PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

LYNPARZA®

Olaparib Tablets

Tablets, 100 mg and 150 mg, oral use

Antineoplastic agent

LYNPARZA (olaparib) indicated as:

- *monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed (PSR) BRCA wild type high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.*
- *adjuvant treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (BRCAm), human epidermal growth factor receptor 2 (HER2)-negative high risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy. Patients must have confirmation of germline BRCA mutation before LYNPARZA treatment is initiated.*

has been issued ***marketing authorization with conditions****, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for LYNPARZA, please refer to Health Canada's Notice of Compliance with conditions - drug products website:* https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html

LYNPARZA indicated as monotherapy for the:

- *Maintenance treatment of adult patients with advanced BRCA-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to first-line platinum-based chemotherapy. Patients must have confirmation of BRCA mutation (identified by either germline or tumour testing) before LYNPARZA treatment is initiated.*
- *Maintenance treatment of adult patients with platinum-sensitive relapsed (PSR) BRCA-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.*
- *Treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm), HER2-negative metastatic breast cancer who have previously been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have progressed on or be considered inappropriate for endocrine therapy. Germline BRCA mutation must be confirmed before LYNPARZA treatment is initiated.*
- *Maintenance treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) metastatic adenocarcinoma of the pancreas whose disease has not progressed on a minimum of 16 weeks of first-line platinum-based chemotherapy. Germline BRCA mutation must be confirmed before LYNPARZA treatment is initiated.*
- *Treatment of adult patients with deleterious or suspected deleterious germline and/or somatic BRCA or ATM mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with a new hormonal agent. BRCA* or *ATM* mutations must be confirmed before LYNPARZA treatment is initiated.

has been issued ***marketing authorization without conditions.***

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What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

RECENT MAJOR LABEL CHANGES

1 Indication	07-2022
4 Dosage and Administration, 4.1 Dosing Considerations	05-2021
4 Dosage and Administration, 4.2 Recommended Dose and Dosage Adjustment	07-2022
7 Warnings and Precautions, Carcinogenesis and Mutagenesis	03-2021
7 Warnings and Precautions, Cardiovascular	08-2020
7 Warnings and Precautions, Driving and Operating Machinery	05-2021
7 Warnings and Precautions, Monitoring and Laboratory Test	07-2022
7 Warnings and Precautions, Reproductive Health Female and Male Potential	07-2022
7 Warnings and Precautions, 7.1.1 Pregnant Women	07-2022
7 Warnings and Precautions, Cardiovascular	08-2022

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATION

Breast Cancer

LYNPARZA (olaparib) is indicated for the adjuvant treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated (g*BRCA*m), human epidermal growth factor receptor 2 (HER2)-negative high risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy. Patients must have confirmation of a germline *BRCA* mutation before LYNPARZA treatment is initiated.

- Marketing authorization with conditions issued based on invasive disease-free survival (iDFS) and distant disease-free survival (DDFS) (see 14 CLINICAL TRIALS). Continued approval for this indication may be contingent upon verification and description of clinical benefit in subsequent analyses.

LYNPARZA is indicated as monotherapy for the treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated (g*BRCA*m), HER2- negative metastatic breast cancer who have previously been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have progressed on or be considered inappropriate for endocrine therapy. Germline *BRCA* mutation must be confirmed before LYNPARZA treatment is initiated.

Ovarian Cancer

LYNPARZA is indicated as monotherapy for the maintenance treatment of adult patients with advanced *BRCA*-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to first-line platinum-based chemotherapy. Patients must have confirmation of *BRCA* mutation (identified by either germline or tumour testing) before LYNPARZA treatment is initiated.

- Marketing authorization without conditions issued for ovarian cancer patients with *BRCA* mutation who are in response to first-line platinum-based chemotherapy was based on results from a randomized, placebo-controlled phase III trial (SOLO1) demonstrating that olaparib tablet is superior to placebo in prolonging progression-free survival (PFS) in patients with *BRCA* mutation, as assessed by investigator using RECIST 1.1 (see 14 CLINICAL TRIALS).

LYNPARZA is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed (PSR) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

- Marketing authorization with conditions issued for ovarian cancer patients with *BRCA* wild type status was based on promising evidence of superior benefit in prolonging PFS of olaparib capsule versus placebo in a phase II trial (Study 19) in patients with *BRCA* wild type status, as assessed by investigator using RECIST 1.0. For comparative bioavailability evidence between the capsule and tablet formulation, see 14 CLINICAL TRIALS, Comparative Bioavailability Studies.

- Marketing authorization without conditions issued for PSR ovarian cancer patients with *BRCA* mutation was based on results from a randomized, placebo-controlled phase III trial

(SOLO2) demonstrating that olaparib tablet is superior to placebo in prolonging PFS in patients with *BRCA* mutation, as assessed by investigator using RECIST 1.1 (see 14 CLINICAL TRIALS).

Platinum-sensitive relapse is defined as disease progression occurring at least 6 months following completion of platinum chemotherapy.

Adenocarcinoma of the Pancreas
LYNPARZA is indicated as monotherapy for the maintenance treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated (g*BRCA*m) metastatic adenocarcinoma of the pancreas whose disease has not progressed on a minimum of 16 weeks of first-line platinum-based chemotherapy. Germline *BRCA* mutation must be confirmed before LYNPARZA treatment is initiated.

Prostate Cancer
LYNPARZA is indicated as monotherapy for the treatment of adult patients with deleterious or suspected deleterious germline and/or somatic *BRCA* or *ATM* mutated metastatic castration-resistant Prostate Cancer (mCRPC) who have progressed following prior treatment with a new hormonal agent. *BRCA* or *ATM* mutations must be confirmed before LYNPARZA treatment is initiated.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (>65 years of age): There are limited clinical data in patients aged 75 years and older.

2 CONTRAINDICATIONS

LYNPARZA (olaparib) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Treatment with LYNPARZA (olaparib) should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.
- Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML) has been reported in patients exposed to LYNPARZA. The majority of the reports have been fatal. (See 7 Carcinogenesis and Mutagenesis and 8.1 Myelodysplastic syndrome/Acute myeloid leukemia).
- Pneumonitis has been reported in a small number of patients receiving LYNPARZA, and

some reports have been fatal. (See 7 Respiratory).

- LYNPARZA could cause fetal harm when administered to a pregnant woman (see 7 Reproductive Health Female and Male Potential).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

LYNPARZA should not be given in combination with other anti-cancer therapy.

Patients should not start treatment with LYNPARZA until they have recovered from hematological toxicity caused by previous anti-cancer therapy (hemoglobin, platelet, and neutrophil levels should be ≤CTCAE grade 1, see 7 Hematologic).

Health Canada has not authorized an indication for pediatric use (see 1.1 Pediatrics).

Grapefruit, star fruit, pomegranate and Seville oranges or their juices which are known to inhibit CYP3A should not be consumed while taking LYNPARZA (see 9 DRUG INTERACTIONS).

4.2 Recommended Dose and Dosage Adjustment

Recommended Total Daily Dose for Tablet

The recommended total daily dose of LYNPARZA tablets is 600 mg, taken as two 150 mg tablets twice daily. The 100 mg tablet is available for dose reduction.

For adjuvant treatment of g*BRCA*m HER2-negative high risk early breast cancer: It is recommended that patients are treated for a total of 1 year, or until disease recurrence or unacceptable toxicity, whichever occurs first. Patients with hormone receptor positive breast cancer should continue concurrent treatment with endocrine therapy as per current clinical practice guidelines.

For treatment of metastatic HER2-negative *gBRCAm* breast cancer: It is recommended that LYNPARZA treatment be continued until progression of the underlying disease or unacceptable toxicity.

For maintenance treatment of patients with *BRCAm* advanced ovarian cancer who are in response to first-line platinum-based chemotherapy:
Patients can continue treatment for 2 years or until disease progression.

Patients with a complete response (no radiological evidence of disease) at 2 years should stop treatment.

Patients with evidence of disease at 2 years, who in the opinion of the treating physician can derive further benefit from continuous treatment, can be treated beyond 2 years.

For maintenance treatment of PSR ovarian cancer: Patients should start treatment with LYNPARZA no later than 8 weeks after completion of their final dose of the platinum-containing

regimen. Patients should have recovered from prior hematologic toxicities prior to starting LYNPARZA therapy (hemoglobin, platelet, and neutrophil levels should be ≤ CTCAE grade 1) (see 8 ADVERSE REACTIONS). It is recommended that LYNPARZA treatment be continued until progression of the underlying disease or unacceptable toxicity.

For maintenance treatment of patients with *gBRCAm* metastatic adenocarcinoma of the pancreas who are in response to first-line platinum-based chemotherapy: It is recommended that treatment be continued until progression of the underlying disease or unacceptable toxicity.

For treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) and mutations in the *BRCA* and *ATM genes*:
It is recommended that LYNPARZA treatment be continued until progression of the underlying disease or unacceptable toxicity. Patients receiving LYNPARZA for mCRPC should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently, or should have had bilateral orchiectomy.

Dose Adjustments

For Adverse Events: Treatment may be interrupted to manage adverse events and dose reduction can be considered. The recommended reduced total daily dose of LYNPARZA (olaparib tablets) is 500 mg. If a further dose reduction is required, the recommended reduced total daily dose of LYNPARZA (olaparib tablets) is 400 mg (see 8 ADVERSE REACTIONS).

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 reduced total daily dose of LYNPARZA (olaparib tablets) is 200 mg. If a moderate CYP3A inhibitor must be co-administered, the recommended reduced total daily dose of LYNPARZA (olaparib tablets) is 300 mg (see 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS).

For Patients with Renal Insufficiency: For patients with moderate renal impairment (creatinine clearance 31 - 50 ml/min) the recommended reduced total daily dose of LYNPARZA (olaparib tablets) is 400 mg. LYNPARZA is not recommended for patients with severe renal impairment or end-stage renal disease (creatinine clearance ≤30 ml/min), as safety and pharmacokinetics have not been studied in these patients. LYNPARZA can be administered to patients with mild renal impairment (creatinine clearance 51 - 80 ml/min) with no dose adjustment (see 10.3 Pharmacokinetics).

Reduced Total Daily Doses for Tablet:
Adult Dose 500 mg: take one 150 mg tablet and one 100 mg tablet twice a day.

Adult Dose 400 mg: take two 100 mg tablets twice a day.

Adult Dose 300 mg: take one 150 mg tablet twice a day.

Adult Dose 200 mg: take one 100 mg tablet twice a day.

Pediatrics (<18 years of age): LYNPARZA is not indicated for use in pediatric patients, as safety and efficacy of LYNPARZA in children and adolescents have not been established.

Geriatrics (>65 years): No adjustment in starting dose is required for elderly patients. There are limited clinical data in patients aged 75 years and older (see 10.3 Pharmacokinetics).

Hepatic Insufficiency: LYNPARZA (olaparib tablets) can be administered to patients with mild or moderate hepatic impairment (Child-Pugh classification A or B) with no dose adjustment (see 10.3 Pharmacokinetics). 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.

4.4 Administration

LYNPARZA is for oral use.

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

4.5 Missed Dose

If a patient misses a dose of LYNPARZA, they should take their next normal dose at its scheduled time. The patient should not take a double dose to make up for forgotten tablets.

5 OVERDOSAGE

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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral Use	Tablet 100 mg, 150 mg	Colloidal silicon dioxide, copovidone, hypromellose, iron oxide black (150 mg tablet only), iron oxide yellow, macrogol 400, mannitol, sodium stearyl fumarate, titanium dioxide.

Dosage Form Description
LYNPARZA (olaparib) 150 mg tablet is a green to green/grey film-coated, oval, bi-convex tablet debossed with “OP 150” on one side and plain on the reverse.

LYNPARZA (olaparib) 100 mg tablet is a yellow to dark yellow film-coated, oval, bi-convex tablet debossed with “OP 100” on one side and plain on the reverse.

Packaging
LYNPARZA is available in 60 tablets or 120 tablets per bottle for each strength in high-density polyethylene (HDPE) plastic bottles, containing desiccant, with a child-resistant closure.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Interactions with other medicinal products

Co-administration of LYNPARZA (olaparib) with strong or moderate CYP3A inhibitors is not recommended (see 9 DRUG INTERACTIONS). If a strong or moderate CYP3A inhibitor must be co-administered, the dose of LYNPARZA should be reduced (see 4.2 Recommended Dose and Dosage Adjustment).

Co-administration of LYNPARZA with strong or moderate CYP3A inducers is not recommended. In the event that a patient already receiving LYNPARZA requires treatment with a strong or moderate CYP3A inducer, the prescriber should be aware that the efficacy of LYNPARZA may be substantially reduced (see 9 DRUG INTERACTIONS).

Carcinogenesis and Mutagenesis

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML) was reported with an incidence of approximately 1% in patients treated in clinical trials with LYNPARZA monotherapy, including long-term survival follow up. In a Phase III clinical trial (SOLO2), a substantially higher incidence was reported in patients with *BRCAm* platinum-sensitive relapsed ovarian cancer who had received at least two prior lines of platinum chemotherapy and were followed up for 5 years (see 8.1 Myelodysplastic syndrome/Acute myeloid leukemia). The majority of events had a fatal outcome. The duration of therapy with LYNPARZA in patients who developed MDS/AML varied from < 6 months to > 4 years. All patients had potential contributing factors for the development of MDS/AML, having received previous chemotherapy with platinum agents. Many had also received other DNA damaging treatments. The majority of reports were in g*BRCA*m carriers and some of the patients had a history of more than one primary malignancy or of bone marrow dysplasia. If MDS and/or AML or other clonal blood disorders are confirmed while on treatment with LYNPARZA, it is recommended that LYNPARZA should be discontinued and the patient be treated appropriately.

Cardiovascular

Venous Thromboembolic Events

Venous thromboembolic events (VTE), including pulmonary embolism, have occurred in patients treated with LYNPARZA and had no consistent clinical pattern. A higher incidence was observed in patients with metastatic castration-resistant prostate cancer who, also received androgen deprivation therapy, compared with other approved indications. Monitor patients for clinical signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate.

Driving and Operating Machinery

Asthenia, fatigue and dizziness have been reported in patients receiving LYNPARZA treatment. Patients experiencing these symptoms should use caution when driving or operating machines.

Hematologic

Hematological toxicity has been reported in patients treated with LYNPARZA, including clinical diagnoses and/or laboratory findings of generally mild or moderate (Common Terminology Criteria for Adverse Events [CTCAE] grade 1 or 2) anemia, neutropenia, thrombocytopenia and lymphopenia, however, there were reports of CTCAE grade 3 and higher events. Anemia was the most common CTCAE grade ≥3 adverse reaction reported in clinical studies. Patients

should not start treatment with LYNPARZA until they have recovered from hematological toxicity caused by previous anti-cancer therapy (hemoglobin, 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.

If a patient develops severe hematological toxicity or blood transfusion dependence, treatment with LYNPARZA should be interrupted and appropriate hematological 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.

Monitoring and Laboratory Tests
Genetic Testing

BRCA and *ATM* mutation status should be determined by an experienced laboratory using a validated test method.

For adjuvant treatment of gBRCAm HER2-negative high risk early breast cancer: Patients must have confirmation of a deleterious or suspected deleterious germline *BRCA* mutation before LYNPARZA treatment is initiated.

For treatment of metastatic HER2-negative gBRCAm breast cancer: Patients must have confirmation of a deleterious or suspected deleterious *BRCA* mutation (identified by germline testing) before LYNPARZA treatment is initiated.

For maintenance treatment of patients with BRCAm advanced ovarian cancer who are in response to first-line platinum-based chemotherapy: Patients must have confirmation of *BRCA* mutation (identified by either germline or tumour testing) before LYNPARZA treatment is initiated.

For maintenance treatment of patients with gBRCAm metastatic adenocarcinoma of the pancreas who are in response to first-line platinum-based chemotherapy: Patients must have confirmation of a deleterious or suspected deleterious *BRCA* mutation (identified by germline testing) before LYNPARZA treatment is initiated.

For treatment of BRCA or ATM-gene mutated metastatic castration-resistant prostate cancer (mCRPC):
Patients must have confirmation of a deleterious or suspected deleterious germline and/or somatic *BRCA* or *ATM* gene mutation before LYNPARZA treatment is initiated.

Hematologic Testing
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 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data).

If a patient develops severe hematological toxicity or blood transfusion dependence, treatment with LYNPARZA should be interrupted and appropriate hematological 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. If MDS/AML is confirmed, discontinue LYNPARZA and treat appropriately (See 7 Hematologic).

Pregnancy Testing

A pregnancy test should be performed on all women of childbearing potential prior to treatment, and pregnancy tests should be performed at regular intervals during treatment and for 6 months after receiving the last dose of LYNPARZA (see 7.1 Special Populations).

Reproductive Health Female and Male Potential

Reproduction

Based on its mechanism of action (PARP inhibition), LYNPARZA could cause fetal harm when administered to a pregnant woman. Studies in rats have shown that olaparib caused embryofetal toxicity that included increases in post implantation loss and teratogenic effects at exposures below those of patients receiving LYNPARZA at the recommended human dose of 300 mg twice daily (see 7.1 Special Populations and 16 NON-CLINICAL TOXICOLOGY).

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.

Since it cannot be excluded that LYNPARZA may reduce exposure to substrates of CYP2C9 through enzyme induction, the efficacy of some hormonal contraceptives may be reduced if co-administered with LYNPARZA. Therefore, an additional non-hormonal contraceptive method should be considered during treatment (see 9.4 Drug-Drug Interactions). For women with hormone dependent cancer, two non-hormonal contraceptive methods should be considered.

Male patients should be advised that they must use effective contraception during LYNPARZA treatment 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. Male patients should not donate sperm during therapy and for 3 months after receiving the last dose of LYNPARZA (see 7.1.1 Pregnant Women).

Respiratory

Pneumonitis (grade 3 or higher) has been reported in 0.9% of patients treated with LYNPARZA monotherapy in clinical studies. The reports of pneumonitis had no consistent clinical pattern and were confounded by a number of pre-disposing factors (cancer and/or metastases in lungs, underlying pulmonary disease, smoking history, and/or previous chemotherapy and radiotherapy). When LYNPARZA was used in clinical studies in combination with other therapies, there have been events with a fatal outcome. If patients present with new or worsening respiratory symptoms such as dyspnea, cough and fever, or a radiological chest abnormality occurs, LYNPARZA treatment should be interrupted and prompt investigation initiated. If pneumonitis is confirmed, LYNPARZA treatment should be discontinued and the patient treated appropriately.

7.1 Special Populations

7.1.1 Pregnant Women

There are no clinical data regarding the use of LYNPARZA in pregnant women or the impact on fertility. LYNPARZA should not be used during pregnancy due to the potential teratogenic, genotoxic and embryofetal effects (see 16 NON-CLINICAL TOXICOLOGY). Female partners of male patients taking LYNPARZA should also avoid pregnancy.

If a female patient or a female partner of a male patient receiving LYNPARZA becomes pregnant, she should be apprised of the potential hazard to a fetus and the potential risk for loss of the pregnancy.

Contraception and pregnancy testing

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. A pregnancy test should be performed on all women of childbearing potential prior to treatment, and pregnancy tests should be performed at regular intervals during treatment and for 6 months after receiving the last dose of LYNPARZA.

Since it cannot be excluded that LYNPARZA may reduce exposure to substrates of CYP2C9 through enzyme induction, the efficacy of some hormonal contraceptives may be reduced if co-administered with LYNPARZA. Therefore, an additional non-hormonal contraceptive method should be considered during treatment (see 9.4 Drug-Drug Interactions). For women with hormone dependent cancer, two non-hormonal contraceptive methods should be considered.

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.

7.1.2 Breast-feeding

There are no data on the use of LYNPARZA in breast-feeding women. The excretion of olaparib in milk has not been studied in animals or in breast-feeding mothers. A risk to the newborn breast-feeding child cannot be excluded. Breast-feeding mothers are advised not to breast-feed during treatment with LYNPARZA and for one month after the last dose of LYNPARZA.

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (>65 years of age): No adjustment in starting dose is required for elderly patients. There are limited clinical data in patients aged 75 years and older.

7.1.5 Hepatic insufficiency

LYNPARZA (olaparib tablets) can be administered to patients with mild or moderate hepatic impairment (Child-Pugh classification A or B) with no dose adjustment. 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 (see 4 DOSAGE AND ADMINISTRATION and 10.3 Pharmacokinetics).

7.1.6 Renal insufficiency

For patients with moderate renal impairment (creatinine clearance 31 - 50 ml/min) the

recommended reduced total daily dose of LYNPARZA (olaparib tablets) is 400 mg (two 100 mg tablets twice daily). LYNPARZA is not recommended for patients with severe renal impairment or end-stage renal disease (creatinine clearance ≤30 ml/min), as safety and pharmacokinetics have not been studied in these patients. LYNPARZA can be administered to patients with mild renal impairment (creatinine clearance 51 - 80 ml/min) with no dose adjustment (see 4 DOSAGE AND ADMINISTRATION and 10.3 Pharmacokinetics).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of LYNPARZA (olaparib) was evaluated in a pooled safety dataset of 4098 patients with solid tumours treated with LYNPARZA monotherapy (capsule and tablet formulation) in clinical trials at the recommended dose. The overall safety profile of the two formulations are similar (See Table 2).

The most commonly reported adverse reactions (in ≥20% of patients) from LYNPARZA monotherapy pooled studies (n=4098) were nausea, fatigue (including asthenia), anemia, vomiting, diarrhea and decreased appetite. These reactions were generally CTCAE grade 1 or 2, intermittent in nature and managed by standard supportive treatments or LYNPARZA dose modification. The most commonly reported adverse reactions (in ≥1% of patients) with CTCAE grade ≥3 severity were anemia, neutropenia, fatigue (including asthenia), leukopenia, thrombocytopenia, lymphopenia, vomiting, nausea, diarrhea and dyspnea.

Nausea was generally reported very early, with first onset within the first month of LYNPARZA treatment in the majority of affected patients. Vomiting was reported early, with first onset within the first two months of LYNPARZA treatment in the majority of affected patients. Most of these events improved over time while continuing LYNPARZA without the need for medical intervention.

The most commonly reported serious adverse event (SAE) (in ≥1% of patients) was anemia (4.1%).

The overall frequency of adverse events leading to discontinuation of LYNPARZA was 5.9%.The frequencies of adverse reactions (in >0.2% of patients) leading to discontinuation of LYNPARZA treatment were anemia (1.7%), nausea (1.0%), fatigue (including asthenia) (0.9%), thrombocytopenia (0.7%), neutropenia (0.6%), vomiting (0.5 %), leukopenia (0.3%) and MDS/AML (0.3%).

The following adverse reactions have been identified in completed clinical trials with patients receiving LYNPARZA monotherapy where patient exposure is known. Adverse Drug Reactions are organized by MedDRA System Organ Class (SOC) and then by MedDRA preferred term in Table 2. Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); and very rare (<1/10,000) including isolated reports.

