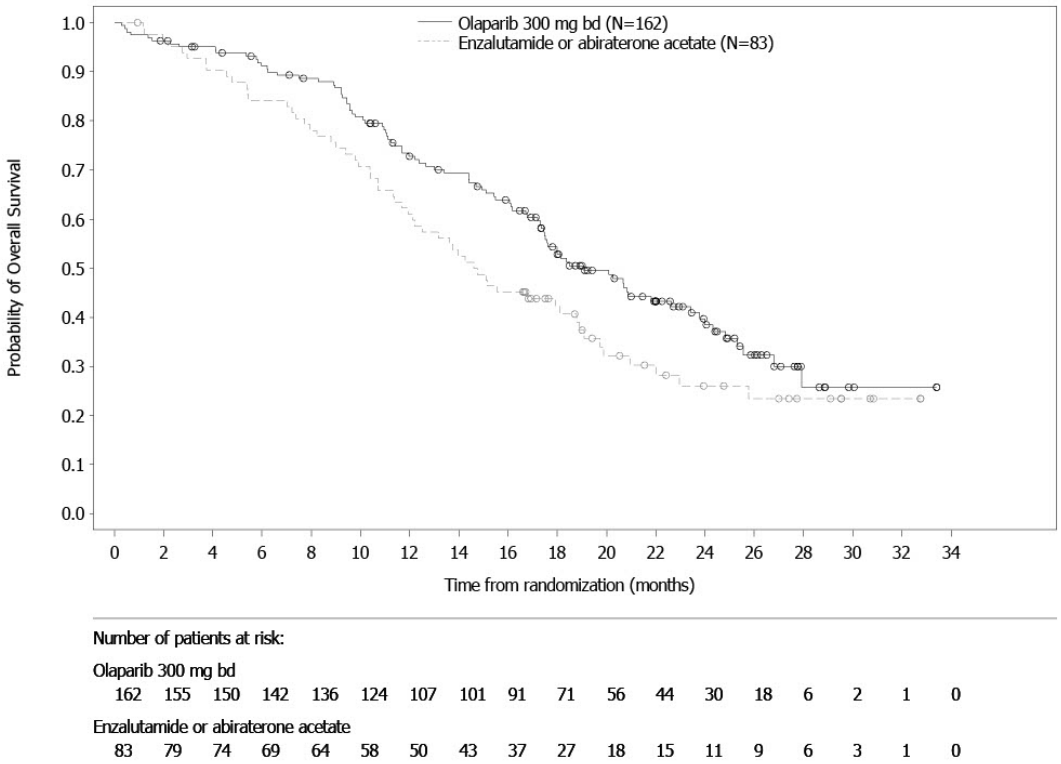
CI Confidence interval

Figure 15 Kaplan-Meier Curves of BICR-Assessed Radiological Progression-Free Survival – PROfound – Cohort A



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

Figure 16 Kaplan-Meier Curves of Overall Survival – PROfound – Cohort A



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

Table 23 Response Rate and Duration of Response by HRR Mutation in Patients withMeasurable Disease at Baseline on the Lynparza Arm – PROfound (BICR-assessed)

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

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

* No patients with *FANCL* or *RAD51C* enrolled. Three patients with *PPP2R2A* mutations had measurable disease, however, Lynparza is not indicated for patients with *PPP2R2A* mutation.
† In patients with a single *BRCA2* mutation the median duration of response in the Lynparza arm (n=24) was 5.6 months (95% C.I: 5.5, 9.2). In the 3 responders with a single *ATM* mutation in the Lynparza arm, the duration of response ranged from 5.8+ to 9.0 months. In the 2 responders with a single *CDK12* mutation in the Lynparza arm, the duration of response was 3.7 and 7.2 months. + denotes ongoing response.
PR Partial response; SD Stable disease; PD Progressive disease; NE Not evaluable; NA Not applicable due to small numbers or lack of response.