Table 2 Adverse Drug Reactions reported in Clinical Trials

MedDRA SOC	MedDRA Term	CIOMS descriptor/ Overall Frequency (All CTCAE grades)	Frequency of CTCAE grade 3 and above
Blood and lymphatic system disorders	Anemia[a]	Very common	Very common
	Neutropenia[a]	Very common	Common
	Leukopenia[a]	Very common	Common
	Thrombocytopenia[a]	Common	Common
	Lymphopenia[a]	Common	Common
Immune system disorders	Hypersensitivity[a]	Uncommon	Rare
Metabolism and nutrition disorders	Decreased appetite	Very common	Uncommon
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Myelodysplastic syndrome/Acute myeloid leukemia[a]	Uncommon	Uncommon
Nervous system disorders	Dizziness	Very common	Uncommon
	Headache	Very common	Uncommon
	Dysgeusia[a]	Very common	-
Respiratory, thoracic and mediastinal disorders	Dyspnea[a]	Very common	Common
	Cough[a]	Very common	Uncommon
Gastrointestinal disorders	Vomiting	Very common	Common
	Diarrhea	Very common	UnCommon
	Nausea	Very common	Common
	Dyspepsia	Very common	Rare
	Stomatitis[a]	Common	Uncommon
	Upper abdominal pain	Common	Rare
Skin and subcutaneous tissue disorders	Rash[a]	Common	Uncommon
	Dermatitis[a]	Uncommon	Rare
	Erythema nodosum	Rare	-
General disorders	Fatigue (including asthenia)	Very common	Common
Investigations	Blood creatinine increased	Common	Rare

MedDRA SOC	MedDRA Term	CIOMS descriptor/ Overall Frequency (All CTCAE grades)	Frequency of CTCAE grade 3 and above
	Mean cell volume increased	Uncommon	-
Vascular disorders	Thromboembolism (venous)	Common	Common

a Anemia includes preferred terms (PTs) of anemia, anemia macrocytic, erythropenia, hematocrit decreased, hemoglobin decreased, normochromic anemia and red blood cell count decreased.
Cough includes PTs of cough and productive cough.
Dermatitis includes PTs of dermatitis and dermatitis allergic.
Dysgeusia includes PTs of dysgeusia and taste disorder.
Dyspnea includes PTs of dyspnea and dyspnea exertional.
Hypersensitivity includes PTs of drug hypersensitivity and hypersensitivity.
Leukopenia includes PTs of leukopenia and white blood cell count decreased.
Lymphopenia includes PTs of lymphocyte count decreased and lymphopenia
MDS/AML includes PTs of acute myeloid leukemia, myelodysplastic syndrome and myeloid leukemia.
Neutropenia includes PTs of febrile neutropenia, neutropenia, neutropenic infection, neutropenic sepsis and neutrophil count decreased.
Stomatitis includes PTs of aphthous ulcer, mouth ulceration and stomatitis.
Thrombocytopenia includes PTs of platelet count decreased and thrombocytopenia.
Thromboembolism (venous) includes PTs of embolism, pulmonary embolism, thrombosis, deep vein thrombosis and venous thrombosis.
Rash includes PTs of erythema, exfoliative rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular and rash pruritic.

MedDRA version 24; CTCAE Common Terminology Criteria for Adverse Events

Hematological toxicity

Anemia was the most common CTCAE grade ≥3 adverse reaction reported in clinical studies with first onset generally reported in the first 3 months of treatment. An exposure-response relationship between LYNPARZA (olaparib) and decreases in hemoglobin has been demonstrated (See 7 Hematologic). Other hematological toxicities were generally CTCAE grade 1 or 2, however, there were reports of CTCAE grade 3 and higher events.

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

Myelodysplastic syndrome/Acute myeloid leukemia (MDS/AML)

In clinical studies, across all indications and formulations, MDS/AML occurred uncommonly in patients on treatment and during the 30-day safety follow up, and <1.5% at any time after starting LYNPARZA, including cases actively solicited during the long term follow up for overall survival.

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 LYNPARZA treatment ≥ 2 years in 45% of patients), the incidence of MDS/AML was 8.2% in patients receiving LYNPARZA and 4.0% in patients receiving placebo at a follow-up of 5 years. In the LYNPARZA arm, 9 out of 16 MDS/AML cases occurred after discontinuation of LYNPARZA during the survival follow-up. The incidence of MDS/AML was observed in the context of extended overall survival in the LYNPARZA arm and late onset of MDS/AML (See 8.2 Clinical Trial Adverse Reactions, SOLO2).

The risk of MDS/AML remains < 1.5% at 5 year follow up in the maintenance setting when

LYNPARZA is given to patients who are in response to first-line platinum chemotherapy for a duration of 2 years (SOLO 1) (See 8.2 Clinical Trial Adverse Reactions, SOLO1 and 7 Carcinogenesis and Mutagenesis).

Other laboratory findings
Data from a double-blind placebo-controlled study showed median increase in blood creatinine up to 23% from baseline remaining consistent over time and returning to baseline after treatment discontinuation, with no apparent clinical sequelae. Ninety percent of patients had creatinine values of CTCAE grade 0 at baseline and 10% were CTCAE grade 1 at baseline.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful for identifying and approximating rates of adverse drug reactions in real-world use.

Adjuvant Treatment of g*BRCA*m HER2-negative High Risk Early Breast Cancer (OlympiA)

The safety of LYNPARZA as monotherapy for the adjuvant treatment of patients with *gBRCAm* HER2-negative high risk early breast cancer was investigated in OlympiA. This study was a Phase III, randomized, double-blind, placebo-controlled, multicentre study in which a total of 1815 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, whichever occurred first (see 14 CLINICAL TRIALS). The median duration of study treatment was 341 days in patients who received LYNPARZA and 358 days in patients who received placebo.

Table 3 summarizes adverse drug reactions associated with LYNPARZA treatment in the OlympiA study.

Table 3 Adverse Drug Reactions Reported in OlympiA (Safety Analysis Set)

	LYNPARZA 300 mg bid (N=911)		Placebo (N=904)	
System organ class / MedDRA preferred term	All CTCAE Grades n (%)	CTCAE Grades ≥3 n (%)	All CTCAE Grades n (%)	CTCAE Grades ≥3 n (%)
Blood and lymphatic system disorders				
Anemia [a]	217 (23.8)	79 (8.7)	35 (3.9)	3 (0.3)
Neutropenia [a]	150 (16.5)	48 (5.3)	60 (6.6)	7 (0.8)
Thrombocytopenia	38 (4.2)	2 (0.2)	12 (1.3)	1 (0.1)
Lymphopenia [a]	64 (7.0)	12 (1.3)	15 (1.7)	0
Leukopenia [a]	154 (16.9)	27 (3.0)	54 (6.0)	3 (0.3)
Gastrointestinal disorders				
Nausea	519 (57.0)	7 (0.8)	212 (23.5)	0

Table 3 Adverse Drug Reactions Reported in OlympiA (Safety Analysis Set)				
	LYNPARZA 300 mg bid (N=911)		Placebo (N=904)	
System organ class / MedDRA preferred term	All CTCAE Grades n (%)	CTCAE Grades ≥3 n (%)	All CTCAE Grades n (%)	CTCAE Grades ≥3 n (%)
Vomiting	206 (22.6)	6 (0.7)	74 (8.2)	0
Diarrhea	160 (17.6)	3 (0.3)	124 (13.7)	3 (0.3)
Dyspepsia	55 (6.0)	0	37 (4.1)	0
Abdominal pain upper	45 (4.9)	0	35 (3.9)	1 (0.1)
Stomatitis [a]	93 (10.2)	1 (0.1)	41 (4.5)	0
General disorders and administration site conditions				
Fatigue (including asthenia) [a]	386 (42.4)	16 (1.8)	257 (28.4)	6 (0.6)
Immune system disorders				
Hypersensitivity [a]	10 (1.1)	0	5 (0.6)	1 (0.1)
Investigations				
Increase in creatinine	18 (2.0)	0	3 (0.3)	0
Increase in mean corpuscular volume	2 (0.2)	0	0	0
Metabolism and nutrition disorders				
Decreased appetite	119 (13.1)	2 (0.2)	53 (5.9)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)				
MDS/AML [a,b]	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)
Nervous system disorders				
Headache	179 (19.6)	2 (0.2)	152 (16.8)	1 (0.1)
Dysgeusia [a]	110 (12.1)	0	43 (4.8)	0
Dizziness	104 (11.4)	1 (0.1)	66 (7.3)	1 (0.1)
Respiratory, thoracic and mediastinal disorders				
Cough [a]	84 (9.2)	0	76 (8.4)	0
Dyspnoea	38 (4.2)	2 (0.2)	32 (3.5)	0
Skin and subcutaneous tissue disorders				
Rash [a]	44 (4.8)	1 (0.1)	42 (4.6)	0
Dermatitis [a]	5 (0.5)	1 (0.1)	5 (0.6)	0

a Represents a group term

b MDS/AML events are reported for AEs with an onset date between the date of first dose of continuous treatment and 30 days following the date of last dose of continuous treatment.

CTCAE = Common Terminology Criteria for Adverse Events, version 4.03

Dose interruptions due to AEs of any grade occurred in 31.2 % of patients receiving LYNPARZA

and 11.0% of patients receiving placebo. Dose reduction due to AEs of any grade occurred in 23.4% of patients receiving LYNPARZA and 3.7% of patients receiving placebo.

The most frequent adverse reactions (≥1%) leading to dose interruption of LYNPARZA were anemia (11.4%), neutropenia (5.9%), nausea (5.4%), leukopenia (3.6%), fatigue (2.9%), vomiting (2.9%) and diarrhea (1%). The most frequent adverse reactions (≥1%) leading to dose reduction of LYNPARZA were anemia (8.5%), nausea (4.7%), neutropenia (4.5%), fatigue (3.3%), leukopenia (1.9%), and vomiting (1.6%).

Discontinuation occurred in 10.6% of patients receiving LYNPARZA and 4.6% of patients receiving placebo due to adverse events. The adverse reactions (≥1%) that most frequently led to discontinuation of LYNPARZA were nausea (2.1%), anemia (1.8%), and fatigue (1.5%).

The most commonly reported SAE (≥1%) in the LYNPARZA group vs. placebo group was anemia (1.6% vs 0.1%).

Treatment of g*BRCA*m HER2-Negative Metastatic Breast Cancer (OlympiAD)

The safety of LYNPARZA (olaparib) tablets as monotherapy was evaluated in g*BRCA*m patients with HER2-negative metastatic breast cancer in the OlympiAD study. This study was a Phase III, randomized, active-controlled, open-label, multicentre study in which 296 patients received either LYNPARZA 300 mg twice daily (N=205) or a chemotherapy (capecitabine, eribulin, or vinorelbine) of the physician's choice (N=91) until disease progression or unacceptable toxicity (see 14 CLINICAL TRIALS). The median duration of study treatment was 8.2 months in patients who received LYNPARZA and 3.4 months in patients who received chemotherapy.

Table 4 summarizes adverse drug reactions associated with LYNPARZA treatment in the OlympiAD study with frequencies reported regardless of causality.

Table 4 Adverse Drug Reactions Reported in OlympiAD (Safety Analysis Set)

System Organ Class/Preferred Term	LYNPARZA Tablets 300 mg bid N=205		Physician's Choice of Chemotherapy[a] N=91	
	All CTCAE Grades n (%)	CTCAE Grades ≥3 n (%)	All CTCAE Grades n (%)	CTCAE Grades ≥3 n (%)
Blood and Lymphatic System Disorders				
Anemia[b]	82 (40.0)	33 (16.1)	24 (26.4)	4 (4.4)
Neutropenia[b]	56 (27.3)	19 (9.3)	45 (49.5)	24 (26.4)
Leukopenia[b]	52 (25.4)	11 (5.4)	28 (30.8)	12 (13.2)
Thrombocytopenia[b]	23 (11.2)	8 (3.9)	11 (12.1)	2 (2.2)
Lymphopenia[b]	17 (8.3)	4 (2.0)	2 (2.2)	1 (1.1)
Gastrointestinal Disorders				
Nausea	119 (58.0)	0	32 (35.2)	1 (1.1)
Vomiting	61 (29.8)	0	14 (15.4)	1 (1.1)
Diarrhea	42 (20.5)	1 (0.5)	20 (22.0)	0

Table 4 Adverse Drug Reactions Reported in OlympiAD (Safety Analysis Set)

System Organ Class/Preferred Term	LYNPARZA Tablets 300 mg bid N=205		Physician's Choice of Chemotherapy[a] N=91	
	All CTCAE Grades n (%)	CTCAE Grades ≥3 n (%)	All CTCAE Grades n (%)	CTCAE Grades ≥3 n (%)
Dyspepsia	16 (7.8)	0	4 (4.4)	0
Upper abdominal pain	15 (7.3)	0	5 (5.5)	1 (1.1)
Stomatitis	15 (7.3)	0	10 (11.0)	0
Gastroesophageal reflux disease	6 (2.9)	0	0	0
General Disorders and Administration Site Conditions				
Fatigue (including asthenia)	75 (36.6)	8 (3.9)	33 (36.3)	1 (1.1)
Pyrexia	29 (14.1)	0	16 (17.6)	0
Investigations				
Increase in blood creatinine	6 (2.9)	0	0	0
Infections and infestations				
Cystitis	3 (1.5)	0	2 (2.2)	0
Metabolism and Nutrition Disorders				
Decreased appetite	33 (16.1)	0	11 (12.1)	0
Nervous System Disorders				
Headache	41 (20.0)	2 (1.0)	14 (15.4)	2 (2.2)
Dysgeusia	19 (9.3)	0	6 (6.6)	0
Dizziness	16 (7.8)	0	7 (7.7)	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough[b]	37 (18.0)	0	6 (6.6)	0
Pulmonary embolism	2 (1.0)	2 (1.0)	1 (1.1)	0
Skin and Subcutaneous Tissue Disorders				
Rash[b]	10 (4.9)	0	5 (5.5)	0
Dermatitis[b]	1 (0.5)	0	0	0
Erythema nodosum	1 (0.5)	0	0	0
Vascular Disorders				
Embolism	0	0	1 (1.1)	1 (1.1)
Venous thrombosis	0	0	1 (1.1)	1 (1.1)

a Physician's choice of chemotherapy consists of either capecitabine (2500 mg/m^2 oral daily, divided in 2 doses for 14 days, repeated every 21 days), eribulin (1.4 mg/m^2 IV Day 1 and Day 8, repeated every 21 days) or vinorelbine (30 mg/m^2 IV Day 1 and Day 8, repeated every 21 days).

b Represents a grouped term.

MedDRA version 19.1; CTCAE Common Terminology Criteria for Adverse Events

Dose modifications (dose reduced or dose interrupted) due to an AE of any grade occurred in 38.0% of patients receiving LYNPARZA and 41.8% of those receiving chemotherapy. The most common AEs (reported in ≥2% patients in the LYNPARZA arm) leading to dose modifications in the LYNPARZA arm vs chemotherapy arm respectively, were anemia (17.6% vs 3.3%), neutropenia (8.3% vs 16.5%), white blood count decreased (4.4% vs 4.4%), leukopenia (4.4% vs 3.3%), neutrophil count decreased (3.4% vs 7.7%), fatigue (2.9% vs 2.2%), nausea (2.9% vs 2.2%), vomiting (2.4% vs 2.2%), platelet count decreased (2.4% vs 1.1%), alanine aminotransferase increased (2.4% vs 2.2%), aspartate aminotransferase increased (2.0% vs 2.2%), pyrexia (2.0% vs 1.1%), and thrombocytopenia (2.0% vs 1.1%).

The most common serious adverse reaction reported was anemia (2.4% olaparib vs 2.2% chemotherapy). The following serious ADRs were reported in one patient each: dermatitis allergic, neutrophil count decreased and platelet count decreased.

The proportion of patients who permanently discontinued LYNPARZA due to adverse events was 4.9% in the LYNPARZA arm compared with 7.7% in the chemotherapy arm. Anemia and platelet count decrease were the only adverse reactions leading to discontinuation of LYNPARZA in more than one patient (LYNPARZA: 4/205 and 2/205, respectively vs chemotherapy: 2/91 and 0/91, respectively).

Maintenance Treatment of Advanced Ovarian Cancer (SOLO1)

The SOLO1 study is a randomized, phase III, double-blind, placebo-controlled trial of LYNPARZA 300 mg twice daily (2 x 150 mg tablets) maintenance monotherapy in patients with advanced *BRCA*-mutated ovarian, fallopian tube or primary peritoneal cancer who were in response to first-line platinum-based chemotherapy (n=390 [n=260 on LYNPARZA and n=130 on placebo]). The total median exposure to study treatment was 24.6 months in the LYNPARZA group and 13.9 months in the placebo group. Table 5 summarizes adverse drug reactions associated with LYNPARZA tablets with frequencies reported regardless of causality.

Table 5 Adverse Drug Reactions Reported in SOLO1 (Safety Analysis Set)

	LYNPARZA Tablets 300 mg bid N = 260		Placebo N = 130	
System Organ Class/ Preferred Term	**All Grades n (%)**	**CTCAE ≥Grade 3 n (%)**	**All Grades n (%)**	**CTCAE ≥Grade 3 n (%)**
Blood and Lymphatic System Disorders				
Anemia[a]	101 (38.8)	56 (21.5)	13 (10.0)	2 (1.5)
Neutropenia[a]	60 (23.1)	22 (8.5)	15 (11.5)	6 (4.6)
Thrombocytopenia[a]	29 (11.2)	2 (0.8)	5 (3.8)	2 (1.5)
Lymphopenia[a]	16 (6.2)	4 (1.5)	2 (1.5)	1 (0.8)
Leukopenia[a]	33 (12.7)	8 (3.1)	10 (7.7)	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough[a]	46 (17.7)	0	28 (21.5)	0
Dyspnea[a]	40 (15.4)	0	8 (6.2)	0

Table 5 Adverse Drug Reactions Reported in SOLO1 (Safety Analysis Set)

System Organ Class/ Preferred Term	LYNPARZA Tablets 300 mg bid N = 260		Placebo N = 130	
	All Grades n (%)	CTCAE ≥Grade 3 n (%)	All Grades n (%)	CTCAE ≥Grade 3 n (%)
Pulmonary embolism	4 (1.5)	2 (0.8)	1 (0.8)	0
Gastrointestinal Disorders				
Nausea	201 (77.3)	2 (0.8)	49 (37.7)	0
Vomiting	104 (40.0)	1 (0.4)	19 (14.6)	1 (0.8)
Diarrhea	89 (34.2)	8 (3.1)	32 (24.6)	0
Constipation	72 (27.7)	0	25 (19.2)	0
Dyspepsia	43 (16.5)	0	16 (12.3)	0
Upper Abdominal Pain	46 (17.7)	0	17 (13.1)	0
Stomatitis[a]	28 (10.8)	0	3 (2.3)	0
General Disorders and Administration Site Conditions				
Fatigue (including asthenia)	165 (63.5)	10 (3.8)	54 (41.5)	2 (1.5)
Immune System Disorders				
Hypersensitivity[a]	5 (1.9)	0	1 (0.8)	0
Infections and Infestations				
Urinary tract infection	31 (11.9)	2 (0.8)	8 (6.2)	0
Investigations				
Increase in blood creatinine	21 (8.1)	0	2 (1.5)	0
Metabolism and Nutrition Disorders				
Decreased appetite	51 (19.6)	0	13 (10.0)	0
Nervous System Disorders				
Headache	59 (22.7)	1 (0.4)	31 (23.8)	3 (2.3)
Dysgeusia	68 (26.2)	0	5 (3.8)	0
Dizziness	51 (19.6)	0	20 (15.4)	1 (0.8)
Skin and Subcutaneous Tissue Disorders				
Rash[a]	27 (10.4)	0	14 (10.8)	0
Dermatitis[a]	2 (0.8)	0	0	0
Vascular Disorders				

Table 5 Adverse Drug Reactions Reported in SOLO1 (Safety Analysis Set)

System Organ Class/ Preferred Term	LYNPARZA Tablets 300 mg bid N = 260		Placebo N = 130	
	All Grades n (%)	CTCAE ≥Grade 3 n (%)	All Grades n (%)	CTCAE ≥Grade 3 n (%)
Thrombosis	2 (0.8)	0	0	0
Deep vein thrombosis	1 (0.4)	0	0	0
Embolism	1 (0.4)	0	0	0
Venous thrombosis	0	0	1 (0.8)	0

a Represents a grouped term.
CTCAE Common Terminology Criteria for Adverse Events

An analysis of time to onset for AEs has shown that first occurrence of most AEs/SAEs is within the first 3 months of exposure to LYNPARZA.

Dose interruptions due to adverse reactions of any grade occurred in 51.9% of patients receiving LYNPARZA and 16.9% of those receiving placebo; dose reductions due to an adverse reactions occurred in 28.5% of LYNPARZA patients and 3.1% of placebo patients. The most frequent adverse reactions leading to dose interruption and/or reduction of LYNPARZA were anemia (23.1%), nausea (14.2%), and vomiting (9.6%).

Discontinuation occurred in 11.5% of LYNPARZA patients and 2.3% in placebo patients due to adverse events. Anemia, fatigue and nausea were the only adverse reactions leading to discontinuation of LYNPARZA in more than two patients.

The most commonly reported SAE (≥1%) in the LYNPARZA arm vs. placebo arm was anemia (6.5% vs. 0%).

Overall, based on the long-term collection of data beyond treatment discontinuation and follow-up of 5 years in the SOLO1 study, there were 3 cases of MDS/AML (1.2%) in patients randomized to LYNPARZA and no cases were reported in patients randomized to placebo.

Maintenance Treatment of PSR Ovarian Cancer (SOLO2)

The SOLO2 study is a randomized, phase III, double-blind, placebo-controlled trial of LYNPARZA 300 mg twice daily (2 x 150 mg tablets) maintenance monotherapy in patients with platinum-sensitive relapsed (PSR) ovarian, fallopian tube or primary peritoneal cancer (n=295 [n=196 on LYNPARZA and n=99 on placebo]). The total median exposure to study treatment was 19.4 months in the LYNPARZA group and 5.6 months in the placebo group. Table 6 summarizes adverse drug reactions associated with LYNPARZA tablets with frequencies reported regardless of causality.

Table 6 Adverse Drug Reactions Reported in SOLO2 (Safety Analysis Set)

System Organ Class/ Preferred Term	LYNPARZA Tablets 300 mg bid N = 195		Placebo N = 99	
	All Grades n (%)	CTCAE ≥Grade 3 n (%)	All Grades n (%)	CTCAE ≥Grade 3 n (%)
Blood and Lymphatic System Disorders				
Anemia[a]	89 (45.6)	41 (21.0)	10 (10.1)	2 (2.0)
Neutropenia[a]	46 (23.6)	14 (7.2)	6 (6.1)	4 (4.0)
Leukopenia[a]	34 (17.4)	7 (3.6)	2 (2.0)	0
Thrombocytopenia[a]	32 (16.4)	4 (2.1)	4 (4.0)	1 (1.0)
Lymphopenia[a]	12 (6.2)	5 (2.6)	0	0
Gastrointestinal Disorders				
Nausea	148 (75.9)	6 (3.1)	35 (35.4)	0
Vomiting	78 (40.0)	5 (2.6)	20 (20.2)	1 (1.0)
Diarrhea	67 (34.4)	2 (1.0)	20 (20.2)	0
Dyspepsia	29 (14.9)	0	9 (9.1)	0
Upper Abdominal Pain	24 (12.3)	1 (0.5)	13 (13.1)	0
Stomatitis[a]	23 (11.8)	3 (1.5)	7 (7.1)	0
General Disorders and Administration Site Conditions				
Fatigue (including asthenia)[a]	130 (66.7)	11 (5.6)	39 (39.4)	2 (2.0)
Immune System Disorders				
Hypersensitivity[a]	4 (2.1)	0	0	0
Investigations				
Increase in blood creatinine	21 (10.8)	0	1 (1.0)	0
Mean cell volume increased	1 (0.5)	0	0	0
Metabolism and Nutrition Disorders				
Decreased appetite	44 (22.6)	1 (0.5)	11 (11.1)	0
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)				
MDS/AML[a]	7 (3.6)	7 (3.6)	0	0
Nervous System Disorders				
Dysgeusia[a]	52 (26.7)	0	7 (7.1)	0
Headache	50 (25.6)	1 (0.5)	14 (14.1)	0

Table 6 Adverse Drug Reactions Reported in SOLO2 (Safety Analysis Set)

System Organ Class/ Preferred Term	LYNPARZA Tablets 300 mg bid N = 195		Placebo N = 99	
	All Grades n (%)	CTCAE ≥Grade 3 n (%)	All Grades n (%)	CTCAE ≥Grade 3 n (%)
Dizziness	34 (17.4)	1 (0.5)	6 (6.1)	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough[a]	40 (20.5)	2 (1.0)	6 (6.1)	0
Dyspnea[a]	29 (14.9)	2 (1.0)	1 (1.0)	0
Pulmonary embolism	4 (2.1)	2 (1.0)	0	0
Skin and Subcutaneous Tissue Disorders				
Rash[a]	25 (12.8)	0	10 (10.1)	0
Dermatitis[a]	2 (1.0)	0	2 (2.0)	0
Vascular Disorders				
Deep vein thrombosis	4 (2.1)	3 (1.5)	1 (1.0)	1 (1.0)
Thrombosis	1 (0.5)	0	0	0

a. Represents a grouped term.
CTCAE = Common Terminology Criteria for Adverse Events
MDS Acute Myeloid Leukemia /AML = myelodysplastic syndrome

The most commonly reported AEs (>2%) that led to dose modification in the LYNPARZA arm vs. placebo arm were anemia (23.6% vs. 0%), vomiting (9.2% vs.1.0%), nausea (6.7% vs. 4.0%) , neutropenia (6.2% vs. 3.0%), fatigue (5.6% vs. 0%), asthenia(5.1% vs. 1.0%), leukopenia (4.1% vs. 0%), abdominal pain (4.1% vs. 2.0%), diarrhea (4.1% vs. 0%), thrombocytopenia (3.6% vs. 1.0%), neutrophil count decreased (2.6% vs. 0%), pyrexia (2.6% vs. 0%), dyspnea (2.1% vs. 0%), intestinal obstruction (2.1% vs. 0%) and pneumonia (2.1% vs. 0%).

The most commonly reported SAEs (≥1%) in the LYNPARZA arm vs. placebo arm were anemia (4.1% vs. 0%), myelodysplastic syndrome (2.1% vs. 0%), acute myeloid leukemia (1.5% vs. 0%), abdominal pain (2.1% vs. 0%), intestinal obstruction (2.1% vs. 1.0%), deep vein thrombosis (1.5% vs.1.0%), cough (1.0% vs 0%) and urinary tract infection (1.0% vs. 1.0%).

Overall, based on the long-term collection of data beyond treatment discontinuation and follow-up of 5 years in the SOLO-2 study (up to the data cut-off for the final analysis), there were 16 cases of MDS/AML (8.2%) in patients randomized to LYNPARZA and 4 cases (4.0%) in patients randomized to placebo.

Maintenance Treatment of *gBRCAm* Adenocarcinoma of the Pancreas (POLO)

The POLO study is a randomized, phase III, double-blind, placebo-controlled trial of LYNPARZA 300 mg twice daily (2 x 150 mg tablets) maintenance therapy in patients with *gBRCAm*

metastatic adenocarcinoma of the pancreas who were in response to first-line platinum-based chemotherapy (n=154 [n=92 on LYNPARZA and n=62 on placebo]) until disease progression or unacceptable toxicity. The median exposure to study treatment was 7.5 months in the LYNPARZA group and 3.7 months in the placebo group. Table 7 summarizes adverse drug reactions associated with LYNPARZA tablets with frequencies reported regardless of causality.

Table 7 Adverse Drug Reactions Reported in POLO (Safety Analysis Set)

System Organ Class/ Preferred Term	LYNPARZA Tablets 300 mg bid N = 90		Placebo N = 61	
	All Grades n (%)	CTCAE ≥Grade 3 n (%)	All Grades n (%)	CTCAE ≥Grade 3 n (%)
Blood and Lymphatic System Disorders				
Anemia[a]	29 (32.2)	11 (12.2)	10 (16.4)	2 (3.3)
Neutropenia[a]	14 (15.6)	6 (6.7)	5 (8.2)	2 (3.3)
Thrombocytopenia[a]	14 (15.6)	3 (3.3)	4 (6.6)	0
Lymphopenia[a]	5 (5.6)	3 (3.3)	1 (1.6)	0
Leukopenia[a]	7 (7.8)	1 (1.1)	2 (3.3)	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough[a]	10 (11.1)	0	2 (3.3)	0
Dyspnea[a]	12 (13.2)	0	3 (4.9)	1 (1.6)
Pulmonary embolism	2 (2.2)	1 (1.1)	0	0
Gastrointestinal Disorders				
Nausea	44 (48.9)	1 (1.1)	15 (24.6)	1 (1.6)
Vomiting	23 (25.6)	2 (2.2)	10 (16.4)	1 (1.6)
Diarrhea	34 (37.8)	1 (1.1)	10 (16.4)	0
Dyspepsia	9 (10.0)	0	5 (8.2)	0
Upper Abdominal Pain	8 (8.9)	0	9 (14.8)	2 (3.3)
Stomatitis[a]	12 (13.3)	0	3 (4.9)	0
General Disorders and Administration Site Conditions				
Fatigue (including asthenia)[a]	57 (63.3)	6 (6.7)	22 (36.1)	1 (1.6)
Immune System Disorders				
Hypersensitivity[a]	1 (1.1)	0	1 (1.6)	0
Investigations				
Increase in blood creatinine	7 (7.8)	0	2 (3.3)	0

Table 7 Adverse Drug Reactions Reported in POLO (Safety Analysis Set)

System Organ Class/ Preferred Term	LYNPARZA Tablets 300 mg bid N = 90		Placebo N = 61	
	All Grades n (%)	CTCAE ≥Grade 3 n (%)	All Grades n (%)	CTCAE ≥Grade 3 n (%)
Metabolism and Nutrition Disorders				
Decreased appetite	25 (27.8)	3 (3.3)	4 (6.6)	0
Nervous System Disorders				
Headache	7 (7.8)	0	8 (13.1)	0
Dysgeusia[a]	10 (11.1)	0	3 (4.9)	0
Dizziness	8 (8.9)	0	3 (4.9)	0
Skin and Subcutaneous Tissue Disorders				
Rash[a]	16 (17.8)	0	4 (6.6)	0
Erythema nodosum	0	0	1 (1.6)	0
Vascular Disorders				
Deep vein thrombosis	0	0	1 (1.6)	1 (1.6)
Thrombosis	1 (1.1)	0	0	0

a Represents a grouped term.
Includes AEs with an onset date between the date of first dose of continuous treatment and 30 days following the date of last dose of continuous treatment.
MedDRA version 23.0. CTCAE Version 4.03.
CTCAE Common Terminology Criteria for Adverse Events

An analysis of time to onset for AEs has shown that first occurrence of most AEs/SAEs is within the first 3 months of exposure to LYNPARZA.

Dose interruptions due to adverse reactions of any grade occurred in 41.1% of patients receiving LYNPARZA and 6.6% of those receiving placebo; dose reductions due to an adverse reactions occurred in 17.8% of LYNPARZA patients and 4.9% of placebo patients. The most frequent adverse reactions leading to dose interruption and/or reduction of LYNPARZA were anemia (12.2%), vomiting (5.6%), abdominal pain (4.4%), asthenia (3.3%) and fatigue (3.3%).

Discontinuation occurred in 8.9% of LYNPARZA patients and 1.6% in placebo patients due to adverse events. The adverse reaction that most frequently lead to discontinuation was fatigue (2.2%).

The most commonly reported SAE (≥1%) in the LYNPARZA arm vs. placebo arm was anemia (7.8% vs. 0%).

Treatment of HRR Mutation Positive Metastatic Castration Resistant Prostate Cancer (PROfound)

The PROfound study is a randomized, open-label, multicentre, phase III trial comparing

LYNPARZA 300 mg twice daily (2 x 150 mg tablets) monotherapy against Investigator's Choice of new hormonal agents (NHAs) in patients with HRR mutation positive metastatic castration resistant prostate cancer (n=387 [n=256 on LYNPARZA and n=131 on NHAs]). The total median exposure to study treatment was 230.0 days in the LYNPARZA group and 120.0 days in the Investigator's Choice NHA group. Table 8 summarizes adverse drug reactions associated with LYNPARZA tablets with frequencies reported regardless of causality.

Table 8 Adverse Drug Reactions Reported in PROfound (Safety Analysis Set)

System Organ Class/ Preferred Term	LYNPARZA Tablets 300 mg bid N = 256		Investigator's Choice of NHA's N = 130[a]	
	All Grades n (%)	CTCAE ≥Grade 3 n (%)	All Grades n (%)	CTCAE ≥Grade 3 n (%)
Blood and Lymphatic System Disorders				
Anemia[b]	127 (49.6)	58 (22.7)	20 (15.4)	7 (5.4)
Neutropenia[b]	24 (9.4)	15 (5.9)	4 (3.1)	2 (1.5)
Thrombocytopenia[b]	33 (12.9)	14 (5.5)	4 (3.1)	0 (0)
Lymphopenia[b]	19 (7.4)	4 (1.6)	1 (0.8)	1 (0.8)
Leukopenia[b]	19 (7.4)	4 (1.6)	0 (0)	0 (0)
Gastrointestinal Disorders				
Nausea	110 (43.0)	4 (1.6)	27 (20.8)	0(0)
Vomiting	51 (19.9)	6 (2.3)	17 (13.1)	1 (0.8)
Diarrhea	55 (21.5)	2 (0.8)	9 (6.9)	0 (0)
Dyspepsia	20 (7.8)	0 (0)	3 (2.3)	0 (0)
Upper Abdominal Pain	4 (1.6)	0 (0)	2 (1.5)	0 (0)
Stomatitis[b]	15 (5.9)	1 (0.4)	2 (1.5)	0 (0)
General Disorders and Administration Site Conditions				
Fatigue (including asthenia)	107 (41.8)	8 (3.1)	43 (33.1)	7 (5.4)
Immune System Disorders				
Hypersensitivity[b]	2 (0.8)	1 (0.4)	1 (0.8)	0 (0)
Investigations				
Increase in blood creatinine	10 (3.9)	0 (0)	1 (0.8)	0 (0)
Metabolism and Nutrition Disorders				
Decreased appetite	80 (31.3)	4 (1.6)	24 (18.5)	1 (0.8)
Nervous System Disorders				

Table 8 Adverse Drug Reactions Reported in PROfound (Safety Analysis Set)

System Organ Class/ Preferred Term	LYNPARZA Tablets 300 mg bid N = 256		Investigator's Choice of NHA's N = 130[a]	
	All Grades n (%)	CTCAE ≥Grade 3 n (%)	All Grades n (%)	CTCAE ≥Grade 3 n (%)
Headache	16 (6.3)	0 (0)	3 (2.3)	0 (0)
Dysgeusia[b]	19 (7.4)	0 (0)	2 (1.5)	0 (0)
Dizziness	18 (7.0)	0 (0)	5 (3.8)	0 (0)
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea[b]	30 (11.7)	6 (2.3)	6 (4.6)	0 (0)
Cough[b]	29 (11.3)	0 (0)	5 (3.8)	0 (0)
Pulmonary embolism	12 (4.7)	7 (2.7)	1 (0.8)	1 (0.8)
Skin and Subcutaneous Tissue Disorders				
Rash[b]	14 (5.5)	1 (0.4)	4 (3.1)	0 (0)
Dermatitis[b]	1 (0.4)	0 (0)	1 (0.8)	0 (0)
Vascular Disorders				
Deep vein thrombosis	4 (1.6)	0	2 (1.5)	1 (0.8)
Embolism	4 (1.6)	2 (0.8)	0	0
Thrombosis	0	0	1 (0.8)	0
Vena cava thrombosis	1 (0.4)	0	0	0
Venous thrombosis	1 (0.4)	0	1 (0.8)	0

[a] Of the 131 patients randomized to the NHA arm of the trial, one patient did not receive study treatment.
[b] Represents a grouped term.
CTCAE = common terminology criteria for adverse events

Discontinuation due to adverse events occurred in 19.9 % of patients in the LYNPARZA treatment arm and 8.5% of patients in the Investigator's Choice of NHA arm. The most commonly reported adverse reactions leading to discontinuation (≥ 1%) in the LYNPARZA arm versus Investigator's Choice NHA arm are were: anemia (7.8% vs. 0.8%), thrombocytopenia (2.0% vs. 0%) neutropenia (1.6% vs. 0%) and fatigue (1.2% vs. 1.5%).

Dose interruptions due to adverse events of any grade occurred in 46.5% of patients receiving LYNPARZA and 19.2% of those receiving Investigator's Choice of NHA; dose reductions due to an adverse event occurred in 23.4% of LYNPARZA patients and 5.4% of NHA patients. The most commonly reported adverse reactions leading to dose interruption (≥ 2%) in the LYNPARZA arm vs Investigator's Choice of NHA arm were: anemia (26.2% vs. 1.5%), thrombocytopenia (5.5% vs. 0%), neutropenia (3.5% vs. 0%), vomiting (2.7% vs. 3.1%), nausea (2.0% vs. 3.1%), fatigue (2.0% vs. 1.5%), platelet count decreased (2.0% vs. 0.8%) and diarrhea (2.0% vs. 0%). The most commonly reported adverse reactions leading to dose

reduction (≥ 2%) in the LYNPARZA arm versus Investigator's Choice of NHA arm were: anemia (16.4% vs. 0%), nausea (2.3% vs. 1.5%) and vomiting (2.0% vs. 0%).

The most commonly reported SAEs (≥2%) in the LYNPARZA arm vs. Investigator's Choice of NHA arm were anemia (9.0% vs. 0%), pneumonia (4.3% vs. 2.3%), urinary tract infection (2.0% vs. 3.1%), and pulmonary embolism (2.0% vs. 0.8%).

8.3 Less Common Clinical Trial Adverse Reactions

See adverse drug reaction tables in 8.2 Clinical Trial Adverse Reactions

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Table 9 summarizes the frequency of laboratory abnormalities associated with LYNPARZA treatment in the OlympiA study.

Table 9 Laboratory Abnormalities Reported in ≥15% of Patients in OlympiA

Laboratory Parameter [a]	LYNPARZA Tablets 300mg bid N = 911 [b]		Placebo N = 904 [b]	
	CTCAE Grades 1-4 (%)	CTCAE Grades 3-4 (%)	CTCAE Grades 1-4 (%)	CTCAE Grades 3-4 (%)
Increase in serum creatinine	97	0.2	87	0.1
Decrease in lymphocytes	66	11	52	4
Decrease in hemoglobin	65	8	29	1
Decrease in leukocytes	64	5	41	1
Increase in mean corpuscular volume [c]	64	0	5	0
Decrease in absolute neutrophil count	27	5	18	1
Decrease in platelets	16	0.3	8	0.3

a Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.
b 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.
c Represents the proportion of subjects whose mean corpuscular volume was > upper limit of normal (ULN).

Table 10 summarizes the frequency of laboratory abnormalities associated with LYNPARZA treatment in the OlympiAD study.

Table 10 Laboratory Abnormalities Reported in OlympiAD

Laboratory Parameter[b]	LYNPARZA Tablets 300 mg bid N=205		Physician's Choice of Chemotherapy[a] N=91	
	CTCAE Grades 1-4 (%)	CTCAE Grades 3-4 (%)	CTCAE Grades 1-4 (%)	CTCAE Grades 3-4 (%)
Decrease in hemoglobin	82	17	66	3
Decrease in lymphocytes	73	21	63	3
Decrease in leukocytes	71	8	70	23
Increase in MCV[c]	71	-	33	-
Decrease in absolute neutrophil count	46	11	65	38
Decrease in platelets	33	3	28	0
Increase in serum creatinine	18	0.5	9	0

[a] Physician's choice of chemotherapy consisting of either capecitabine, eribulin or vinorelbine.
[b] Patients were allowed to enter study with laboratory values of CTCAE Grade 1.
[c] Represents the proportion of subjects whose MCV was > upper limit of normal (ULN).
CTCAE Common Terminology Criteria for Adverse Events; MCV Mean corpuscular volume

Table 11 summarizes the frequency of laboratory abnormalities associated with LYNPARZA treatment in the SOLO1 study.

Table 11 Laboratory Abnormalities Reported in ≥25% of Patients in SOLO1

Laboratory Parameter	LYNPARZA Tablets 300 mg bid N=260		Placebo N=130	
	CTCAE Grades 1-4 (%)	CTCAE Grades 3-4 (%)	CTCAE Grades 1-4 (%)	CTCAE Grades 3-4 (%)
Decrease in hemoglobin	87	19	63	2
Decrease in absolute neutrophil count	51	9	38	6
Decrease in platelets	35	1	20	2
Decrease in lymphocytes	67	14	29	5
Decrease in leukocytes	70	7	52	1
Increase in MCV[a]	79	-	14	-
Increase in serum creatinine	34	0	18	0

a Represents the proportion of subjects whose MCV was low or normal at baseline and increased to above normal reference range.
CTCAE Common Terminology Criteria for Adverse Events; MCV Mean corpuscular volume

Table 12 summarizes the frequency of laboratory abnormalities associated with LYNPARZA treatment in the SOLO2 study.

Table 12 Laboratory Abnormalities Reported in ≥25% of Patients in SOLO2

Laboratory parameter[a]	LYNPARZA Tablets 300 mg bid N=195		Placebo N=99	
	CTCAE Grades 1-4 (%)	CTCAE Grades 3-4 (%)	CTCAE Grades 1-4 (%)	CTCAE Grades 3-4 (%)
Decrease in hemoglobin	84	19	69	0
Decrease in lymphocytes	70	15	39	1
Decrease in absolute neutrophil count	53	8	34	3
Decrease in leukocytes	70	8	48	1
Decrease in platelets	43	4	22	1
Increase in serum creatinine	49	0	30	0
Increase in MCV[b]	80	-	22	-

a Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.
b Represents the proportion of subjects whose mean corpuscular volume was low or normal at baseline and increased to above normal reference range.
CTCAE Common Terminology Criteria for Adverse Events; MCV Mean corpuscular volume.

Table 13 summarizes the frequency of laboratory abnormalities associated with LYNPARZA treatment in the POLO study.

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

Laboratory parameter[a]	LYNPARZA Tablets 300 mg bid N=90[b]		Placebo N=61[b]	
	CTCAE Grades 1-4 (%)	CTCAE Grades 3-4 (%)	CTCAE Grades 1-4 (%)	CTCAE Grades 3-4 (%)
Increase in serum creatine	99	1	92	0
Decrease in hemoglobin	89	12	61	0
Increase in MCV[c]	65	-	3	-
Decrease in lymphocytes	65	12	25	2
Decrease in platelets	58	2	39	0
Decrease in leukocytes	49	3	25	0
Decrease in absolute neutrophil count	29	5	14	0

a Patients were allowed to enter POLO with haemoglobin ≥9 g/dL (CTCAE Grade 2) and other laboratory values of CTCAE Grade 1.
b 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.
c Represents the proportion of subjects whose MCV was low or normal at baseline and increased to above normal reference range.
CTCAE Common Terminology Criteria for Adverse Events; MCV Mean corpuscular volume.

Table 14 summarizes the frequency of laboratory abnormalities associated with LYNPARZA treatment in the PROfound study.

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

Laboratory parameter[a]	LYNPARZA Tablets 300 mg bid N=256[b]		Investigator's Choice of NHA N=130[b]	
	CTCAE Grades 1-4 (%)	CTCAE Grades 3-4 (%)	CTCAE Grades 1-4 (%)	CTCAE Grades 3-4 (%)
Decrease in hemoglobin	98	13	73	4
Decrease in absolute neutrophil count	34	3	9	0
Decrease in platelets	24	2	12	0
Decrease in lymphocytes	62	23	34	13
Decrease in leukocytes	53	4	21	0
Increase in MCV[c]	73	-	11	-
Increase in serum creatinine	95	2	68	1

a Patients were allowed to enter PROfound with laboratory values of CTCAE Grade 1. If liver metastases were present patients were allowed to enter with AST (SGOT) ≤5 × institutional ULN (CTCAE Grade 2).
b 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.
c Represents the proportion of subjects whose MCV was low or normal at baseline and increased to above normal reference range.
CTCAE Common Terminology Criteria for Adverse Events; MCV Mean corpuscular volume

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-approval use of LYNPARZA:

Immune system disorders: Angioedema (0.1%)

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Clinical studies of LYNPARZA (olaparib) in combination with other anti-cancer agents, including DNA damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity. The recommended LYNPARZA monotherapy dose is not suitable for combination with myelosuppressive anti-cancer agents.

Olaparib is predominantly metabolised by CYP3A (see 10 CLINICAL PHARMACOLOGY). Co-administered CYP3A inhibitors or inducers may respectively increase or decrease olaparib plasma concentration.

In vitro, olaparib is an inhibitor and inducer of CYP3A4 and an inducer of CYP2B6. Olaparib is a weak CYP3A inhibitor *in vivo*. It also inhibits drug transporter proteins OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K (see 10 CLINICAL PHARMACOLOGY).

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either PBPK modeling reports, drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 15 Established or Potential Drug-Drug Interactions

Common name	Source of Evidence	Effect	Clinical comment
Pharmacokinetic Interactions (Drugs that may affect the exposure to olaparib)			
Strong inhibitors of CYP3A (e.g., itraconazole, clarithromycin, telithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir)	CT/ T	In patients, a co-administered strong CYP3A inhibitor increased olaparib mean C_{max} and mean AUC.	Co-administration is not recommended. If it must be co-administered, the dose of LYNPARZA should be reduced (see 4 DOSAGE AND ADMINISTRATION).
Strong inducers of CYP3A (e.g., rifampicin, phenobarbital, phenytoin, rifabutin, rifapentine, carbamazepine, nevirapine)	CT/ T	In patients, a co-administered strong CYP3A inducer decreased olaparib mean C_{max} and mean AUC.	Co-administration is not recommended. If a strong CYP3A inducer cannot be avoided, there is a potential for decreased efficacy of LYNPARZA (see 7 WARNINGS AND PRECAUTIONS).
Moderate inhibitors of CYP3A (e.g., ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil)	T	Olaparib is predominantly metabolised by CYP3A. Moderate CYP3A inhibitors may increase the exposure to olaparib when co-administered.	Co-administration is not recommended. If it must be co-administered, the dose of LYNPARZA should be reduced (see 4 DOSAGE AND ADMINISTRATION).
Moderate inducers of CYP3A (e.g., bosentan, efavirenz, etravirine, modafinil)	T	Olaparib is predominantly metabolised by CYP3A. Moderate CYP3A inducers may decrease the exposure to olaparib when co-administered.	Co-administration is not recommended. If a moderate CYP3A inducer cannot be avoided, there is a potential for decreased efficacy of LYNPARZA.
Pharmacokinetic Interactions (Drugs for which the exposure may be affected by olaparib)			
Substrates of CYP2B6 (e.g., bupropion and efavirenz)	T	Olaparib induces CYP2B6 *in vitro;* olaparib may decrease the exposure to co-administered substrates of CYP2B6.	Caution should be exercised when co-administered. Patients should be closely monitored.

Table 15 Established or Potential Drug-Drug Interactions

Common name	Source of Evidence	Effect	Clinical comment
Substrates of CYP3A (e.g., simvastatin, cyclosporine, cisapride, ergot alkaloids, fentanyl, midazolam, pimozide, sirolimus, tacrolimus, quetiapine)	T / CT	Olaparib is predicted to be a weak CYP3A inhibitor *in vivo*; olaparib may increase the exposure to substrates of CYP3A through enzyme inhibition when co-administered.	Caution should be exercised when co-administered as exposure to substrates may be increased. Patients should be closely monitored (see 7 WARNINGS AND PRECAUTIONS).
Substrates of hepatic uptake transporters OATP1B1, OCT1 (e.g., bosentan, glibenclamide, repaglinide, statins, valsartan, metformin)	T	Olaparib inhibits OATP1B1 and OCT1 *in vitro*; olaparib may increase the exposure of substrates of these transporters when co-administered.	Caution should be exercised when co-administered - especially in combination with any statin. Patients should be closely monitored.
Substrates of renal uptake transporters OCT2, OAT3, MATE1 and MATE2K (e.g., amantadine, cimetidine, furosemide, methotrexate, metformin, cisplatin)	T	Olaparib inhibits OCT2, OAT3, MATE1, and MATE2K *in vitro*; olaparib may increase the exposure of substrates of these transporters when co-administered.	Caution should be exercised when co-administered. Patients should be closely monitored.
Substrates of CYP2C9 (e.g., hormonal contraceptives)	T	The potential for Olaparib to reduce exposure to substrates of CYP2C9 through enzyme induction could not be excluded.	The efficacy of some hormonal contraceptives may be reduced if co-administered with Olaparib. Consider a non-hormonal contraceptive method during treatment. For women with hormone dependent cancer, two non-hormonal contraceptive methods should be considered (see 7.1.1 Pregnant Women)
Pharmacodynamic Interactions			
Myelosuppressive anticancer agents, including DNA damaging agents	CT	Potentiation and prolongation of myelo-suppressive toxicity.	LYNPARZA monotherapy dose is not suitable for combination with myelosuppressive anticancer agents.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical / PBPK modelling
Acronyms: MDR1 = Multi-Drug Resistance protein-1; OATP1B1 = Organic Anion Transporter polypeptide 1B1; OCT1 or OCT2 = Organic Cation Transporter-1 or -2; OAT 3 = Organic Anion Transporter 3, MATE1 or MATE2K = multidrug and toxin extrusion protein-1 or -2
See 10 CLINICAL PHARMACOLOGY

9.5 Drug-Food Interactions

Co-administration with food slowed the rate (median t_{max} delayed by 2.5 hours and mean C_{max} reduced by approximately 21%) but did not significantly affect the extent of absorption of olaparib (AUC treatment ratio: 1.08; 90% CI: 1.01, 1.16). Consequently, patients should take LYNPARZA without regard to food. See 4.4 Administration.