Treatment of patients in the first-line mCRPC setting PROpel

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

The study randomised 796 patients (1:1 randomisation; 399 olaparib/abiraterone:397 placebo/ abiraterone) who had evidence of histologically confirmed prostate adenocarcinoma and metastatic status defined as at least one documented metastatic lesion on either a bone or CT/MRI scan and who were treatment naïve with no prior chemotherapy or NHA in the mCRPC setting. Prior to the mCRPC stage, treatment with NHAs (except abiraterone) without PSA progression (clinical or radiological) during treatment was allowed, provided the treatment was stopped at least 12 months before randomisation. Treatment with first-generation antiandrogen agents (e.g., bicalutamide, nilutamide, flutamide) was also allowed, provided there was a washout period of 4 weeks. Docetaxel treatment was allowed during neoadjuvant/adjuvant treatment for localised prostate cancer and at metastatic hormone-sensitive prostate cancer (mHSPC) stage, as long as no signs of disease progression occurred during or immediately after such treatment. All patients received a GnRH analogue or had prior bilateral orchiectomy. Patients were stratified by metastases (bone only, visceral or other) and docetaxel treatment at mHSPC stage (yes or no). Treatment was continued until radiological progression of the underlying disease or unacceptable toxicity.

Demographic and baseline characteristics were balanced between the two treatment arms. The median age of patients was 69 years overall, and the majority (71%) of patients were in the ≥65 years age group. One hundred and eighty-nine patients (24%) had prior docetaxel treatment at mHSPC stage. In total, 434 (55%) patients had bone metastases (metastases in the bone and no other distant site), 105 (13%) patients had visceral

metastases (distant soft tissue metastases in an organ e.g., liver, lung) and 257 (32%) patients had other metastases (this could include, for example, patients with bone metastases and distant lymph nodes or patients with disease present only in distant lymph nodes).
Most patients in both arms (70%) had an ECOG performance status of 0. There were 103 (25.8%) symptomatic patients in the olaparib group and 80 (20.2%) patients in the placebo group. Symptomatic patients were characterized by Brief Pain Inventory-Short Form (BPI-SF) item #3 score ≥ 4 and/or opiate use at baseline.

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

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

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

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

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

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

	ib/abiraterone N = 399	**bo/abiraterone N = 397**
rPFS (by investigator assessment) (50% maturity) (DCO 30 July 2021)		
Number of events: Total number of patients (%)	168:399 (42.1)	226:397 (56.9)
Median time (95% CI) (months)	24.8 (20.5, 27.6)	16.6 (13.9, 19.2)
HR (95% CI)[a]	0.66 (0.54, 0.81)	
p-value[b]	<0.0001	
Final OS (48% maturity) (DCO 12 October 2022)		
Number of events: Total number of patients (%)	176:399 (44.1)	205:397 (51.6)

Median time (95% CI) (months)	42.1 (38.4, NC)	34.7 (31.0, 39.3)

	Olaparib/abiraterone N = 399	**Placebo/abirateron e N = 397**
HR (95% CI)[a]	0.81 (0.67, 1.00)	
p-value[b]	p=0.0544	
% Alive at 36 months (95% CI) [c]	56.9 (51.7, 61.7)	49.5 (44.3, 54.5)

[a] The HR and CI were calculated using a Cox proportional hazards model adjusted for the variables selected in the primary pooling strategy: metastases, docetaxel treatment at mHSPC stage. The Efron approach was used for handling ties. A HR <1 favours olaparib 300 mg bd + abiraterone 1000 mg qd.

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

[c] Calculated using the Kaplan-Meier technique.

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

	Olaparib/abiraterone	**Placebo/abiraterone**
Radiological Progression-Free Survival (rPFS) by investigator assessment		
Aggregate HRRm Subgroup Analyses [a]		
HRRm	**N=111**	**N=115**
Number of events: Total number of patients (%)	43:111 (38.7)	73:115 (63.5)
Median (months)	NC	13.86
Hazard ratio (95% CI) [b]	0.50 (0.34, 0.73)	
Non-HRRm	**N=279**	**N=273**
Number of events: Total number of patients (%)	119:279 (42.7)	149:273 (54.6)
Median (months)	24.11	18.96
Hazard ratio (95% CI) [b]	0.76 (0.60, 0.97)	
Aggregate BRCAm Subgroup Analyses [a]		
BRCAm	**N=47**	**N=38**
Number of events: Total number of patients (%)	14:47 (29.8)	28:38 (73.7)
Median (months)	NC	8.38
Hazard ratio (95% CI) [b]	0.23 (0.12, 0.43)	
Non-BRCAm	**N=343**	**N=350**
Number of events: Total number of patients (%)	148:343 (43.1)	194:350 (55.4)
Median (months)	24.11	18.96
Hazard ratio (95% CI) [b]	0.76 (0.61, 0.94)	