Grapefruit, star fruit, pomegranate and Seville oranges or their juices are known to inhibit CYP3A and may increase olaparib plasma concentration. Patients should avoid these fruits during LYNPARZA treatment.

9.6 Drug-Herb Interactions

Co-administration of St. John's Wort, a potent inducer of CYP3A, may decrease exposure to olaparib and should be avoided.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

LYNPARZA (olaparib) is a selective inhibitor of human poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1, PARP2, and PARP3. PARP enzymes are involved in normal cellular functions, such as DNA transcription and DNA repair. Olaparib has been shown to inhibit growth of select tumour cell lines *in vitro* and decrease tumour growth in mouse xenograft models of human cancer both as monotherapy or following platinum-based chemotherapy. Increased cytotoxicity and anti-tumour activity following treatment with olaparib were noted in cell lines and mouse tumour models with deficiencies in BRCA and non-BRCA proteins involved in the homologous recombination repair (HRR) of DNA damage and correlated with platinum response. *In vitro* studies have shown that olaparib-induced cytotoxicity involves DNA damage resulting from the inhibition of PARP enzymatic activity and increased formation of trapped PARP-DNA complexes, resulting in cancer cell death.

10.2 Pharmacodynamics

Effect on the QT interval

There is no clinically relevant effect of olaparib on cardiac repolarisation (as evaluated by an effect on the QT interval) following 300 mg tablet twice daily multiple dosing of olaparib in 109 patients.

10.3 Pharmacokinetics

The pharmacokinetics (PK) of olaparib at a single 300 mg tablet dose (two 150 mg tablets) are characterised in Table 16 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.

Table 16 LYNPARZA (tablet formulation) Pharmacokinetic Parameters in Patients with Advanced Solid Tumours

	C_{max} (µg/mL)[a]	t_{max} (h)[c]	$t_{½}$ (h)	$AUC_{0-\infty}$ (µg.h/mL)[a]	CL/F (L/h)[b]	Vd/F (L)[b]
Single 300 mg dose mean (SD or %GCV), n	7.3 (34), 102	1.5 (0.5 – 6), 102	15 (8.2), 100	47 (59), 100	~7.4 (3.9), 100	~158 (136), 100

[a] For C_{max} and AUC geometric mean (geometric percentage coefficient of variation) is shown.
[b] For $t_{1/2}$, CL/F and Vd/F arithmetic mean (standard deviation) is presented.
[c] For t_{max} median (range) is shown.

Absorption:

The absolute bioavailability of olaparib is unknown. Following a single oral administration of olaparib 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 (median t_{max} delayed by 2.5 hours and mean C_{max} reduced by approximately 21%) but did not significantly affect the extent of absorption of olaparib (AUC treatment ratio: 1.08; 90% CI: 1.01, 1.16). Consequently, patients should take LYNPARZA without regard to food (see 4.4 Administration).

Population pharmacokinetic analyses have shown that the steady state exposure (AUC) following 300 mg tablet twice daily was 77% higher compared to that following 400 mg capsule twice daily. The olaparib geometric mean AUC and C_{max} following a single 300 mg tablet dose were 42.1 µg*h/mL (n=204) and 5.8 µg/mL (n=204), respectively, and the steady state geometric mean AUC and C_{max} following 300 mg tablet twice daily were 49.0 µg*h/mL (n=227) and 7.7 µg/mL (n=227), respectively. Olaparib showed time-dependent PK such that the steady state clearance decreased by 15% after multiple dosing.

Distribution:

The *in vitro* plasma protein binding is approximately 82% at 10 µg/mL which is approximately C_{max}.

In vitro, human plasma protein binding of olaparib was dose-dependent; the fraction bound was approximately 91% at 1 µg/mL, reducing to 82% at 10 µg/mL and to 70% at 40 µg/mL. In solutions of purified proteins, the olaparib fraction bound to albumin was approximately 56%, which was independent of olaparib concentrations. Using the same assay, the fraction bound to alpha-1 acid glycoprotein was 29% at 10 µg/mL with a trend of decreased binding at higher concentrations.

Metabolism:

In vitro, CYP3A4/5 were shown to be the enzymes primarily responsible for the metabolism of olaparib.

Following oral dosing of 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 with the main site of metabolism being the piperazine and fluorobenzyl ring structures. The majority of the metabolism was attributable to oxidation reactions with a number of the components produced undergoing subsequent glucuronide or sulphate conjugation. Up to 20, 37 and 20 metabolites were detected in plasma, urine and faeces respectively, the majority of them representing <1% of the dosed material. A ring-open piperazin-3-ol moiety, and two mono-oxygenated metabolites (each~10%) were the major circulating components, with one of the mono-oxygenated metabolites also being the major metabolite in the excreta (6% and 5% of the urinary and faecal radioactivity respectively).

In vitro, olaparib produced little/no inhibition of UGT1A4, UGT1A9, UGT2B7, or CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and is not expected to be a clinically significant time dependent inhibitor of any of these CYP enzymes. Olaparib inhibited UGT1A1 *in vitro,* however, PBPK simulations suggest this is not of clinical importance. *In vitro,* olaparib is a substrate of and inhibits the efflux transporter P-gp (IC50 = 76µM), however, this is unlikely to be of clinical significance. The potential for olaparib to induce CYP2C9 or CYP2C19 could not be excluded. Therefore, olaparib upon co-administration may reduce the exposure to substrates of these metabolic enzymes.

Olaparib caused a slight increase in CYP1A2 mRNA without apparent increase in enzyme activity which may suggest any clinical change will be small.

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

Elimination:

Following a single dose of ^{14}C-olaparib, ~86% of the dosed radioactivity was recovered within a 7-day collection period, ~44% via the urine and ~42% via the feces. The majority of the material was excreted as metabolites.

Special Populations and Conditions

- ***Pediatrics:*** No studies have been conducted to investigate the pharmacokinetics of olaparib in pediatric patients.

- ***Age, Bodyweight or Ethnic origin:*** In population based PK analyses, patient age, gender, body weight or race (including Caucasian and Asian patients) were not significant covariates.

- ***Hepatic Insufficiency:*** In a pharmacokinetic study, following a single oral 300 mg dose of olaparib (tablet formulation) to patients with mild hepatic impairment (Child-Pugh classification A) mean AUC increased by 15% and mean C_{max} by 13% and to patients with moderate hepatic impairment (Child-Pugh classification B) mean AUC increased by 8% and mean C_{max} decreased by 13% compared with patients with normal hepatic function. No LYNPARZA dose adjustment is required in patients with mild or moderate hepatic impairment (see 4.2 Recommended Dose and Dosage Adjustment).

  LYNPARZA has not been studied in patients with severe hepatic impairment (Child-

Pugh classification C).

- ***Renal Insufficiency:*** In a pharmacokinetic study, following a single oral 300 mg dose of olaparib (tablet formulation) to patients with mild renal impairment (creatinine clearance: 51 to 80 mL/min), mean AUC increased by 24% and mean C_{max} by 15% compared with patients with normal renal function. No LYNPARZA dose adjustment is required for patients with mild renal impairment.

  Following a single oral 300 mg dose of LYNPARZA to patients with moderate renal impairment (creatinine clearance: 31 to 50 mL/min), mean AUC increased by 44% and mean C_{max} by 26% compared with patients with normal renal function. LYNPARZA dose reduction is recommended for patients with moderate renal impairment (see 4.2 Recommended Dose and Dosage Adjustment)

  LYNPARZA has not been studied in patients with severe renal impairment or end-stage renal disease (creatinine clearance ≤30 ml/min).

11 STORAGE, STABILITY AND DISPOSAL

Store LYNPARZA (olaparib) between 2 - 30°C in the original package in order to protect from moisture.

12 SPECIAL HANDLING INSTRUCTIONS

Do not use this medicine after the expiry date which is stated on the bottle after EXP. The expiry date refers to the last day of that month.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

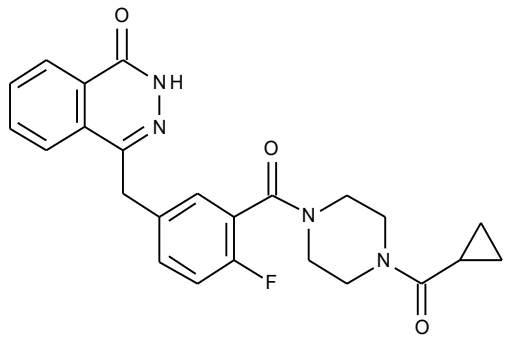
Drug Substance

Proper name/Common name: olaparib

Chemical name: 4-[(3-{[4-(cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2H)-one

Molecular formula and molecular mass: $C_{24}H_{23}FN_4O_3$ 434.46

Structural formula:



Physicochemical properties: Olaparib is a crystalline powder and is classified as poorly soluble. The melting point (defined as the temperature onset) of olaparib is at 199-206°C as measured by differential scanning calorimetry. The octanol/water (pH=7.4) partition coefficient: Log D =1.49. Olaparib is achiral.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Adjuvant Treatment of g*BRCA*m HER2-negative High Risk Early Breast Cancer (OlympiA)

Table 17 Summary of Selected Demographic and Patient Characteristics at Baseline (Full Analysis Set) in the OlympiA Study

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Sex
D081CC00006 (OlympiA)	Phase III randomized (1:1), double-blind, parallel group, placebo-controlled, multicentre study	300 mg LYNPARZA (2 x 150 mg tablets) orally twice daily or placebo for 1 year Patients with hormone receptor positive tumours received concomitant endocrine therapy as per current clinical guidelines.	LYNPARZA n=921 Placebo n=915	LYNPARZA 43.0 years (22 – 77 years) Placebo 43.6 years (24 – 78 years)	LYNPARZA Female: n=919 Male: n=2 Placebo Female: n=911 Male: n=4

The efficacy of LYNPARZA was investigated in OlympiA (D081CC0006) a randomized, double-blind, parallel group, placebo-controlled, multicentre study in patients with *gBRCA*m HER2-negative high risk early breast cancer who had completed definitive local treatment and neoadjuvant or adjuvant chemotherapy. Patients enrolled based on local *gBRCA* test results provided a sample for retrospective confirmatory central testing by Myriad BRACAnalysis® test. Patients were randomized in a 1:1 ratio to either LYNPARZA tablets 300mg twice daily (n=921) or placebo (n=915). Treatment was continued for a total of 1 year, or until disease recurrence or unacceptable toxicity, whichever occurred first. Patients with hormone receptor positive (estrogen (ER) and/or progesterone (PgR) positive) tumours were receiving concomitant endocrine therapy (87% in the LYNPARZA arm and 92% in the placebo arm). Patients were required to have completed at least 6 cycles of neoadjuvant or adjuvant chemotherapy containing anthracyclines, taxanes or both. Prior platinum for previous cancer (e.g. ovarian) or as adjuvant or neoadjuvant treatment for breast cancer was allowed. High risk early breast cancer patients were defined as follows:

- patients who have received prior neoadjuvant chemotherapy (both TNBC and hormone receptor positive) must have had residual invasive cancer in the breast and/or the resected lymph nodes (non-pathological 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 18.

Table 18 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 have received prior adjuvant chemotherapy: TNBC patients must have had node positive disease or node negative disease with a ≥ 2cm primary tumour; patients with hormone receptor positive, HER2-negative patients must have had ≥4 pathologically confirmed positive lymph nodes.

Randomization was stratified by local hormone receptor status (ER and/or PgR positive/ HER2 negative versus TNBC), by prior neoadjuvant versus adjuvant chemotherapy, and by prior platinum use for breast cancer (yes versus no).

Demographic and baseline patient characteristics in OlympiA are summarized below.

Table 19 Summary of Selected Demographic and Patient Characteristics at Baseline (Full Analysis Set) in the OlympiA Study

	Number (%) of patients		
	FAS		
	LYNPARZA 300 mg bd (N=921)	**Placebo (N=915)**	**Total (N=1836)**
Age (years)			
Mean (SD)	43.0 (9.82)	43.6 (10.12)	43.3 (9.97)
Median (range)	42.0 (22-77)	43.0 (24-78)	42.0 (22-78)
Age groups			
<30 years	51 (5.5)	59 (6.4)	110 (6.0)
30-39 years	333 (36.2)	306 (33.4)	639 (34.8)
40-49 years	315 (34.2)	308 (33.7)	623 (33.9)
50-59 years	166 (18.0)	172 (18.8)	338 (18.4)
60-69 years	48 (5.2)	66 (7.2)	114 (6.2)

Table 19 Summary of Selected Demographic and Patient Characteristics at Baseline (Full Analysis Set) in the OlympiA Study

	Number (%) of patients		
	FAS		
	LYNPARZA 300 mg bd (N=921)	Placebo (N=915)	Total (N=1836)
≥70 years	8 (0.9)	4 (0.4)	12 (0.7)
Sex			
Female	919 (99.8)	911 (99.6)	1830 (99.7)
Male	2 (0.2)	4 (0.4)	6 (0.3)
Race			
White	626 (68.0)	599 (65.5)	1225 (66.7)
Asian	259 (28.1)	272 (29.7)	531 (28.9)
Black or African American	19 (2.1)	29 (3.2)	48 (2.6)
Other	17 (1.8)	15 (1.6)	32 (1.7)
Hormone Receptor Status			
TNBC [a]	753 (81.8)	758 (82.8)	1511 (82.3)
ER and/or PgR positive, HER2-negative	168 (18.2)	157 (17.2)	325 (17.7)
Prior Platinum			
No	674 (73.2)	677 (74.0)	1351 (73.6)
Yes	247 (26.8)	238 (26.0)	485 (26.4)
Prior Chemotherapy			
Adjuvant	461 (50.1)	455 (49.7)	916 (49.9)
Neoadjuvant	460 (49.9)	460 (50.3)	920 (50.1)
Prior Chemotherapy by Hormone Receptor Status			
Adjuvant TNBC	397 (43.1)	390 (42.6)	787 (42.9)
Adjuvant ER and/or PgR positive, HER2-negative	64 (6.9)	65 (7.1)	129 (7.0)
Neoadjuvant TNBC[a]	356 (38.7)	368 (40.2)	724 (39.4)
Neoadjuvant ER and/or PgR positive, HER2-negative	104 (11.3)	92 (10.1)	196 (10.7)
Baseline *BRCA* Status			
BRCA1	656 (71.2)	669 (73.1)	1325 (72.2)
BRCA2	260 (28.2)	238 (26.0)	498 (27.1)
BRCA1&2	2 (0.2)	5 (0.5)	7 (0.4)
No *gBRCA* mutation	2 (0.2)	3 (0.3)	5 (0.3)

Table 19 Summary of Selected Demographic and Patient Characteristics at Baseline (Full Analysis Set) in the OlympiA Study

	Number (%) of patients		
	FAS		
	LYNPARZA 300 mg bd (N=921)	Placebo (N=915)	Total (N=1836)
Missing	1 (0.1)	0	1 (0.1)
Prior Neoadjuvant/Adjuvant Chemotherapy for Primary Breast Cancer			
Anthracycline and taxane regimen	871 (94.6)	849 (92.8)	1720 (93.7)
Anthracycline regimen (without taxane)	7 (0.8)	13 (1.4)	20 (1.1)
Taxane regimen (without anthracycline)	43 (4.7)	52 (5.7)	95 (5.2)
Missing	0	1 (0.1)	1 (0.1)
Menopausal status			
Premenopausal	572 (62.1)	553 (60.4)	1125 (61.3)
Postmenopausal	347 (37.7)	358 (39.1)	705 (38.4)
Male	2 (0.2)	4 (0.4)	6 (0.3)
ECOG performance status			
(0) Fully Active	824 (89.5)	804 (87.9)	1628 (88.7)
(1) Restricted work	97 (10.5)	111 (12.1)	208 (11.3)

a Post randomization, 2 patients (included as TNBC) were found not to have confirmed negative HER2 status.
bd = twice daily; *BRCA* = breast cancer susceptibility gene; eCRF = electronic case report form; ER = estrogen receptor; gBRCA = germline *BRCA*; HER2 = human epidermal growth factor receptor 2; N = total number of patients; PgR = progesterone receptor; SD = standard deviation; TNBC = triple negative breast cancer.

The primary endpoint 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, secondary primary non-breast invasive malignancy or death from any cause. Secondary objectives included OS, distant disease free survival (DDFS, defined as the time from randomization until evidence of first distant recurrence of breast cancer).The endpoints IDFS and DDFS were defined as per the Standardised Definitions for Efficacy End Points (STEEP) criteria.

Study Results

The study demonstrated a statistically significant and clinically meaningful improvement in IDFS and DDFS in the LYNPARZA arm compared with the placebo arm. The IDFS and DDFS data was 15.5% and 13% mature in the Full Analysis Set (FAS) at the time of interim analysis (DCO at 27 March 2020) with median duration of follow-up 2.3 years in the LYNPARZA arm and 2.5 years in the placebo arm. Interim overall survival (8% maturity, Data Cut Off (DCO) 27 March 2020) did not meet the pre-specified boundary for statistical significance.

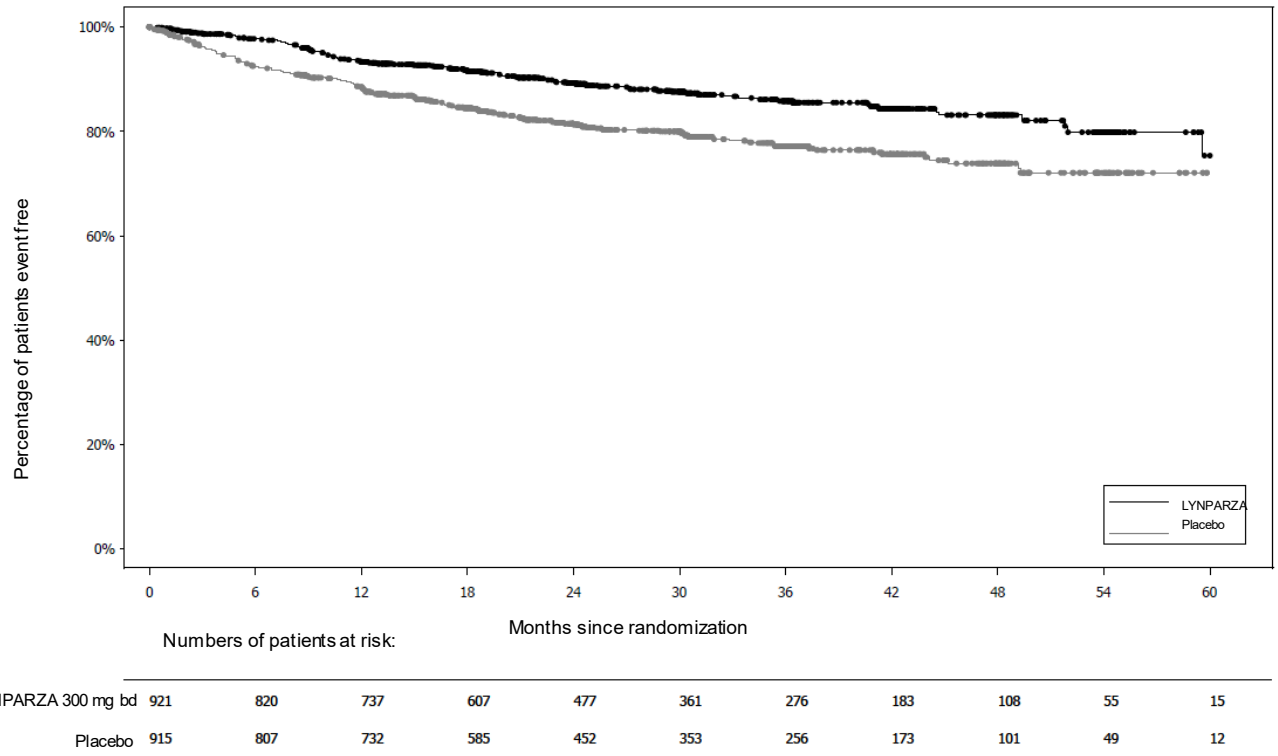
Efficacy results from the FAS are presented in Table 20, Figure 1 and Figure 2.

Table 20 Summary of Key Efficacy Findings in g*BRCAm* HER2-negative high risk early breast cancer patients in OlympiA

	LYNPARZA 300 mg bd tablets (N=921)		Placebo (N=915)
IDFS (15.5% maturity)[a]			
Number of events/total number of patients (%)	106/921 (12)		178/915 (20)
HR (99.5% CI) [b]		0.58 (0.41, 0.82)	
p-value (2-sided) [c]		0.0000073	
3-year event rate (95%CI)[d]	86 (83, 88)		77 (74, 80)
DDFS (13% maturity)[a]			
Number of events/total number of patients (%)	89/921 (10)		152/915 (17)
HR (99.5% CI) [b]		0.57 (0.39, 0.83)	
p-value (2-sided) [c]		0.0000257	
3-year event rate (95%CI)[d]	88 (85, 90)		80 (77, 83)
Interim OS (8% maturity) [a]			
Number of events/total number of patients (%)	59/921 (6)		86/915 (9)
HR (99% CI) [b]		0.68 (0.44, 1.05)	
p-value (2-sided) [c]		0.0236	
3-year event rate (95%CI)[d]	92 (90, 94)		88 (85, 91)

a DCO 27 March 2020
b Based on the stratified Cox's Proportional Hazards Model.
c p-value from a stratified log-rank test.
d Percentages are calculated using KM estimates and the 95% CIs were calculated using Greenwood's formula.
bd = twice daily; CI = confidence interval; DDFS = distant disease free survival; IDFS = invasive disease free survival; KM = Kaplan-Meier; OS = overall survival.

Figure 1 Kaplan-Meier plot of IDFS in patients with g*BRCAm* HER2-negative high risk early breast cancer in the OlympiA study[1]

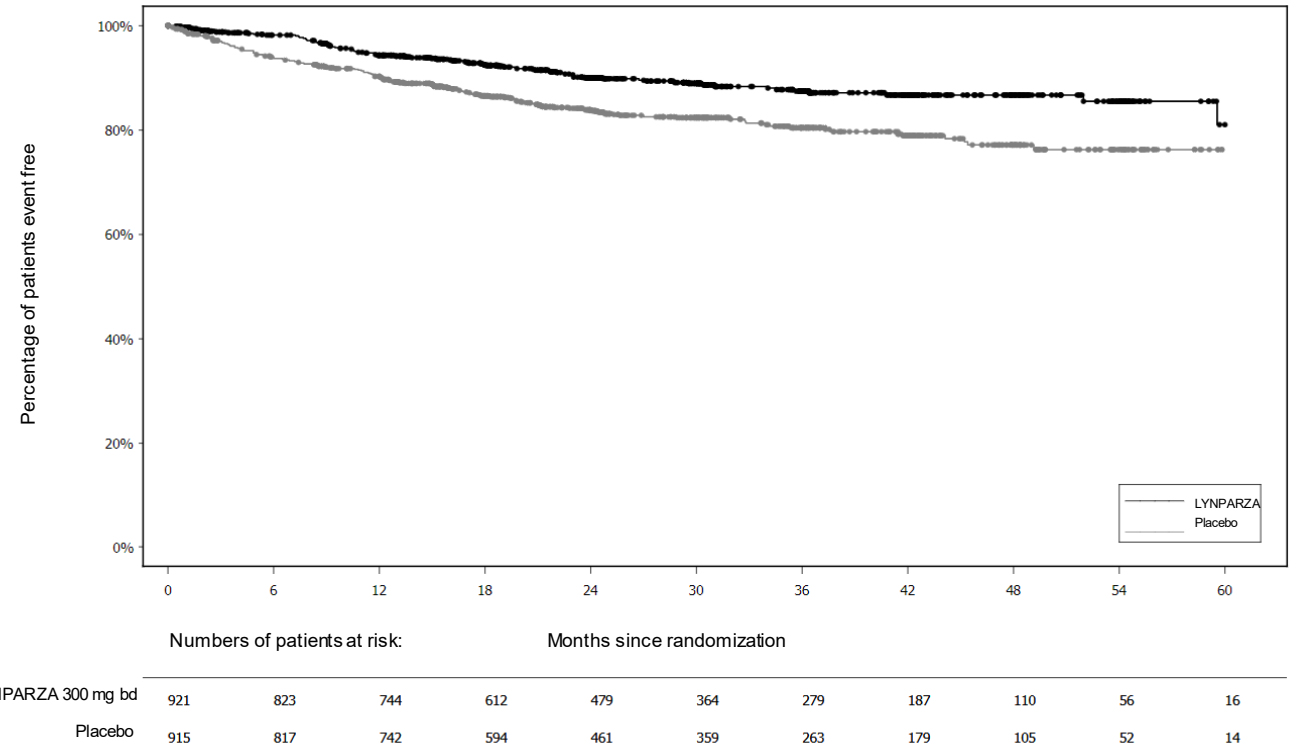


Numbers of patients at risk:

LYNPARZA 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

[1]DCO 27 March 2020

Figure 2 Kaplan-Meier plot of DDFS in patients with g*BRCAm* HER2-negative high risk early breast cancer in the OlympiA study[1]



[1]DCO 27 March 2020

IDFS benefit was observed across all patient stratification subgroups of hormone receptor status (ER and/or PgR positive: HR 0.70, 95%CI 0.38, 1.27; TNBC: HR 0.56, 95% 0.43,0.73), prior chemotherapy status (Neoadjuvant: HR 0.56, 95% CI 0.41, 0.75; Adjuvant: HR 0.60, 95%CI 0.39, 0.90), and prior platinum status (Yes: HR 0.77, 95%CI 0.49, 1.21; No: HR 0.52, 95%CI 0.39, 0.69).

Treatment of g*BRCA*m HER2-Negative Metastatic Breast Cancer (OlympiAD)

The safety and efficacy of LYNPARZA (olaparib) in the treatment of g*BRCA*m HER2-negative metastatic breast cancer was studied in a Phase III, randomized, open-label, multicentre, active-controlled trial, OlympiAD (Study D0819C00003). A total of 302 patients were randomized 2:1 to receive LYNPARZA 300 mg (2 x 150 mg tablets) twice daily or the active comparator (physician's choice of chemotherapy: capecitabine, eribulin, or vinorelbine, at standard doses [see Table 21]) until progression or unacceptable toxicity. Randomization was stratified by prior use of chemotherapy for metastatic disease (yes vs no), hormone receptor status (hormone receptor positive vs triple negative), and previous use of platinum-based chemotherapy (yes vs no). The g*BRCA*m was confirmed using Myriad g*BRCA* test.

All patients had received prior treatment with anthracycline (unless contraindicated) and a taxane in either the neoadjuvant or metastatic setting. Patients with hormone receptor-positive disease must have received and progressed on at least one endocrine therapy (adjuvant or metastatic) or had disease that the treating physician believed to be inappropriate for endocrine

therapy. Patients with prior platinum therapy were required to have no evidence of disease progression during platinum treatment. No prior treatment with a PARP inhibitor was permitted. Patients could not have received more than 2 prior lines of cytotoxic chemotherapy for metastatic disease.

Table 21 Summary of Trial Design for Clinical Trials in g*BRCA*m HER2-Negative Metastatic Breast Cancer Patients

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Sex
D0819C00003 (OlympiAD)	Phase III randomized (2:1), open-label, active-controlled study, that investigated LYNPARZA 300 mg twice daily tablet formulation as treatment for patients with g*BRCA*m HER2-negative metastatic breast cancer	300 mg (2 x 150 mg tablets) orally twice daily	LYNPARZA n=205 Physicians' choice of chemotherapy[a] n=97	LYNPARZA 45.0 years (22 – 76 years) Physicians' choice of chemotherapy[a] 45.9 years (24 – 68 years)	LYNPARZA Female: n=200 Male: n=5 Physicians' choice of chemotherapy[a] Female: n=95 Male: n=2

[a] Physician's choice of chemotherapy consisting of either capecitabine (2500 mg/m^2 oral daily, divided in 2 doses for 14 days, repeated every 21 days), eribulin (1.4 mg/m^2 IV Day 1 and Day 8, repeated every 21 days), or vinorelbine (30 mg/m^2 IV Day 1 and Day 8, repeated every 21 days).

Demographic and baseline patient characteristics were generally balanced between treatment groups in OlympiAD and are summarized below.

Table 22 Summary of Selected Demographic and Patient Characteristics at Baseline (Full Analysis Set) in the OlympiAD Study

	LYNPARZA Tablets 300 mg bid (n=205)	Physician's Choice of Chemotherapy[a] (n=97)
Demographics		
Age (years)		
Mean (SD)	45.0 (10.9)	45.9 (10.3)
Median (range)	44.0 (22 – 76)	45.0 (24 – 68)

Table 22 Summary of Selected Demographic and Patient Characteristics at Baseline (Full Analysis Set) in the OlympiAD Study

	LYNPARZA Tablets 300 mg bid (n=205)	Physician's Choice of Chemotherapy[a] (n=97)
Age group (years), n (%)		
<50	138 (67.3)	63 (64.9)
≥50 to <65	56 (27.3)	30 (30.9)
≥65	11 (5.4)	4 (4.1)
Sex, n (%)		
Female	200 (97.6)	95 (97.9)
Male	5 (2.4)	2 (2.1)
Race, n (%)		
Caucasian	134 (65.4)	63 (64.9)
Asian	66 (32.2)	28 (28.9)
Black/African American	1 (0.5)	4 (4.1)
Other	4 (2.0)	2 (2.1)
Disease Characteristics		
ECOG performance status, n (%)		
Grade 0	148 (72.2)	62 (63.9)
Grade 1	57 (27.8)	35 (36.1)
Germline *BRCA* status		
BRCA1	114 (55.6)	50 (51.5)
BRCA2	84 (41.0)	45 (46.4)
BRCA1 and *BRCA2*	4 (2.0)	0
Missing[b]	3 (1.5)	2 (2.1)
At the Time of Randomization, was the Patient's Breast Cancer Progressing?		
Yes	159 (77.6)	73 (75.3)
De Novo Metastatic Disease[c]		
Yes	26 (12.7)	12 (12.4)

Table 22 Summary of Selected Demographic and Patient Characteristics at Baseline (Full Analysis Set) in the OlympiAD Study

	LYNPARZA Tablets 300 mg bid (n=205)	Physician's Choice of Chemotherapy[a] (n=97)
Prior Endocrine Therapy		
For metastatic disease	68 (33.2)	30 (30.9)
For localised disease (adjuvant and/or neoadjuvant)	80 (39.0)	36 (37.1)
Stratification Factors (IVRS Data)		
Received prior chemotherapy regimens for metastatic breast cancer[d], n (%)		
No	59 (28.8)	28 (28.9)
Yes	146 (71.2)	69 (71.1)
ER and PgR status[e], n (%)		
ER and/or PgR positive	103 (50.2)	49 (50.5)
ER and PgR negative	102 (49.8)	48 (49.5)
Prior use of platinum for breast cancer, n (%)[f]		
Yes	60 (29.3)	26 (26.8)

a Physician's choice of chemotherapy consisting of either capecitabine, eribulin or vinorelbine.
b Patients with Missing status were not confirmed as g*BRCA*m using the Myriad CDx g*BRCA* test. Within the LYNPARZA arm all 3 cases were determined as *BRCA1* by local or CLIA testing and within the physician's choice of chemotherapy arm 1 patient was *BRCA1* and 1 patient was *BRCA2*.
c Metastatic disease at time of initial diagnosis of breast cancer.
d According to the electronic case report form data, 68 patients in the LYNPARZA arm and 31 patients in the physician's choice of chemotherapy arm had not received prior chemotherapy regimens for metastatic breast cancer.
e According to the electronic case report form data, 102 patients in the LYNPARZA arm and 47 patients in the physician's choice of chemotherapy arm were ER and/or PgR positive. Patient E2806008 did not have PgR status assessed but was stratified to the ER negative and PgR negative subgroup for randomization. The patient was excluded from summaries of eCRF data.
f According to the electronic case report form data, 55 patients in the LYNPARZA arm and 21 patients in the physician's choice of chemotherapy arm had prior use of platinum for breast cancer.

bid Twice daily; *BRCA* Breast cancer susceptibility gene; CDx Companion diagnostic; CLIA Clinical laboratory improvement amendments; ECOG Eastern cooperative oncology arm; eCRF electronic case report form; ER Estrogen receptor; FAS Full analysis set; g*BRCA* Germline *BRCA*; IVRS Interactive Voice Response System; PgR Progesterone receptor; SD Standard deviation.

Study Results

The primary endpoint in the OlympiAD study was progression-free survival (PFS) assessed by blinded independent central review (BICR) using RECIST 1.1. Secondary endpoints included time to second progression or death (PFS2), overall survival (OS) and objective response rate (ORR). Response was assessed every 6 weeks for the first 24 weeks, and then every 12 weeks relative to date of randomization, until disease progression. A summary of key efficacy findings is presented in Table 23 and Figure 3.

The study met its primary objective demonstrating a statistically significant and clinically meaningful improvement in PFS for LYNPARZA compared with the comparator arm with a hazard ratio (HR) of 0.58 (95% CI 0.43-0.80; p=0.0009; median 7.0 months [95% CI 5.68-8.31]

for LYNPARZA vs. 4.2 months [95% CI 2.79-4.27] for comparator). A sensitivity analysis using investigator-assessed PFS was consistent.

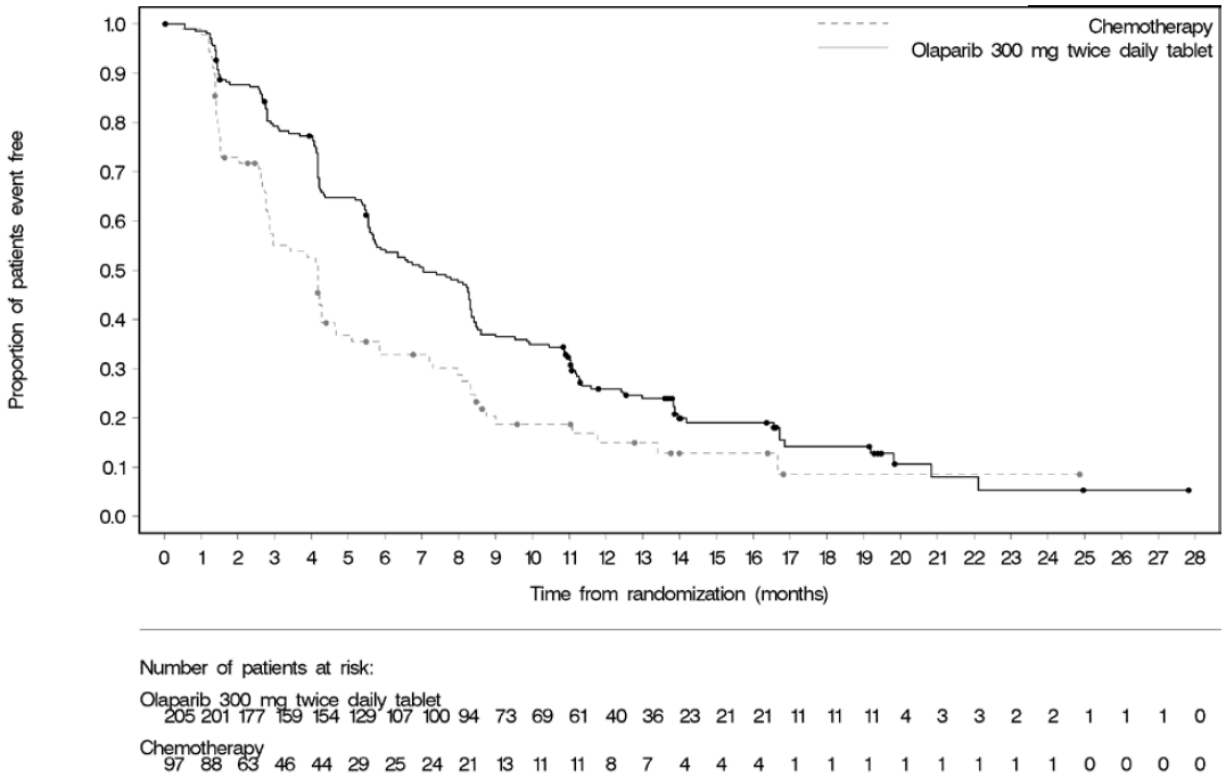
A statistically significant improvement in PFS2 was also observed with a HR of 0.57 (95% CI 0.40-0.83; p=0.0033; median 13.2 months for LYNPARZA vs 9.3 months for comparator). The median time to onset of response was 47 days for LYNPARZA vs 45 days for comparator. The median duration of response was 6.4 months (95% CI 5.0-7.2) for LYNPARZA vs 7.1 months (95% CI 3.2-12.2) for comparator. The OS data was 64% mature in the Full Analysis Set (FAS) at the time of the final OS analysis (DCO 25 September 2017), with a median follow-up for censored patients of 25.3 months for LYNPARZA vs. 26.3 months for comparator (HR 0.90; 95% CI 0.66-1.23; p=0.5131; median 19.3 months for LYNPARZA vs 17.1 months for control). Consistent results were observed across patient subgroups.

Table 23 Summary of Key Efficacy Findings for Patients with g*BRCA*m HER2-Negative Metastatic Breast Cancer in the OlympiAD Study

	LYNPARZA Tablets 300 mg bid		Physician's Choice of Chemotherapy[a]
PFS (77% Maturity)			
Number of events: Total number of patients (%)	163:205 (80)		71:97 (73)
Median time (months)	7.0		4.2
Median time (95% CI)	5.7-8.3		2.8-4.3
HR (95% CI)		0.58 (0.43-0.80)	
P value (2-sided)		P=0.0009	
Final OS (64% Maturity)			
Number of events: Total number of patients (%)	130:205 (63)		62:97 (64)[b]
Median time (months)	19.3		17.1
Median time (95% CI)	17.2-21.6		13.9-21.9
HR (95% CI)		0.90 (0.66-1.23)	
P value (2-sided)		P=0.5131	
ORR			
Number of objective responders: Total number of patients with measurable disease (%)[c]	100:167 (60)		19:66 (29)
95% CI	52.0 to 67.4		18.3 to 41.3

a Physician's choice of chemotherapy consisting of either capecitabine, eribulin or vinorelbine.
b Approximately a tenth of patients in the physician's choice group (8/97; 8.2%) received a subsequent PARP inhibitor.
c The complete response rate was 9% for LYNPARZA compared to 2% for chemotherapy arm.
bid Twice daily; CI Confidence interval; HR Hazard ratio; ORR Objective response rate; OS Overall survival; PFS Progression-free survival.

Figure 3 Progression Free Survival in Patients with g*BRCA*m HER2-Negative Metastatic Breast Cancer in the OlympiAD Study



Maintenance Treatment of *BRCA*-mutated Advanced Ovarian Cancer (SOLO1)

The efficacy of LYNPARZA (olaparib tablets) in the maintenance treatment setting in advanced (FIGO Stage III-IV) high-grade serous or endometrioid *BRCAm* ovarian cancer patients who are in response following first-line platinum-based chemotherapy was investigated in a Phase III randomized, double-blind, placebo-controlled, multicentre trial (SOLO1). The study randomized 391 patients (2:1 randomization: 260 LYNPARZA and 131 placebo) who were in response (CR [complete response] or PR [partial response]) following completion of first-line platinum-containing chemotherapy. Patients were stratified by response to first-line platinum chemotherapy (CR or PR). Treatment was continued for 2 years or until progression of the underlying disease. For patients who remained in complete clinical response (i.e. no radiological evidence of disease), the maximum duration of treatment was 2 years; however, patients who had evidence of disease that remained stable (i.e. no evidence of disease progression) could continue to receive LYNPARZA beyond 2 years.

Patients with *BRCA* mutations were identified either from germline testing in blood via a local test or central test (i.e. Myriad Integrated BRACAnalysis® test, Myriad BRACAnalysis CDx®, China BGI test) or from testing a tumour sample using a local test. The *BRCAm* status of all patients was confirmed where possible using the Myriad Integrated BRACAnalysis® test, the Myriad BRACAnalysis CDx® or the Foundation Medicine FoundationOne CDx™ Clinical Trial Assay.

Table 24 Trial Design for SOLO1 (Tablet Formulation)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
D0818C00001 (SOLO1 Study)	Phase III randomized (2:1), double-blind, placebo-controlled study, that investigated olaparib 300 mg twice daily tablet formulation as a maintenance treatment for patients with newly diagnosed *BRCA* mutated advanced ovarian cancer	300 mg (2 x 150 mg tablets) orally twice daily	LYNPARZA n=260 Placebo n=131	LYNPARZA = 53.6 years Placebo = 53.4 years	Female

Demographic and baseline patient characteristics in SOLO1 are summarized below.

Table 25 Selected Demographic and Patient Characteristics at Baseline (Full Analysis Set) for SOLO1 (Tablet Formulation)

	LYNPARZA Tablets 300 mg bid (n=260)	Placebo (n=131)
Demographics		
Age (years)		
Mean (SD)	53.6 (9.4)	53.4 (9.8)
Median (range)	53.0 (29-82)	53.0 (31-84)
Age group (years), n (%)		
<50	94 (36.2)	48 (36.6)
≥50 to <65	131 (50.4)	64 (48.9)
≥65	35 (13.5)	19 (14.5)
Race, n (%)		
White	214 (82.3)	106 (80.9)
Asian	39 (15.0)	20 (15.3)
Black/African American	2 (0.8)	2 (1.5)
Other	5 (1.9)	3 (2.4)
Ethnic group, n (%)		
Hispanic or Latino	11 (4.2)	7 (5.3)
Disease Characteristics		
ECOG Performance status, n (%)		
(0) Normal activity	200 (76.9)	105 (80.2)
(1) Restricted activity	60 (23.1)	25 (19.1)
Missing	0	1 (0.8)
Histology type, n (%)		
Serous	245 (94.2)	130 (99.2)
Endometrioid	9 (3.5)	0
Mixed, Epithelial	5 (1.9)	1 (0.8)
Other	1 (0.4)	0

Table 25 Selected Demographic and Patient Characteristics at Baseline (Full Analysis Set) for SOLO1 (Tablet Formulation)

	LYNPARZA Tablets 300 mg bid (n=260)	Placebo (n=131)
Serous, papillary	1 (0.4)	0
Tumour Characteristics		
Primary tumour location, n (%)		
Ovary	220 (84.6)	113 (86.3)
Fallopian tube	22 (8.5)	11 (8.4)
Primary peritoneal	15 (5.8)	7 (5.3)
Other	3 (1.2)	0
BRCA mutation status		
gBRCAm	258 (99.2)	131 (100.0)
sBRCAm	2 (0.8)	0
Response to previous platinum chemotherapy		
As randomized, n (%)		
Complete Response	213 (81.9)	107 (81.7)
Partial Response	47 (18.1)	24 (18.3)
History of Debulking Surgery		
Upfront surgery	161 (61.9)	85 (64.9)
Interval debulking surgery	94 (36.2)	43 (32.8)
Residual macroscopic disease	55 (21.2)	29 (22.1)
No residual macroscopic disease	199 (76.5)	98 (74.8)

bid Twice daily; ECOG Eastern Cooperative Oncology Group; *gBRCAm* germline *BRCA* mutation; *sBRCAm* somatic BRCA mutation; SD Standard deviation

Study Results

The study compared the efficacy of LYNPARZA (olaparib) maintenance treatment (300 mg [2 x 150 mg tablets] twice daily) with placebo in 391 patients with advanced (FIGO Stage III-IV) high-grade serous or endometrioid *BRCAm* ovarian cancer.

The primary endpoint was progression-free survival (PFS), defined as time from randomization to progression determined by investigator assessment using modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, or death. Key secondary efficacy endpoints included time from randomization to second progression or death (PFS2), overall survival (OS), time from randomization to first subsequent anti-cancer therapy or death (TFST) and health related quality of life (HRQoL). Patients had tumour assessments at baseline and every 12 weeks for 3 years, and then every 24 weeks relative to the date of randomization, until objective radiological disease progression. A summary of key efficacy findings is presented in Table 26 and Figure 4.

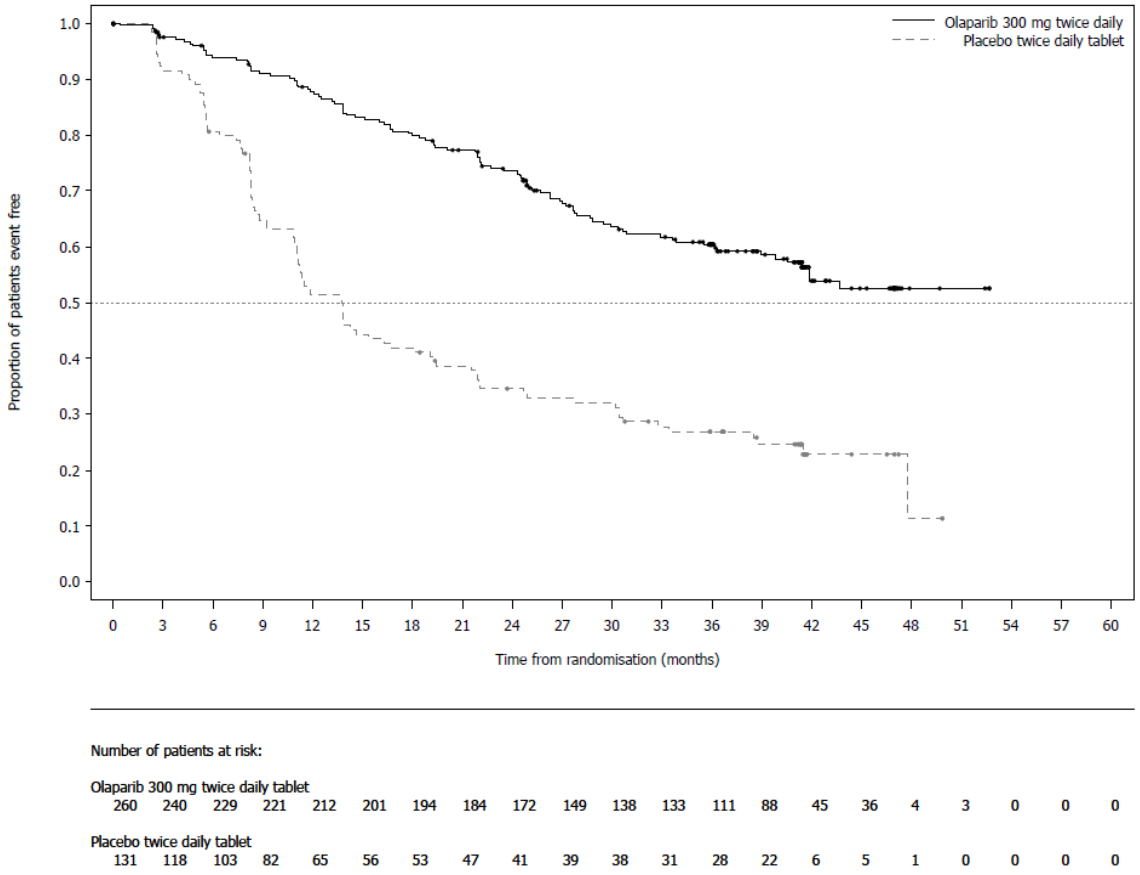
The study met its primary objective, demonstrating a clinically relevant and statistically significant improvement in investigator assessed PFS for LYNPARZA compared to placebo; these results were consistent with the sensitivity analysis of PFS using blinded independent central radiological (BICR) review. Interim OS was immature with events in 21% of patients and suggesting no detriment for patients on the LYNPARZA arm. A clinically meaningful and statistically significant improvement in PFS2 was also observed indicating that the benefit observed with LYNPARZA continued to be evident even with the use of subsequent therapies (see Table 26). Time from randomization to start of first subsequent therapy or death (TFST) demonstrated a HR of 0.30 (95% CI 0.22-0.40, p<0.0001[not controlled for multiplicity], median 51.8 months LYNPARZA vs 15.1 months placebo).