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

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

Figure 17 PROpel: Kaplan-Meier plot of rPFS (investigator assessed) (50% maturity) DCO 30 July 2021

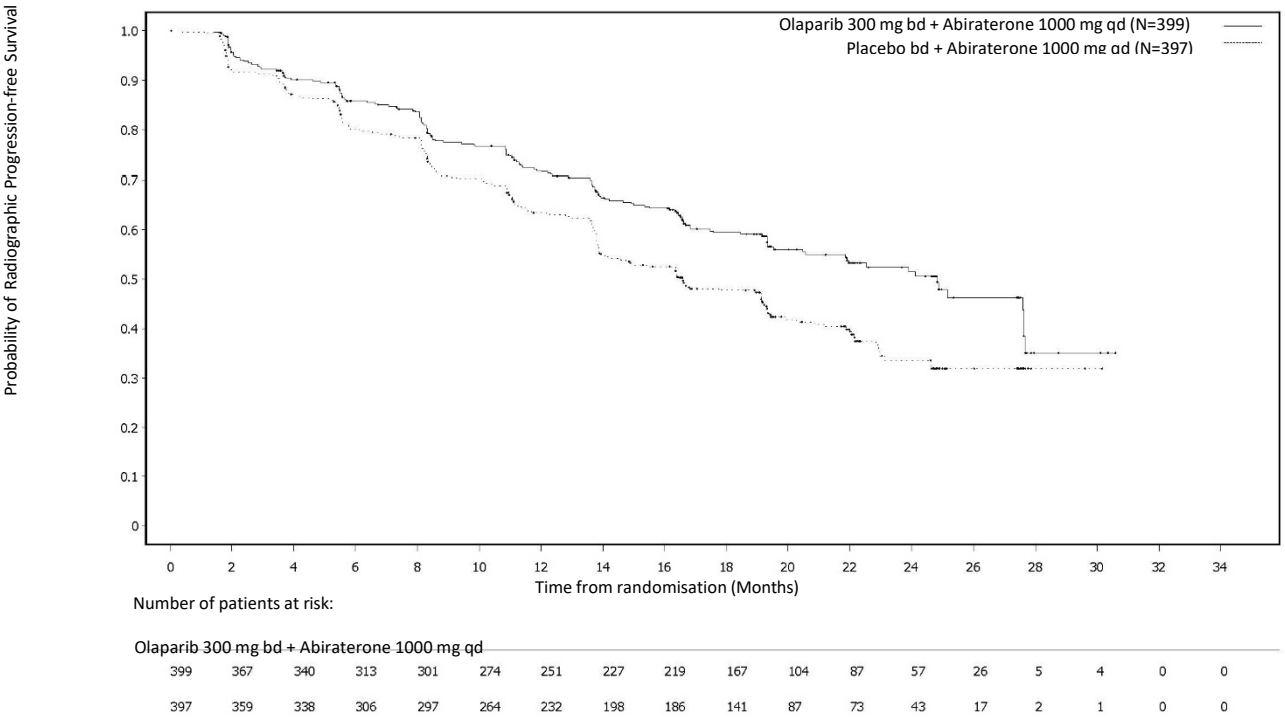


Figure 18 PROpel: Kaplan-Meier plot of OS (48% maturity) DCO 12 October 2022

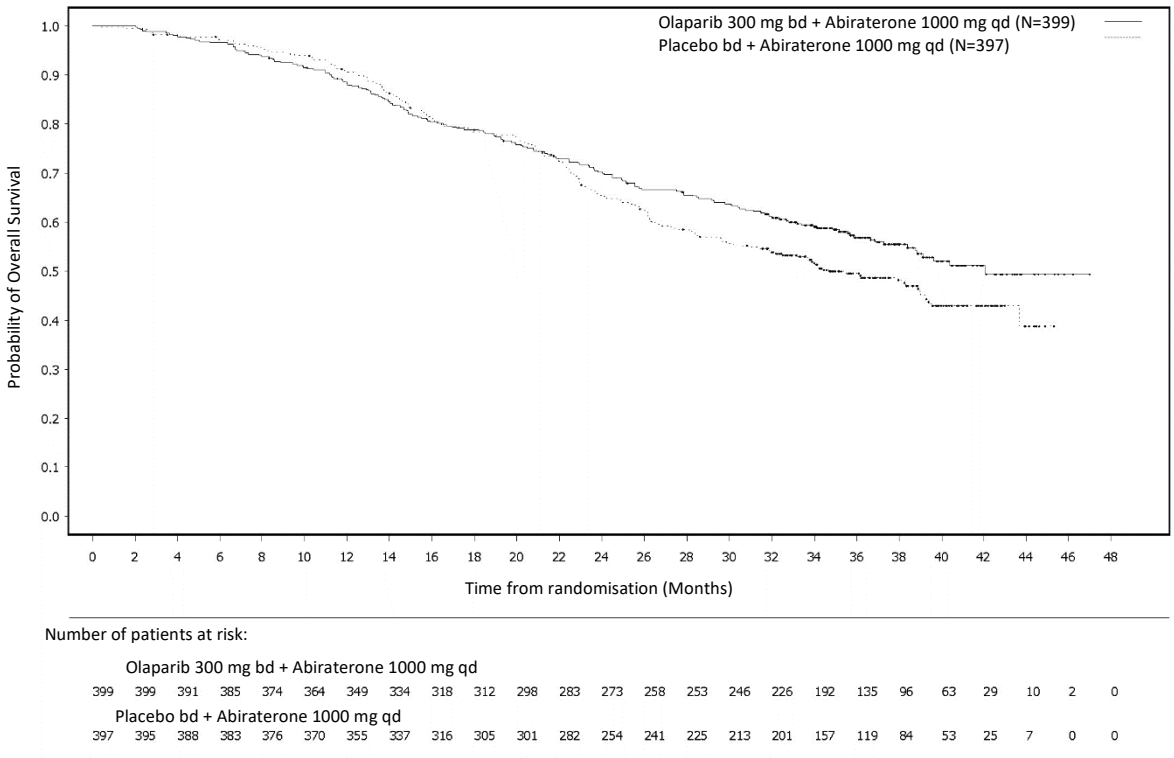
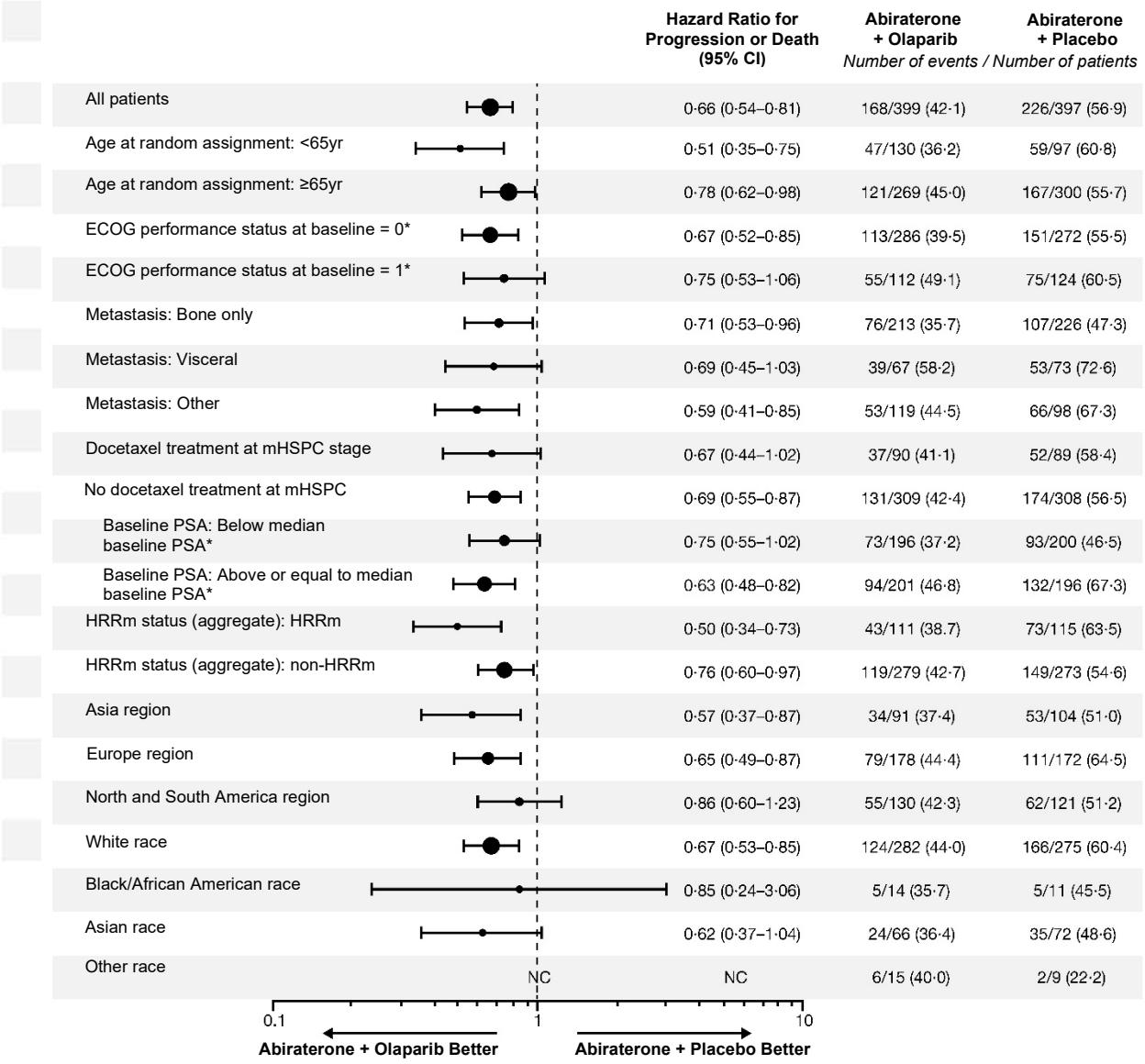