Table 26 Key Efficacy Findings for Patients with *BRCA*-mutated Advanced Ovarian Cancer in SOLO1 (Tablet Formulation)

	LYNPARZA Tablets 300 mg bid	Placebo
PFS (51% maturity)		
Number of events: Total number of patients (%)	102:260 (39)	96:131 (73)[a]
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)[b]	0.50 (0.35-0.72)	
P value (2-sided)	p=0.0002	

a Of the 94 patients on the placebo arm who received subsequent therapy, 49 (52%) received a PARP inhibitor.
b A value <1 favours LYNPARZA. The analysis was performed using a Cox proportional hazards model including response to previous platinum chemotherapy (CR or PR) as a covariate.
bid Twice daily; NR Not reached; CI Confidence interval

Figure 4 Kaplan-Meier Plot of PFS in Patients with *BRCA*-mutated Advanced Ovarian Cancer[a, b] for SOLO1 (Tablet Formulation)



[a] 51% Maturity - Investigator Assessment

[b] 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.

Treatment with LYNPARZA did not negatively impact patient reported outcomes or health related quality of life as assessed by the Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O).

Maintenance Treatment of Platinum-Sensitive Relapsed *BRCA*-mutated Ovarian Cancer (SOLO2)

The efficacy of LYNPARZA (olaparib tablets) in the maintenance treatment setting in platinum-sensitive relapsed (PSR) ovarian, fallopian tube or primary peritoneal cancer was investigated in a randomized phase III double-blind, placebo-controlled trial in patients with PSR, *BRCA*-mutated (*BRCA*m) disease (SOLO2). SOLO2 enrolled PSR patients who were in response following completion of platinum-based chemotherapy and whose disease had recurred more than 6 months after completion of penultimate platinum-based chemotherapy. Patients could not have received prior LYNPARZA or other PARP inhibitor treatment. Patients could have received prior bevacizumab, except in the regimen immediately prior to randomization. Patients with *BRCA* mutations were identified either from germline testing in blood via a local test or the Myriad Clinical Laboratory Improvement Amendments (CLIA) Integrated BRAC*Analysis*® test, or from testing a tumour sample using a local test or a test performed by Foundation Medicine.

Table 27 Trial Design for SOLO2 (Tablet Formulation)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
D0816C00002 (SOLO2 Study)	Phase III randomized (2:1), double-blind, placebo-controlled study, that investigated olaparib 300 mg twice daily tablet formulation as a maintenance treatment for patients with *BRCA* mutated PSR ovarian cancer	300 mg (2 x 150 mg tablets) orally twice daily	LYNPARZA n=196 Placebo n=99	LYNPARZA = 57.0 years Placebo = 56.6 years	Female

Demographic and baseline patient characteristics in SOLO2 are summarized below.

Table 28 Selected Demographic and Patient Characteristics at Baseline (Full Analysis Set) for SOLO2 (Tablet Formulation)

	LYNPARZA Tablets 300 mg bid (n=196)	Placebo (n=99)
Demographics		
Age (years)		
Mean (SD)	57.0 (9.2)	56.6 (8.9)
Median (range)	56.0 (28-83)	56.0 (39-78)
Age group (years), n (%)		
<50	38 (19.4)	25 (25.3)
≥50 to <65	118 (60.2)	52 (52.5)
≥65	40 (20.4)	22 (22.2)
Race, n (%)		
White	173 (88.3)	91 (91.9)
Black/African American	1 (0.5)	0
Asian	22 (11.2)	7 (7.1)
Other	0	1 (1.0)
Ethnic group, n (%)		
Hispanic or Latino	10 (5.1)	1 (1.0)
Disease Characteristics		
ECOG Performance status, n (%)		
(0) Normal activity	162 (82.7)	77 (77.8)
(1) Restricted activity	32 (16.3)	22 (22.2)
(2) In bed <50% of the time	0	0
Unknown	2 (1.0)	0
Histology type, n (%)		
Serous	183 (93.4)	86 (86.9)
Endometrioid	9 (4.6)	8 (8.1)
Mixed, Epithelial	3 (1.5)	4 (4.0)
Other	0	1 (1.0)
Serous, pappilliferum, endometrioid	0	1 (1.0)
Missing	1 (0.5)	0
Tumour Characteristics		
Primary tumour location, n (%)		
Ovary	162 (82.7)	86 (86.9)
Fallopian tube	13 (6.6)	4 (4.0)
Primary peritoneal	18 (9.2)	9 (9.1)
Other	2 (1.0)	0
Missing	1 (0.5)	0
Previous Treatments		
Response to previous platinum chemotherapy (recorded at randomization by IVRS), n (%)[a]		
PR	105 (53.6)	52 (52.5)
CR	91 (46.4)	47 (47.5)
Time to disease progression in the penultimate platinum-based chemotherapy prior to enrolment (recorded at randomization by IVRS), n (%)[b]		
>6 to ≤12 months	79 (40.3)	40 (40.4)
>12 months	117 (59.7)	59 (59.6)
Number of prior chemotherapies, n (%)		
2	108 (55.1)	60 (60.6)
3	54 (27.6)	21 (21.2)

Table 28 Selected Demographic and Patient Characteristics at Baseline (Full Analysis Set) for SOLO2 (Tablet Formulation)

	LYNPARZA Tablets 300 mg bid (n=196)	Placebo (n=99)
4 or more	33 (16.8)	18 (18.2)
Median (range)	2.0 (2-7)	2.0 (2-13)
Number of prior platinum-containing chemotherapies, n (%)		
2	110 (56.1)	62 (62.6)
3	60 (30.6)	20 (20.2)
4 or more	25 (12.8)	17 (17.2)
Median (range)	2.0 (2-7)	2.0 (2-7)

a Objective Response: CR = Patients with no target lesions and no non-target lesions are baseline; PR = Patients with target lesions and/or non-target lesions at baseline. Note: This is the response from the platinum regimen just prior to therapy.
b Platinum sensitivity = time to progression after the completion of platinum chemotherapy. Note: Platinum sensitivity refers to the penultimate platinum not the platinum regimen that was just completed by the patient.
bid Twice daily; CR Complete response; CSR Clinical study report; ECOG Eastern Cooperative Oncology Group; FAS Full analysis set; IVRS Interactive voice response system; PR Partial response; SD Standard deviation

Study Results

The study compared the efficacy of LYNPARZA (olaparib) maintenance treatment (300 mg [2 x 150 mg tablets] twice daily) taken to progression with placebo treatment in 295 patients with high-grade serous or endometrioid PSR ovarian cancer (2:1 randomization: 196 LYNPARZA and 99 placebo) who were in response (CR or PR) following completion of platinum-containing chemotherapy. All patients had evidence of germline *BRCA* mutation (g*BRCA*m) at baseline.

The primary endpoint was progression-free survival (PFS) determined by investigator assessment using RECIST 1.1. A secondary efficacy endpoint was overall survival (OS). A summary of key efficacy findings is presented in Table 29 and Figure 5.

The study met its primary objective demonstrating a clinically meaningful and statistically significant improvement in investigator assessed PFS for LYNPARZA compared with placebo with a HR of 0.30. 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 LYNPARZA vs. 5.5 months for placebo). At 2 years, 43% LYNPARZA-treated patients remained progression-free compared with only 15% placebo-treated patients. At the final analysis of OS (DCO 03 February 2020) the HR did not reach statistical significance.

Table 29 Key Efficacy Findings for Patients with g*BRCA*m PSR Ovarian Cancer in SOLO2 (Tablet Formulation)

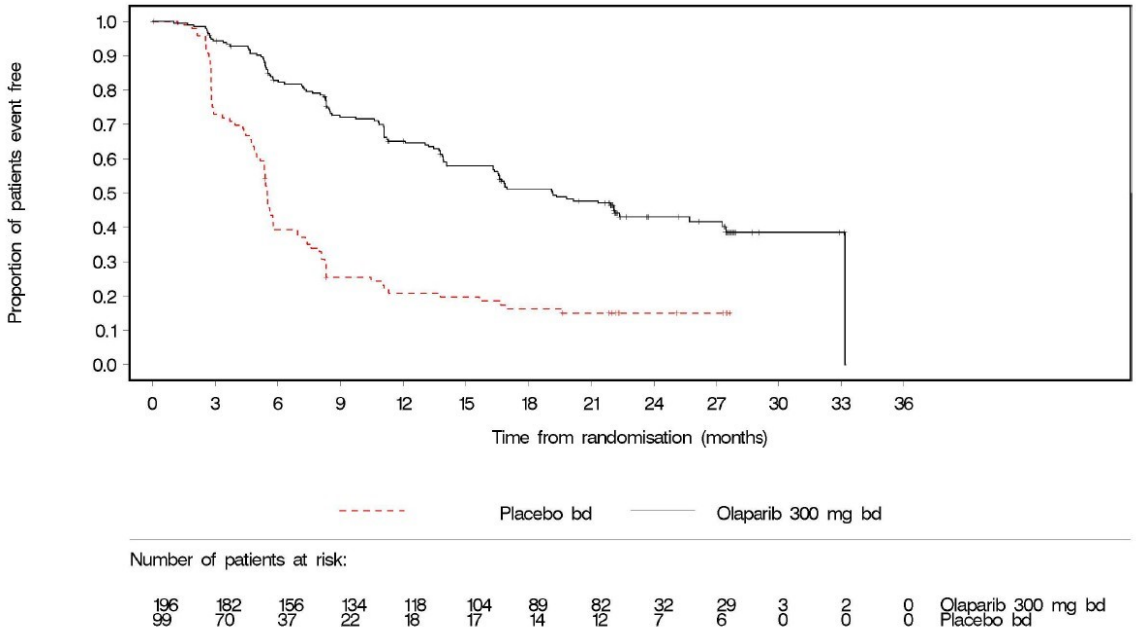
	LYNPARZA Tablets 300 mg bid	Placebo
PFS (63% maturity)		
Number of events: Total number of patients (%)	107:196 (55)	80:99 (81)
Median time (months)	19.1	5.5
HR (95% CI)[a]	0.30 (0.22-0.41)	
P value (2-sided)	p<0.0001	
Final OS (61% maturity)		
Number of events: Total number of patients (%)	116:196 (59)	65:99 (66)[b]
Median time 95% CI, (months)	51.7 (41.5, 59.1)	38.8 (31.4, 48.6)
HR (95% CI)[a]	0.74 (0.54-1.00)	
P value (2-sided)	p=0.0537	

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

[b] 38% (38/99) of placebo-treated patients received a subsequent PARP inhibitor.

bid Twice daily; OS Overall survival; PFS Progression free survival; CI Confidence interval

Figure 5 Kaplan-Meier Plot of PFS in Patients with g*BRCA*m PSR Ovarian Cancer[a] for SOLO2 (Tablet Formulation)



[a] 63% Maturity - Investigator Assessment

The secondary endpoints included time from randomization to second progression or death ([PFS2], HR of 0.50, 95% CI 0.34-0.72, p=0.0002, median not reached for LYNPARZA vs 18.4 months placebo) and time from randomization to start of first subsequent therapy or death ([TFST], HR of 0.37, 95% CI 0.28-0.48, nominal p<0.0001, median 27.4 months LYNPARZA vs 7.2 months placebo).

Treatment with LYNPARZA did not negatively impact patient reported outcomes or health related quality of life as assessed by the Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O).

The use of LYNPARZA in the maintenance treatment setting for *BRCA*m patient population is supported by data from a randomized, phase II, double-blind, placebo-controlled trial (Study 19).

Maintenance Treatment of Platinum-Sensitive Relapsed *BRCA* wild type Ovarian Cancer (Study 19)

The efficacy of LYNPARZA (olaparib capsules) in the maintenance treatment setting in PSR *BRCA*-mutated and *BRCA* wild type ovarian, fallopian tube or primary peritoneal cancer was investigated in a randomized phase II double-blind, placebo-controlled trial in patients with PSR disease (Study 19). Study 19 enrolled PSR patients who were in response following completion of platinum-based chemotherapy and whose disease had recurred more than 6 months after

completion of penultimate platinum-based chemotherapy. Patients could not have received prior LYNPARZA or other PARP inhibitor treatment. Patients could have received prior bevacizumab, except in the regimen immediately prior to randomization. Patients with *BRCA* mutations were identified either from germline testing in blood via a local test or the Myriad Clinical Laboratory Improvement Amendments (CLIA) Integrated BRAC*Analysis*® test, or from testing a tumour sample using a local test or a test performed by Foundation Medicine.

Table 30 Trial Design for Study 19 (Capsule Formulation)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
D0810C00019 (Study 19)	Phase II, randomized, double-blind, placebo-controlled maintenance study of olaparib compared to placebo in PSR high grade serous ovarian cancer patients	400 mg (8 x 50 mg capsules formulation) orally twice daily	**All patients:** LYNPARZA n=136 Placebo n=129 ***BRCA*-mutated patients:** LYNPARZA n=74 Placebo n=62 ***BRCA* wild type patients:** LYNPARZA n=57 Placebo n=61	LYNPARZA = 58.9 years Placebo = 58.5 years	Female

Demographic and baseline patient characteristics were generally well balanced between treatment groups for all patients in Study 19 and are summarized below.

Table 31 Selected Demographic and Patient Characteristics at Baseline for the Overall Population and Subgroups Based on *BRCA* Status (Full Analysis Set) for Study 19 (Capsule Formulation)

	All Patients		*BRCA*-mutated		*BRCA* wild type	
	LYNPARZA Capsules 400 mg bid n=136	Placebo n=129	LYNPARZA Capsules 400 mg bid n=74	Placebo n=62	LYNPARZA Capsules 400 mg bid n=57	Placebo n=61
Demographics						
Age (years)						
Mean (standard deviation)	58.9 (10.95)	58.5 (9.89)	57.6 (10.37)	55.5 (10.53)	60.8 (11.69)	62.1 (7.82)
Median (range)	58.0 (21 to 89)	59.0 (33 to 84)	57.5 (38 to 89)	55.0 (33 to 84)	62.0 (21-80)	63.0 (49-79)

Table 31 Selected Demographic and Patient Characteristics at Baseline for the Overall Population and Subgroups Based on *BRCA* Status (Full Analysis Set) for Study 19 (Capsule Formulation)

	All Patients		*BRCA*-mutated		*BRCA* wild type	
	LYNPARZA Capsules 400 mg bid n=136	Placebo n=129	LYNPARZA Capsules 400 mg bid n=74	Placebo n=62	LYNPARZA Capsules 400 mg bid n=57	Placebo n=61
Age group, n (%)						
<50 years	30 (22.1)	20 (15.5)	19 (25.7)	16 (25.8)	10 (17.5)	1 (1.6)
≥50 to <65 years	61 (44.9)	74 (57.4)	38 (51.4)	35 (56.5)	20 (35.1)	37 (60.7)
≥65 years	45 (33.1)	35 (27.1)	17 (23.0)	11 (17.7)	27 (47.4)	23 (37.7)
Race, n (%)						
White	130 (95.6)	126 (97.7)	70 (94.6)	61 (98.4)	55 (96.5)	59 (96.7)
Black or African American	2 (1.5)	1 (0.8)	2 (2.7)	0	0	1 (1.6)
Asian	2 (1.5)	2 (1.6)	1 (1.4)	1 (1.6)	1 (1.8)	1 (1.6)
Other	2 (1.5)	0	1 (1.4)	0	1 (1.8)	0
Disease Characteristics						
ECOG PS, n (%)						
(0) Normal activity	110 (80.9)	95 (73.6)	62 (83.8)	45 (72.6)	45 (78.9)	45 (73.8)
(1) Restricted activity	23 (16.9)	30 (23.3)	11 (14.9)	15 (24.2)	10 (17.5)	14 (23.0)
(2) In bed ≤50% of the time	1 (0.7)	2 (1.6)	0	1 (1.6)	1 (1.8)	1 (1.6)
Unknown	2 (1.5)	2 (1.6)	1 (1.4)	1 (1.6)	1 (1.8)	1 (1.6)
Tumour Characteristics						
Primary tumour location						
Ovary	119 (87.5)	109 (84.5)	65 (87.8)	54 (87.1)	50 (87.7)	49 (80.3)
Fallopian tube	3 (2.2)	3 (2.3)	1 (1.4)	2 (3.2)	2 (3.5)	1 (1.6)
Primary peritoneal	14 (10.3)	16 (12.4)	8 (10.8)	6 (9.7)	5 (8.8)	10 (16.4)
Other	0	1 (0.8)[a]	0	0	0	1 (1.6)

Table 31 Selected Demographic and Patient Characteristics at Baseline for the Overall Population and Subgroups Based on *BRCA* Status (Full Analysis Set) for Study 19 (Capsule Formulation)

	All Patients		*BRCA*-mutated		*BRCA* wild type	
	LYNPARZA Capsules 400 mg bid n=136	Placebo n=129	LYNPARZA Capsules 400 mg bid n=74	Placebo n=62	LYNPARZA Capsules 400 mg bid n=57	Placebo n=61
Tumour grade						
Well differentiated (G1)	0	0	0	0	0	0
Moderately differentiated (G2)	36 (26.5)	34 (26.4)	17 (23.0)	15 (24.2)	15 (26.3)	16 (26.2)
Poorly differentiated (G3)	97 (71.3)	89 (69.0)	55 (74.3)	46 (74.2)	41 (71.9)	41 (67.2)
Undifferentiated (G4)	2 (1.5)	4 (3.1)	1 (1.4)	0	1 (1.8)	4 (6.6)
Unassessable (GX)	1 (0.7)	2 (1.6)	1 (1.4)	1 (1.6)	0	0
Number of previous chemotherapy regimens						
Mean	3.1	2.9	3.3	3.0	2.8	2.7
Median (range)	3 (2-11)	3 (2-8)	3 (2-11)	3 (2-8)	2 (2-8)	2 (2-8)
Number of previous platinum-containing chemotherapies						
Mean	2.6	2.5	2.8	2.5	2.5	2.4
Median (range)	2 (2-7)	2 (2-8)	2 (2-7)	2 (2-6)	2 (2-5)	2 (1-5)

*BRCA*m = Breast cancer susceptibility gene-mutated; ECOG PS = Eastern Cooperative Oncology Group performance status; n = Total number of patients.
*BRCA*m subgroup included patients with germline and/or somatic *BRCA* mutation.

Study Results

The study compared the efficacy of LYNPARZA (olaparib capsule) maintenance treatment (400 mg [8 x 50 mg capsules] twice daily) taken to progression with placebo treatment in 265 (136 LYNPARZA and 129 placebo) PSR patients who were in response (CR [complete response] or PR [partial response]) following completion of platinum-containing chemotherapy. The primary endpoint was progression-free survival (PFS) based on investigator assessment using Response Evaluation Criteria in Solid Tumors (RECIST) 1.0. Secondary efficacy endpoints included overall survival (OS) and disease control rate (DCR).

A summary of key efficacy findings for all patients regardless of *BRCA* status and patients with *BRCA*m and *BRCA* wild type PSR ovarian cancer in Study 19 is presented in Table 32, Figure 6 and Figure 7. The study met its primary objective demonstrating a statistically significant and clinically relevant improvement in PFS for LYNPARZA compared with placebo with a HR of 0.35. At the final OS analysis at 79% maturity, the HR comparing LYNPARZA with placebo was 0.73.

In the LYNPARZA-treated group, 23.5% of patients remained on treatment for ≥2 years and 13.2% for ≥5 years. In the placebo-treated group, 3.9% of patients remained on treatment for ≥2 years and 0.8% for ≥5 years. TFST and TSST were also longer for LYNPARZA-treated patients.

Table 32 Key Efficacy Findings for the Overall Population and Subgroups Based on *BRCA* Status in Study 19 (Capsule Formulation)

	All Patients		*BRCA*-mutated		*BRCA* wild type	
	LYNPARZA Capsules 400 mg bid	Placebo	LYNPARZA Capsules 400 mg bid	Placebo	LYNPARZA Capsules 400 mg bid	Placebo
PFS						
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)	8.4	4.8	11.2	4.3	7.4	5.5
HR (95% CI)[a]	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	
OS						
Number of events: Total number of patients (%)	98:136 (72)	112:129 (87)	49:74 (66)	50:62 (81)[b]	45:57 (79)	57:61 (93)
Median time (months)	29.8	27.8	34.9	30.2	24.5	26.6
HR (95% CI)[a]	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	

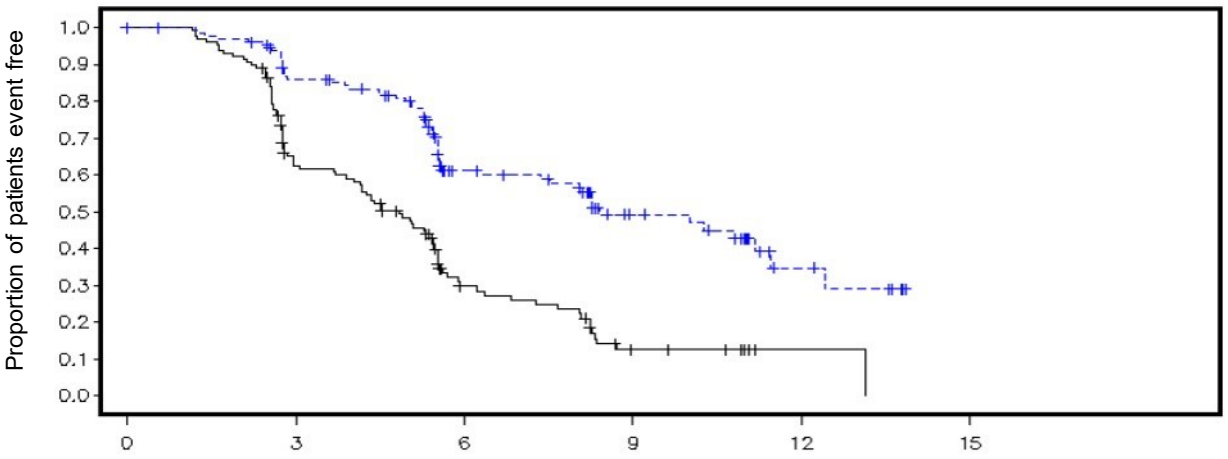
* There was no strategy for multiple testing in place for the sub-group analyses.

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

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

bid Twice daily; OS Overall survival; PFS Progression-free survival; DCO Data cut off; CI Confidence interval.
DCO (PFS 30 June 2010; OS 09 May 2016)

Figure 6 Kaplan-Meier Plot of PFS in the Full Analysis Set[a] for Study 19 (Capsule Formulation)



Time from randomization (months)

----------Placebo bid - - - - - - - - - LYNPARZA 400 mg bid

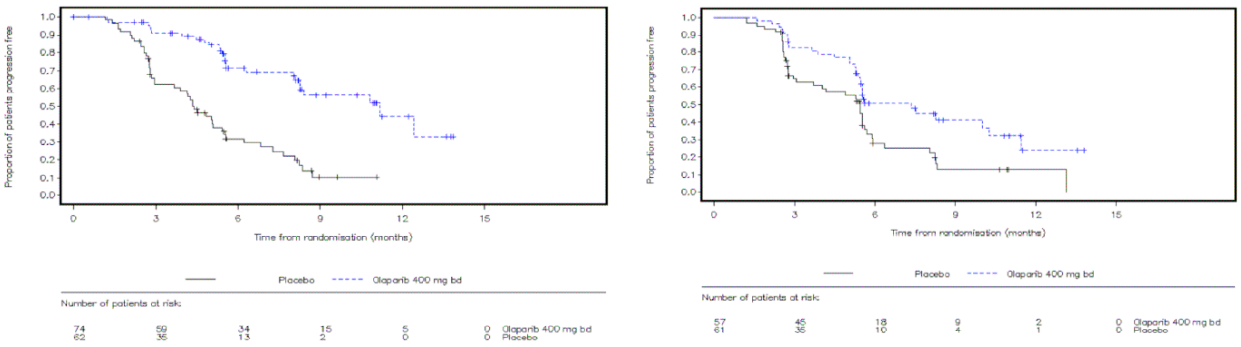
Number of patients at risk:

136	106	53	24	7	0	LYNPARZA 400 mg bid
129	72	24	7	1	0	Placebo

[a] (58% Maturity - Investigator Assessment) DCO 30 June 2010

Figure 7 Kaplan-Meier Plot of PFS in the Full Analysis Set (*BRCA*-mutated and *BRCA* wild type)[a] for Study 19 (Capsule Formulation)

***BRCA*-mutated** ***BRCA* wild type**



[a] (58% Maturity - Investigator Assessment) DCO 30 June 2010

Within the overall population, the DCR at 24 weeks was 53% and 25% for patients in the LYNPARZA and placebo groups, respectively.

Maintenance Treatment of g*BRCA*m Metastatic Adenocarcinoma of the Pancreas (POLO)

The safety and efficacy of LYNPARZA in the maintenance treatment of patients with metastatic g*BRCA*m adenocarcinoma of the pancreas whose disease had not progressed following at least 16 weeks of first-line platinum-based chemotherapy was studied in a Phase III, randomized, double-blind, placebo-controlled, multicentre trial (D081FC00001, POLO). A total of 154 patients were randomized 3:2 to receive LYNPARZA 300 mg (2 x 150 mg tablets) twice daily (n=92) or placebo (n=62 placebo). There was no upper limit to the duration of chemotherapy received. After 16 weeks of continuous platinum-based chemotherapy, the platinum could be discontinued at any time for toxicity and the other agents continued; the patients were eligible for randomization as long as there was no evidence of progression at any time during chemotherapy treatment. All toxicities from previous anti-cancer therapy must have been resolved to CTCAE grade 1, except for alopecia, grade 3 peripheral neuropathy and Hgb ≥ 9 g/dL. LYNPARZA treatment was continued until progression of the underlying disease.

Patients with germline *BRCA* mutations were identified from prior local testing results or by central testing using the Myriad BRACAnalysis® or Myriad BRACAnalysis CDx® test. The *BRCAm* status of all patients identified using prior local testing results was confirmed, where sent, using the Myriad BRACAnalysis® or Myriad BRACAnalysis CDx® test.

Table 33 Trial Design for POLO (Tablet Formulation)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
D081FC00001 (POLO Study)	Phase III randomized (3:2), double-blind, placebo-controlled study, that investigated LYNPARZA 300 mg twice daily tablet formulation as a maintenance treatment for *gBRCAm* patients with metastatic pancreatic adenocarcinoma	300 mg (2 x 150 mg tablets) orally twice daily	LYNPARZA n=92 Placebo n=62	LYNPARZA = 58 years Placebo = 56 years	Female and Male

Demographic and baseline patient characteristics in POLO are summarized below.

Table 34 Selected Demographic and Patient Characteristics at Baseline (Full Analysis Set) for POLO (Tablet Formulation)

	LYNPARZA Tablets 300 mg bid (n=92)	Placebo (n=62)
Demographics		
Age (years)		
Mean (SD)	58.2 (10.3)	56.4 (9.1)
Median (range)	57.0 (37-84)	57.0 (36-75)
Sex, n (%)		
Male	53 (57.6)	31 (50.0)
Female	39 (42.4)	31 (50.0)
Age group (years), n (%)		
<55	35 (38.0)	27 (43.5)
≥55 to <65	29 (31.5)	22 (35.5)
≥65	28 (30.4)	13 (21.0)
Race, n (%)		
White	82 (89.1)	59 (95.2)
Asian	4 (4.3)	2 (3.2)
Black/African American	5 (5.4)	0
American Indian or Alaskan Native and Other	1 (1.1)	1 (1.6)
Disease Characteristics		
ECOG Performance status, n (%)		
(0) Normal activity	65 (70.7)	38 (61.3)
(1) Restricted activity	25 (27.2)	23 (37.1)
Missing	2 (2.2)	1 (1.6)
Histology type (at time of diagnosis), n (%)		
Adenocarcinoma (not otherwise specified)	53 (57.6)	37 (59.7)
Adenocarcinoma: acinar	0	4 (6.5)
Adenocarcinoma: papillary	0	1 (1.6)
Adenocarcinoma: solid with mucus formation	0	1 (1.6)
Pancreatic adenocarcinoma	38 (41.3)	17 (27.4)
Not affected	0	1 (1.6)
Missing	1 (1.1)	1 (1.6)
Extent of disease at baseline		
Metastatic[a]	87 (94.6)	55 (88.7)
Previous disease-related chemotherapy		
Previous chemotherapy[b]		
FOLFIRINOX variants	79 (85.9)	50 (80.6)
Gemcitabine/cisplatin	2 (2.2)	3 (4.8)
Other	10 (10.9)	8 (12.9)
Missing	1 (1.1)	1 (1.6)
Type of previous chemotherapy		
Doublets	15 (16.3)	10 (16.1)
Triplets	73 (79.3)	46 (74.2)
Other	3 (3.3)	5 (8.1)
Missing	1 (1.1)	1 (1.6)

Table 34 Selected Demographic and Patient Characteristics at Baseline (Full Analysis Set) for POLO (Tablet Formulation)

	LYNPARZA Tablets 300 mg bid (n=92)	Placebo (n=62)
Time on first-line treatment until randomisation		
≤6 months	61 (66.3)	40 (64.5)
>6 months	30 (32.6)	21 (33.9)
Missing	1 (1.1)	1 (1.6)
Best response on first-line treatment		
Stable disease	45 (48.9)	31 (50.0)
Partial response/complete response	46 (50.0)	30 (48.4)
Missing	1 (1.1)	1 (1.6)

[a] Sites of metastases at baseline assessed post patient response to first-line chemotherapy, prior to study treatment. Summary includes sites of disease where the extent is recorded as metastatic or both (ie, locally advanced and metastatic).

[b] Ninety-six per-cent (96%) of patients were randomized within 8 weeks of their last dose of platinum-based chemotherapy. The median time from initiation of first-line platinum-based chemotherapy to randomisation was 5.8 months (range 3.4 to 33.4 months).

bid Twice daily; ECOG Eastern Cooperative Oncology Group; *gBRCAm* Germline *BRCA* mutation; SD Standard deviation

Study Results

The study compared the efficacy of LYNPARZA maintenance treatment (300 mg [2 x 150 mg tablets] twice daily) with placebo in 154 patients with *gBRCAm* patients with metastatic pancreatic adenocarcinoma.

The primary endpoint was progression-free survival (PFS), defined as time from randomization to progression determined by BICR using modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, or death. Secondary efficacy endpoints included overall survival (OS), time from randomization to second progression or death (PFS2), time from randomization to first subsequent anti-cancer therapy or death (TFST), time from randomization to discontinuation of treatment or death (TDT), objective response rate (ORR), duration of response (DoR), response rate, time to response and health related quality of life (HRQoL). Patients had tumour assessments at baseline and every 8 weeks for 40 weeks, and then every 12 weeks relative to the date of randomization, until objective radiological disease progression. For PFS, the median follow-up time for censored patients was 9.1 months in the LYNPARZA arm and 3.8 months in the placebo arm. For OS, the median follow-up time for censored patients was 31.3 months in the LYNPARZA arm and 23.9 months in the placebo arm. A summary of key efficacy findings is presented in Table 35 and Figure 8.

The study demonstrated a clinically meaningful and statistically significant improvement in PFS for LYNPARZA compared to placebo, with a HR of 0.53 (95% CI 0.35 to 0.82; p=0.0038; the median was 7.4 months for LYNPARZA vs 3.8 months for placebo). The sensitivity analysis of PFS by investigator assessment (HR 0.51; 95% CI 0.34 to 0.78; p=0.0017; median 6.3 months vs 3.7 months for LYNPARZA vs placebo, respectively) was consistent with the PFS analysis by BICR.

At the time of the PFS analysis the median DoR was longer in the LYNPARZA arm (24.9 months) compared to the placebo arm (3.7 months), with a longer median time to onset of response (5.4 months for LYNPARZA vs 3.6 months for placebo). At the time of final OS analysis (DCO 21 July 2020), the HR for PFS2 (60% maturity, not controlled for multiplicity) was

0.66 (95% CI 0.43 – 1.02; nominal p=0.0613) with a difference in median of 7.6 months in favour of LYNPARZA (median 16.9 months for LYNPARZA vs 9.3 months for placebo). A clinically meaningful and statistically significant improvement in TFST and TDT was observed for LYNPARZA-treated patients. At the final analysis of OS (70% maturity) the HR for OS did not reach statistical significance. The percentage of patients that were alive and in follow-up was 28% in the LYNPARZA arm and 18% in the placebo arm.

Table 35 Key Efficacy Findings for Patients with g*BRCAm* Metastatic Adenocarcinoma of the Pancreas in POLO (Tablet Formulation)

	LYNPARZA Tablets 300 mg bid	Placebo
PFS (68% maturity)		
Number of events: Total number of patients (%)	60:92 (65)	44:62 (71)
Median time (months)	7.4	3.8
HR (95% CI)[a,b]	0.53 (0.35-0.82)	
P value (2-sided)	P=0.0038	
Final OS (70% maturity)		
Number of events: Total number of patients (%)	61:92 (66)	47:62 (76)[c]
Median time (months)	19.0	19.2
HR (95% CI)[b,c]	0.83 (0.56-1.22)	
P value (2-sided)	p=0.3487	
ORR		
Number of objective responders: total number of patients with measurable disease at baseline (%)	18:78 (23.1)	6:52 (11.5)
Complete response (%)	2 (2.6)	0
Partial response (%)	16 (20.5)	6 (11.5)
Odds ratio (95% CI)	2.30 (0.89, 6.76)	
P value* (2-sided)	p=0.1028	

[a] A value <1 favours LYNPARZA.

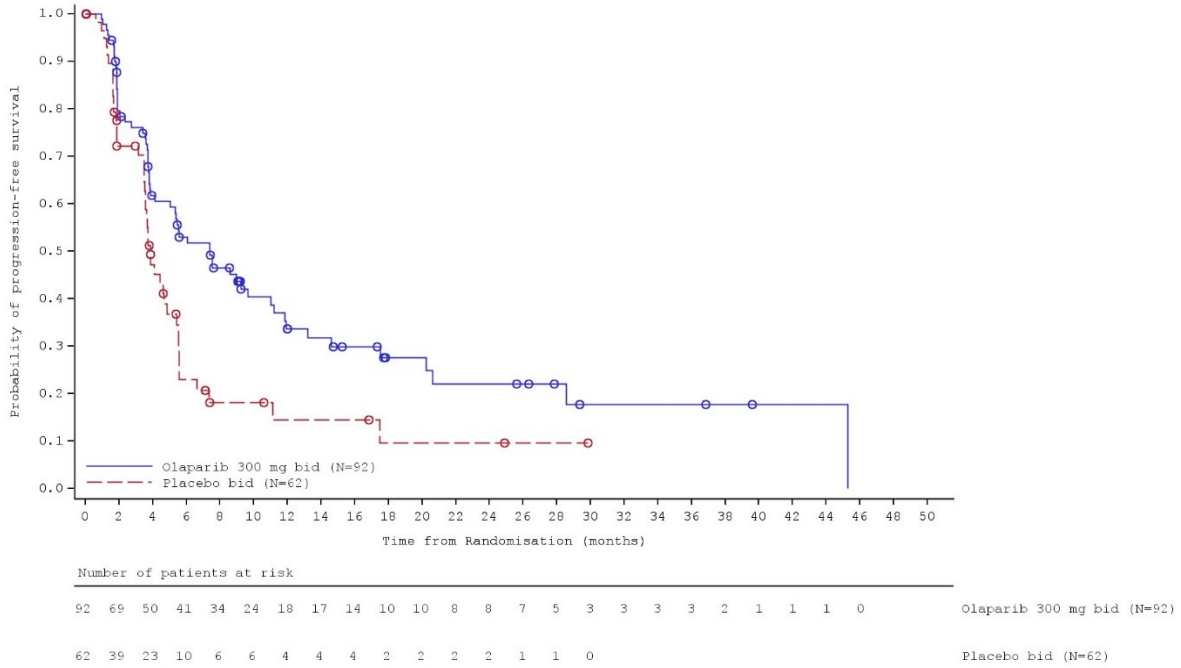
[b] The analysis was performed using a log-rank test.

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

* Not controlled for multiplicity.

bid Twice daily; CI Confidence interval; HR Hazard Ratio; NC Not calculable; ORR Objective Response Rate; OS Overall survival; PFS Progression-free survival;

Figure 8 Kaplan-Meier Plot of PFS in Patients with g*BRCAm metastatic adenocarcinoma of the pancreas*[a, b] for POLO (Tablet Formulation)



[a] 68% Maturity - BICR Assessment
[b] The proportion of patients that were alive and progression-free at 12, 24 and 36 months were 34%, 28% and 22% for LYNPARZA vs 15%, 10% and 10% for placebo

Patient-reported HRQoL data demonstrated no clinically meaningful differences in global HRQoL over the treatment period between arms, as treatment with LYNPARZA did not negatively impact HRQoL compared to placebo.

Treatment of HRR Mutation Positive Metastatic Castration Resistant Prostate Cancer (mCRPC) (PROfound)

The efficacy of LYNPARZA (olaparib tablets) in the treatment of patients with homologous recombination repair (HRR)-mutated (germline and/or somatic) metastatic castration-resistant prostate cancer (mCRPC) following prior treatment with a new hormonal agent (NHA, enzalutamide or abiraterone acetate) was investigated in PROfound, a randomized, open-label, multicentre phase III trial. The study randomized 387 patients (2:1 randomization: 256 LYNPARZA and 131 Investigator's Choice of NHA) who had progressed on a prior NHA and had a tumour mutation in one of 15 genes involved in the 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 (245 patients: 162 LYNPARZA and 83 Investigator's Choice of NHA); 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 (142 patients: 94 LYNPARZA and 48 Investigator's Choice of NHA). Patients with co-mutations

(*BRCA1*, *BRCA2* or *ATM* plus a Cohort B gene) were randomized in Cohort A. Patients were stratified by prior taxane use and evidence of measurable disease. All patients received a GnRH analog or had prior bilateral orchiectomy. Treatment was continued until disease progression. Patients randomized to the comparator arm were given the option to switch to LYNPARZA upon confirmed radiological BICR progression.

Patients with HRR gene mutations were identified based on prostate cancer tissue specimens that were tested centrally. HRR clinical trial assay was performed in a CLIA certified laboratory (CLIA HRR Clinical Trial Assay) or from reanalysis of data from a prior prostate cancer tissue test.

Table 36 Trial Design for PROfound (Tablet Formulation)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
D081DC00007 (PROfound Study)	Phase III randomized (2:1), open-label, multicentre study, that investigated olaparib 300 mg twice daily tablet formulation as a treatment for patients with HRR-mutated mCRPC	300 mg (2 x 150 mg tablets) orally twice daily	LYNPARZA Cohort A: n=162 Cohort A+B: n=256 Investigator's Choice of NHA (abiraterone or enzalutamide) Cohort A: n=83 Cohort A+B: n=131	LYNPARZA Cohort A: 68.0 years (47-86) Cohort A+B: 68.5 years (47-91) Investigator's Choice of NHA Cohort A: 68.1 years (49-86) Cohort A+B: 68.9 (49-87)	Male

Demographic and baseline patient characteristics in PROfound are summarized in Table 37.

Table 37 Selected Demographic and Patient Characteristics at Baseline for the Overall Population (Full Analysis Set) for PROfound

	Cohort A		Cohort A+B	
	LYNPARZA 300 mg bid n=162	Investigator's Choice of NHA n=83	LYNPARZA 300 mg bid n=256	Investigator's Choice of NHA n=131
Demographics				
Age (years)				
Mean (SD)	68.0	68.1	68.5 (8.44)	68.9 (7.58)
Median (range)	68.0	67.0	69.0 (47-91)	69.0 (49-87)
Age group, n (%)				
<65 years	54 (33.3)	23 (27.7)	82 (32.0)	34 (26.0)

	Cohort A		Cohort A+B	
	LYNPARZA 300 mg bid n=162	**Investigator's Choice of NHA n=83**	**LYNPARZA 300 mg bid n=256**	**Investigator's Choice of NHA n=131**
≥65 years	108 (66.7)	60 (72.3)	174 (68.0)	97 (74.0)
Race, n (%)				
White	109 (67.3)	55 (66.3)	163 (63.7)	85 (64.9)
Black or African American	2 (1.2)	1 (1.2)	7 (2.7)	1 (0.8)
Asian	43 (26.5)	19 (22.9)	69 (27.0)	36 (27.5)
Other	1 (0.6)	1 (1.2)	2 (0.8)	1 (0.8)
Disease Characteristics				
ECOG PS, n (%)				
(0) Normal activity	84 (51.9)	34 (41.0)	131 (51.2)	55 (42.0)
(1) Restricted activity	67 (41.4)	46 (55.4)	112 (43.8)	71 (54.2)
(2) In bed ≤50% of the time	11 (6.8)	3 (3.6)	13 (5.1)	4 (3.1)
Unknown	0	0	0	1 (0.8)
Baseline Pain[a]				
0 to <2	83 (51.2)	37 (44.6)	125 (48.8)	57 (43.5)
2 to 3	17 (10.5)	9 (10.8)	31 (12.1)	13 (9.9)
>3	56 (34.6)	34 (41.0)	93 (36.3)	56 (42.7)
Unknown	6 (3.7)	3 (3.6)	7 (2.7)	5 (3.8)
Baseline PSA (µg/L)				
Median	62.180	112.920	68.220	106.490
Range	0.20-7240.74	1.85-7115.00	0.20- 7240.74	1.85- 7115.00
Tumour Characteristics				
Measurable disease at baseline				
Yes (%)	95 (58.6)	46 (55.4)	149 (58.2)	72 (55.0)
No (%)	67 (41.4)	37 (44.6)	107 (41.8)	59 (45.0)
Sites of disease at baseline				
Prostate	27 (16.7)	12 (14.5)	41 (16.0)	21 (16.0)
Locoregional lymph nodes	35 (21.6)	17 (20.5)	54 (21.1)	31 (23.7)
Distant lymph nodes	59 (36.4)	35 (42.2)	99 (38.7)	51 (38.9)
Bone	140 (86.4)	73 (88.0)	218 (85.2)	113 (86.3)
Respiratory	30 (18.5)	11 (13.3)	43 (16.8)	15 (11.5)
Liver	18 (11.1)	13 (15.7)	25 (9.8)	18 (13.7)
Other distant sites	34 (21.0)	15 (18.1)	57 (22.2)	31 (23.7)

	Cohort A		Cohort A+B	
	LYNPARZA 300 mg bid n=162	Investigator's Choice of NHA n=83	LYNPARZA 300 mg bid n=256	Investigator's Choice of NHA n=131
Prior Therapy				
Prior Local Therapy with curative intent				
Yes	71 (43.8)	31 (37.3)	105 (41.0)	57 (43.5)
No	91 (56.2)	52 (62.7)	151 (59.0)	74 (56.5)
Prior NHA				
Enzalutamide	67 (41.4)	40 (48.2)	103 (40.2)	54 (41.2)
Abiraterone	61 (37.7)	29 (34.9)	97 (37.9)	54 (41.2)
Enzalutamide and Abiraterone	32 (19.8)	14 (16.9)	51 (19.9)	23 (17.6)
No Prior NHA[b]	2 (1.2)	0 (0)	5 (2.0)	0 (0)
Prior Taxane				
Yes	106 (65.4)	52 (62.7)	170 (66.4)	84 (64.1)
No	56 (34.6)	31 (37.3)	86 (33.6)	47 (35.9)

[a] Pain assessment based on the "worse pain item (item #3)" of the Brief Pain Inventory-Short Form (BPI-SF) questionnaire. Scores range from minimum of -10 (no pain) to a maximum of 10 (pain as bad as you can imagine). Baseline scores computed as an average of 7-day diary (minimum 4 days required): 0-1 considered no or little pain, 2-3 considered mild pain, >3 considered moderate to severe pain

[b] All patients received prior NHA, however data was not present in the electronic case report form (eCRF) at database lock.

Study Results

The study compared the efficacy of LYNPARZA (olaparib) treatment (300 mg [2x150 mg tablets] twice daily) with Investigator's Choice of prior NHA (enzalutamide or abiraterone acetate) in patients with HRR-mutated mCRPC.

The primary endpoint of the study was radiological progression free survival (rPFS) in Cohort A determined by BICR using RECIST 1.1 (soft tissue) and Prostate Cancer Working Group (PCWG3) (bone). Key secondary endpoints included confirmed objective response rate (ORR) by BICR (Cohort A), rPFS by BICR (Cohort A+B), time to pain progression (TTPP) (Cohort A) and overall survival (OS) (Cohort A). TTPP is defined as at least a 2-point worsening from baseline of the pain score on Brief Pain Inventory-Short Form (BPI-SF) worst pain (Item 3) or an initiation of or an increase in opioid use.

An additional secondary end-point included in Cohort B was rPFS by BICR and additional secondary end-points included in both Cohort B and Cohort A+B, were confirmed ORR by BICR, OS and time to pain progression.

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

In Cohort A there was a statistically significant and clinically meaningful improvement in

confirmed radiological ORR by BICR for patients with measurable disease at baseline in the LYNPARZA arm vs comparator; and an improvement observed in confirmed radiological ORR in Cohort A+B. There was a statistically significant and clinical meaningful delay in TTPP in the LYNPARZA arm compared with the Investigator's Choice of NHA arm in Cohort A and the results in Cohort A+B were consistent with Cohort A.

The final analysis of OS (60% Maturity) demonstrated a statistically significant improvement in OS in patients randomized to LYNPARZA compared to patients in the Investigators Choice of NHA arm in Cohort A. In Cohort A, 56 out of 83 patients (67.5%) in the investigators choice of NHA arm received subsequent treatment with LYNPARZA.