Figure 19 PROpel: Forest plot of subgroup analysis of rPFS (investigator assessed) (50% maturity) DCO 30 July 2021



Each subgroup analysis was performed using a Cox proportional hazards model that contained a term for treatment, factor, and treatment by factor interaction. A hazard ratio < 1 implies a lower risk of progression on olaparib. The size of a circle is proportional to the number of events. All subgroups in this figure are based upon data from the eCRF.

*Excludes patients with no baseline assessment. CI: confidence interval, ECOG: Eastern Cooperative Oncology Group; HRRm: homologous recombination repair gene mutation; mHSPC: metastatic hormone-sensitive prostate cancer; NC: noncalculable; PSA: prostate-specific antigen.

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 (tmax delayed by 2.5 hours and Cmax 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 Cmax. *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 14C-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 14C-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 Cmax 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 Cmax 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 Cmax by 13% and in patients with moderate hepatic impairment (Child-Pugh classification B), AUC increased by 8% and Cmax decreased by 13% compared with patients with normal hepatic function. No Lynparza dose adjustment is required for patients with mild or moderate hepatic impairment (see section 4.2). There are no data in patients with severe hepatic impairment (Child-Pugh classification C).

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

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

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

Carcinogenicity
Carcinogenicity studies have not been conducted with olaparib.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Copovidone k28
Mannitol
Silica, colloidal anhydrous
Sodium stearyl fumarate

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

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage
Store in the original package in order to protect from moisture.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container
Alu/Alu non-perforated blister containing 8 film-coated tablets.
Pack sizes:
56 film-coated tablets (7 blisters).
Multipack containing 112 (2 packs of 56) film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Manufacturer
AstraZeneca UK limited Silk Road Business Park,
Macclesfield, Cheshire SK10 2NA, UK

8. License holder and Importer
AstraZeneca (Israel) Ltd., 1 Atirei Yeda St., Kfar Saba 4464301

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