Table 38 Key Efficacy Findings in Cohort A and Cohort A + B in PROfound

	Cohort A		Cohort A + B	
	LYNPARZA Tablets 300 mg bid (N=162)	**Investigator's Choice of NHA (N=83)**	**LYNPARZA Tablets 300 mg bid (N=256)**	**Investigator's Choice of NHA (N=131)**
PFS by BICR[a,b,h]				
Number of events: Total number of patients (%)	106:162 (65)[c]	68:83 (82)[c]	180:256 (70)[c]	99:131 (76)[c]
Median time (95% CI) (months)	7.4 (6.2, 9.3)	3.6 (1.9, 3.7)	5.8 (5.5, 7.4)	3.5 (2.2, 3.7)
HR (95% CI)[d]	0.34 (0.25-0.47)		0.49 (0.38–0.63)	
P value (2-sided)[e]	p<0.0001		p<0.0001	
Confirmed ORR by BICR[h]				
Number of responders: Total number of patients with measurable disease at baseline (%)	28:84 (33)	1:43 (2)	30:138 (22)	3:67 (5)
Odds ratio (95% CI)	20.86 (4.18, 379.18)		5.93 (2.01, 25.40)	
P-value (2-sided)	<0.0001		0.0006[f]	
Final OS[i]				
Number of events: Total number of patients (%)	91:162 (56)	57:83 (69)	160:256 (63)	88:131 (67)
Median OS (95% CI) [months]	19.1 (17.4, 23.4)	14.7 (11.9, 18.8)	17.3 (15.5, 18.6)	14.0 (11.5, 17.1)
HR (95% CI)	0.69 (0.50, 0.97)		0.79 (0.61, 1.03)	
P-value (2-sided)[a]	0.0175		0.0515[f]	
Time to Pain Progression (TTPP)[g,h]				
Number of events: Total number of patients (%)	21:162 (13)	14:83 (17)	32:256 (13)[f]	16:131 (12)[f]
Median (95% CI) [months]	NR (NR, NR)	9.9 (5.4, NR)	NR (NR, NR)	NR (NR, NR)
HR (95% CI)	0.44 (0.22, 0.91)		0.64 (0.35, 1.21)[f]	

	Cohort A		Cohort A + B	
	LYNPARZA Tablets 300 mg bid (N=162)	**Investigator's Choice of NHA (N=83)**	**LYNPARZA Tablets 300 mg bid (N=256)**	**Investigator's Choice of NHA (N=131)**
P-value (2-sided)	0.0192		0.1490 [f]	

a rPFS (Cohort A), rPFS (Cohort A+B), ORR (Cohort A), TTPP (Cohort A) and OS (Cohort A) were tested and controlled for multiplicity. The multiplicity strategy for primary endpoint and key secondary endpoints was that upon achieving statistical significance on the primary endpoint rPFS in Cohort A, testing of each of the secondary endpoints, ORR (Cohort A), rPFS (Cohort A + B), TTPP (Cohort A) and OS (Cohort A) were performed sequentially.

b Cohort A - the sensitivity analysis of rPFS by investigator assessment (HR=0.24, 95% CI 0.17, 0.34, p<0.0001 [nominal]; median rPFS 9.8 months vs 3.6 months for olaparib vs Investigator's Choice of NHA, respectively) was consistent with the rPFS analysis by BICR assessment. Cohort A+B - the sensitivity analysis of rPFS by investigator assessment (HR=0.36, 95% CI 0.27, 0.47, p<0.0001 [nominal]; median rPFS 7.5 months vs 3.5 months for olaparib vs Investigator's Choice of NHA, respectively) was consistent with the rPFS analysis by BICR.

c rPFS 71% maturity (Cohort A), 72% maturity (Cohort A+B)

d The HR and CI were calculated using a Cox proportional hazards model adjusted for prior taxane use and measurable disease. The Efron approach was used for handling ties. HR <1 favours olaparib

e The analysis was performed using the log-rank test stratified by prior taxane use and measurable disease using the Breslow method for handling ties

f Not controlled for multiplicity

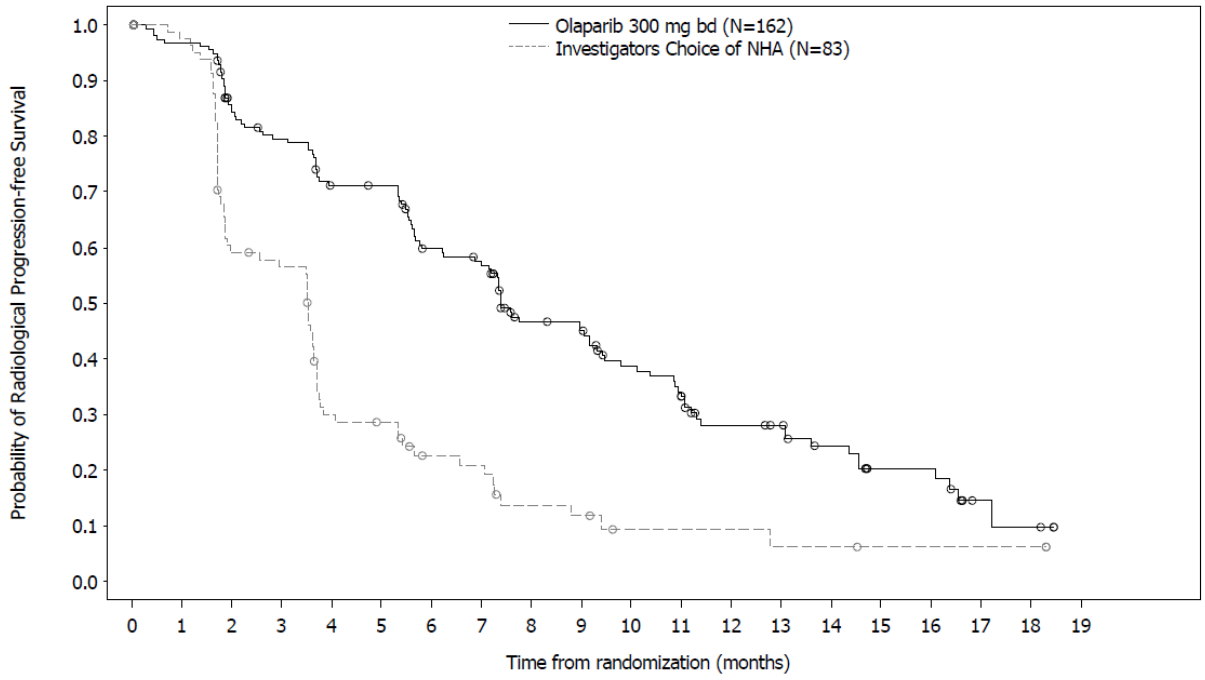
g Time to pain progression was defined as the time from randomisation to the first date of a clinically meaningful worsening (≥2 points increase from baseline on a scale of 0-10) in average BPI-SF worst pain [Item 3] score and/or an increase in or initiation of opioid analgesic use.

h DCO 04 June 2019

i DCO 20 March 2020

bd Twice daily ; BICR Blinded independent central review; CI Confidence interval; HR Hazard ratio; NHA New hormonal agent; NR Not Reached; ORR Objective response rate; OS Overall survival; rPFS Radiological progression free survival; TTPP Time to pain progression.

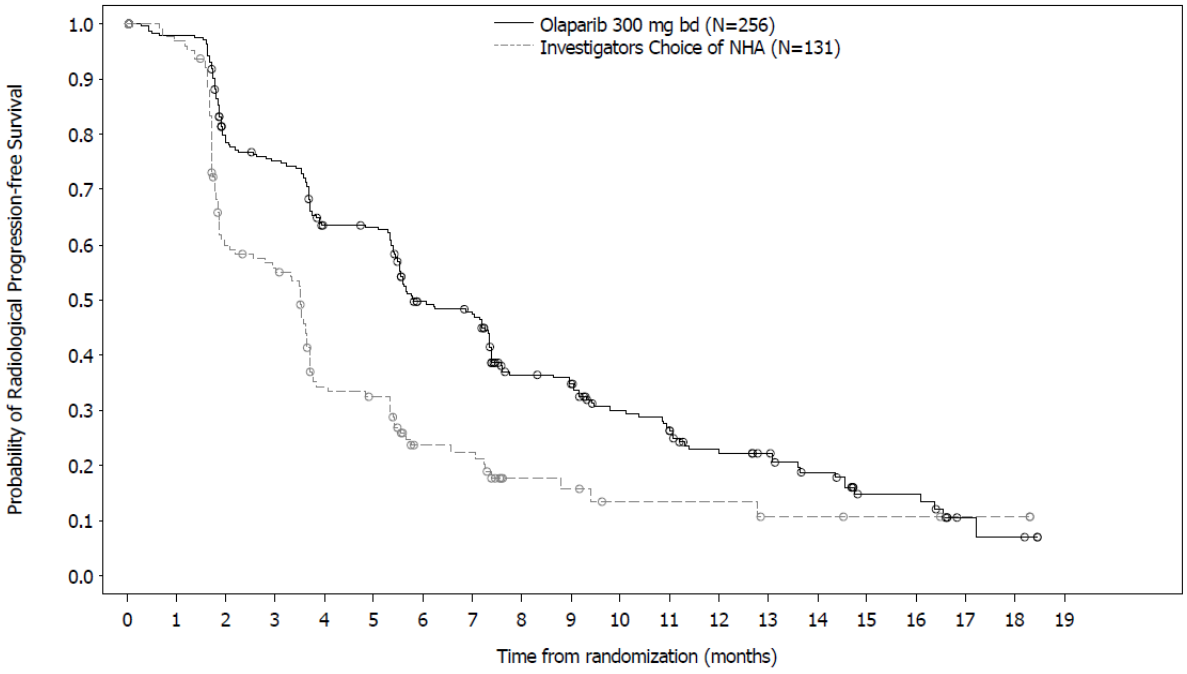
Figure 9 **Cohort A: Kaplan-Meier plot of rPFS (by BICR)**



Number of patients at risk:

Olaparib 300 mg bd	162	149	126	116	102	101	82	77	56	53	42	37	26	24	18	11	11	3	2	0
Investigators Choice of NHA	83	79	47	44	22	20	13	12	7	6	3	3	3	2	2	1	1	1	1	0

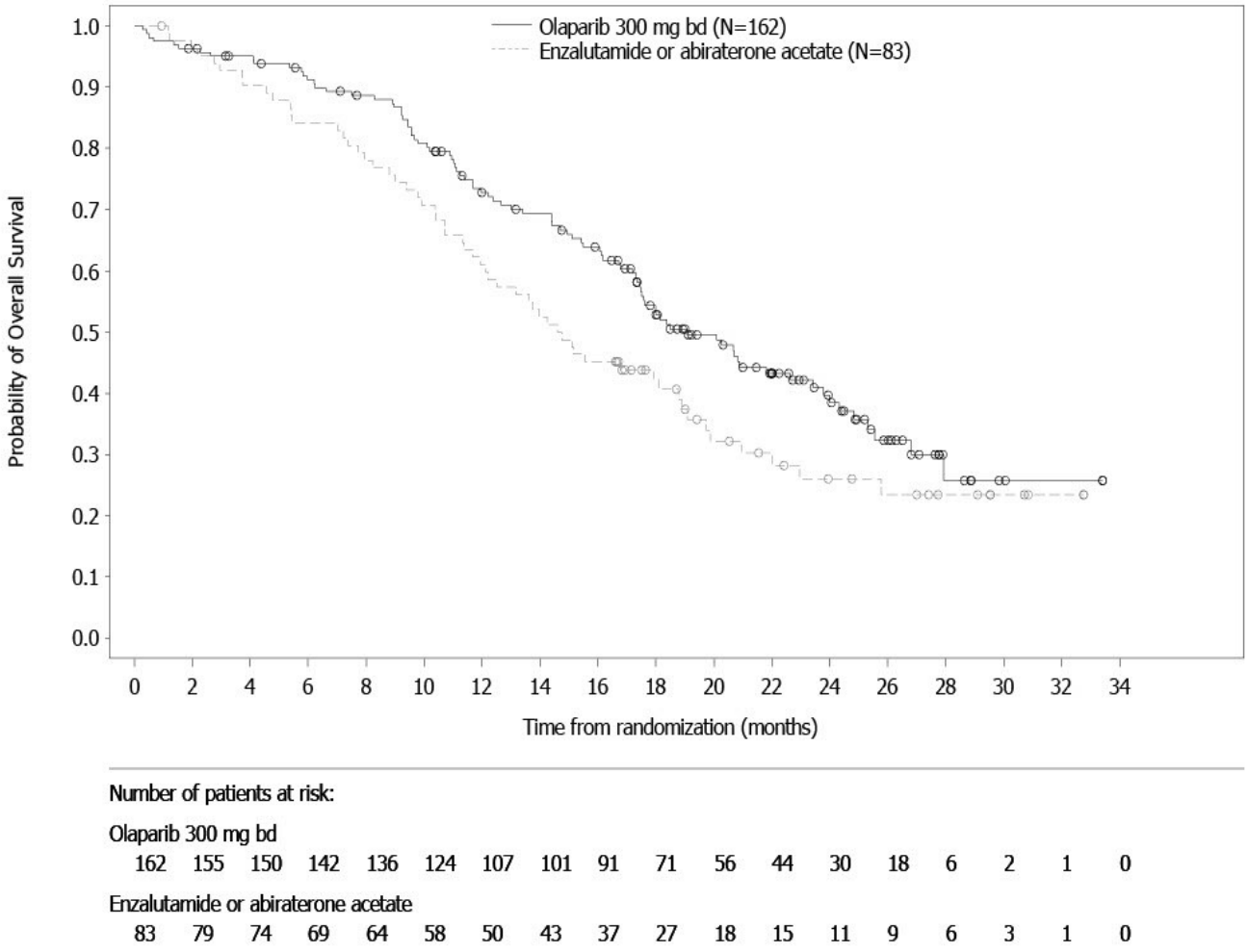
Figure 10 **Cohort A+B: Kaplan-Meier plot of rPFS (by BICR)**



Number of patients at risk:

Olaparib 300 mg bd	256	239	188	176	145	143	106	100	67	63	48	43	31	28	21	11	11	3	2	0
Investigators Choice of NHA	131	123	73	67	38	35	20	19	9	8	5	5	5	3	3	2	2	1	1	0

Figure 11 Cohort A: Kaplan-Meier plot of OS



In the PROfound trial, a PSA50 response was reported in 42.6% of LYNPARZA treated patients in Cohort A and in 30.5% of LYNPARZA treated patients in Cohort A+B.

In Cohort A the benefit of LYNPARZA over Investigator's Choice of NHA was maintained across all pre-defined subgroups. For Cohort A+B, the benefit of LYNPARZA over Investigator's Choice of NHA was maintained across the majority of pre-defined subgroups. Clinically meaningful reductions in the risk of radiological disease progression or death in LYNPARZA-treated patients ranged from 39% to 75% in Cohort A and from 23% to 88% in Cohort A+B.

The prevalence of the mutations in Cohort B did not provide sufficient power to test independently. The Cohort B exploratory analysis demonstrated a trend toward rPFS improvement (median rPFS of 4.8 months for LYNPARZA vs. 3.3 months for Investigator's Choice of NHA) and OS improvement (median OS of 14.1 months for LYNPARZA vs.11.5 months for Investigator's Choice of NHA at final analysis). ORR was [2/54 (3.7%) vs 2/24 (8.3%) LYNPARZA 300 mg bd vs NHA, respectively].

14.2 Comparative Bioavailability Studies

Based on a within patient comparison of capsule and tablet formulation, exposure to olaparib (AUC) following 300 mg single dose was 31% higher than that observed following 400mg capsule single dose (n=6).

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

In rats, repeated daily oral dosing of olaparib at dose levels up to 40 mg/kg/day for 1 month or 15 (in females) or 30 (in males) mg/kg/day for up to 6 months was associated with reductions in body weight, body weight gain and/or food consumption. These dose levels in the rat studies were associated with mean total exposures approximately 7- to 27-fold below those achieved clinically. Oral dosing of dogs with olaparib at 50 mg/kg/day for up to 7 days was associated with adverse clinical signs, body weight loss and inappetence, requiring 1 dog to be euthanized prematurely on Day 5. The mean total exposure to olaparib in these dogs was approximately 3- to 8-fold below that achieved in humans at the clinical dose of 300 mg twice a day. Based on these findings, lower dose levels of olaparib were selected for the 1-month (2.5, 5 and 15 mg/kg/day) and 6-month (1, 3, and 10 mg/kg/day) repeat dose dog studies. These dose levels of olaparib were well tolerated, with no adverse effects on food consumption or body weight, and associated with mean total exposures approximately 5- to 11-fold below those seen at the clinical dose (300 mg twice daily).

In both species, the principal target organ for toxicity following repeat dosing for up to 6 months was the bone marrow, with associated changes in peripheral hematology parameters, although steady state exposures at the highest dose levels of olaparib used in the pivotal 1 and 6 month repeat dose rat and dog toxicity studies were notably lower than those achieved in humans at the 300 mg twice daily clinical dose.

In rats, reductions in red blood cell parameters and white blood cell, neutrophil and/or lymphocyte counts, and increases or decreases in reticulocyte and platelet counts were seen. These changes were generally mild in severity, although more marked decreases in reticulocyte and platelet counts were seen at the high doses of 100 or 200 mg/kg/day used in the 7 day study. In rats, the hematology changes were associated with increases in the erythropoietic and/or myelopoietic cell populations within the bone marrow, and with increases in splenic hemopoiesis, hepatocyte pigmentation (hemosiderin) and/or thymic atrophy. The changes were more notable in female rats as a result of the higher systemic exposures in this sex. The mean total exposures to olaparib, following once daily dosing for 7 days at 100 or 200 mg/kg/day in rats, were approximately the same as the clinical exposure at 300 mg twice daily. Full reversal of compound-related changes in rats was evident following withdrawal of treatment.

In dogs, reductions in red blood cell parameters and white blood cell, neutrophil, lymphocyte, reticulocyte and/or and platelet counts were observed following dosing at 15 mg/kg/day for up to 1 month, and were associated with bone marrow atrophy and with an increase in the myeloid/erythroid (M:E) ratio in the bone marrow smear. Decreases in red and white blood cells and platelets were seen following dosing of dogs at 10 mg/kg/day for 6 months, but were not associated with any microscopic changes in the bone marrow. The mean total exposures in

dogs at these dose levels were approximately 5- to 11-fold below those achieved in humans at the clinical dose of 300 mg twice daily. Full reversal of compound-related bone marrow changes, and partial reversal of the hematology changes was seen following a 1 month recovery period.

Studies using human donor and rat bone marrow cells also showed that direct exposure to olaparib can result in toxicity to bone marrow cells in *ex vivo* assays.

The effects of olaparib on bone marrow and peripheral blood may be related to the pharmacology and mechanism of action of olaparib as an inhibitor of PARP-1 and PARP-2. PARP-2 appears to play a key role in the survival of hematopoietic stem/progenitor cells under steady-state conditions and in response to stress.

Carcinogenicity

Carcinogenicity studies have not been performed with olaparib. However, the absence of PARP in genetically engineered mouse models leads to an increased risk of spontaneous and induced carcinogenesis as compared to PARP wild type counterparts. The significance of this finding in patients is not clear.

Genotoxicity

In genotoxicity studies, olaparib did not demonstrate mutagenic potential in the bacterial reverse mutation (Ames) test, but was clastogenic *in vitro* in a chromosome aberration test and induced micronuclei in the bone marrow of rats following oral dosing for 2 days. This clastogenicity was consistent with genomic instability resulting from the primary pharmacology of olaparib.

Reproductive and Developmental Toxicology

In fertility studies conducted in rats at 0.05, 0.5 or 15 mg/kg/day, olaparib produced no adverse effects on male and female fertility. However, olaparib treatment caused an increase in early embryofetal loss when dosed to adult female rats from 14 days prior to pairing (with undosed males) through to day 6 of pregnancy at 15 mg/kg/day, a dose level that was not associated with any significant maternal toxicity. The mean total exposure at the highest dose in this study was approximately 14-fold lower than that achieved in humans at the recommended therapeutic dose of 300 mg twice daily.

In an independent fertility study conducted in mice, daily olaparib treatment at 50 mg/kg subcutaneous dose (4 mg/kg human equivalent dose) led to a decrease in the number of primordial follicles.

In embryofetal development studies in rats, oral dosing of olaparib during organogenesis caused embryofetal lethality at doses of 5 mg/kg/day and above. The mean total exposure at this dose was about 63-fold lower than the mean clinical exposure at the recommended 300 mg twice daily dose. At a non-maternally toxic dose of 0.5 mg/kg/day, olaparib caused reductions in early embryofetal survival, decreases in fetal weights and increases in the incidence of major eye (anophthalmia, microphthalmia), fetal visceral (slightly non-uniform palate rugal pattern; additional liver lobe(s); left sided umbilical artery; slightly dilated ureter; kinked ureters and an increased incidence of severely dilated ureters), several transient skeletal minor abnormalities and/or variants (affecting cervical, thoracic and caudal vertebra, and sternebrae, hindlimb bones) and vertebrate/rib malformations (Caudal displacement of the thoracolumbar border). The mean total plasma concentration at the 0.5 mg/kg/day olaparib was approximately 360-fold lower than that achieved at the clinical dose of 300 mg twice daily in patients. At the lower dose of 0.05 mg/kg/day, there was still an increased incidence of fetal malformations including those

of the eyes, skeleton and ureters such that a NOAEL for developmental toxicity was not determined. The mean plasma concentration at the 0.05 mg/kg/day was about 450-fold lower than those seen in humans at the clinical dose of 300 mg bid.

Overall, since exposures in rats were substantially lower than those achieved in humans at the 300 mg twice daily clinical dose, this indicates that olaparib has potential to cause adverse effects in the developing fetus at therapeutic exposures. The effects on embryofetal survival seen in rats are considered to be related to PARP inhibition by olaparib, as double knock-out mice lacking both PARP-1 and PARP-2 are not viable and die at the onset of gastrulation. This demonstrates that the expression of both PARP-1 and PARP-2 are essential during early embryogenesis.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

℞LYNPARZA®

Olaparib Tablets

Read this carefully before you start taking **LYNPARZA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **LYNPARZA**.

Serious Warnings and Precautions

- Only a healthcare professional who has experience treating cancer should treat you with LYNPARZA.
- **Myelodysplastic Syndrome or Acute Myeloid Leukemia** is a problem with the bone marrow. You may have abnormal red, white or platelet cell counts. This is serious and can lead to death.
- **Pneumonitis** is a lung inflammation. It makes it hard for the lungs to absorb oxygen and remove carbon dioxide. It is serious and can lead to death or require hospital treatment.
- LYNPARZA can harm your unborn baby if you take it while you are pregnant.

What is LYNPARZA used for?

For the following indication LYNPARZA has been approved with conditions (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

- Cancer of the ovaries and some other closely related cancers in adults without mutations in their *BRCA* genes. When the cancer responds to chemotherapy that contains platinum, LYNPARZA helps to keep that response.
- Human epidermal growth factor receptor 2 (HER2)-negative breast cancer that has not spread to other parts of the body in adults with mutations in their *BRCA* genes. LYNPARZA is given after surgery. Patients should have received chemotherapy before or after surgery to remove the tumour.

For the following indications LYNPARZA has been approved without conditions. This means it has passed Health Canada's review and can be bought and sold in Canada.

- Cancer of the ovaries and some other closely related cancers in adults with mutations in their *BRCA* genes. When the cancer responds to chemotherapy that contains platinum, LYNPARZA helps to keep that response.
- Breast cancer that has spread outside the breast (metastasized) in adults with mutations in their *BRCA* genes and who have already had chemotherapy. Patients may have also had hormone therapy for their breast cancer.

- Pancreatic cancer that has spread outside the pancreas (metastasized) in adults with mutations in their *BRCA* genes. When the cancer has not worsened after chemotherapy that contains platinum, LYNPARZA helps to maintain that response.
- Prostate cancer that has spread outside the prostate (metastasized) in adults with mutations in their *BRCA* or *ATM* genes. The prostate cancer no longer responds to drugs or surgery to lower testosterone. Patients should have already had certain new hormonal treatments.

BRCA genes are known as the breast cancer genes. If you have mutations (changes) in these genes you are at higher risk of getting certain types of cancer. The *ATM* gene is another gene that can increase your chances of getting certain types of cancer if it has mutations. A test will be done before you start taking LYNPARZA to see if you have mutations in your *BRCA* or *ATM* genes.

What is a Notice of Compliance with Conditions (NOC/c)?
A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada. Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How does LYNPARZA work?
LYNPARZA is a type of drug called a PARP (poly [adenosine diphosphate-ribose] polymerase) inhibitor. PARP inhibitors can destroy cancer cells that are not able to repair damage to their DNA (genes).

In some patients with breast cancer, cancer of the ovaries, pancreatic cancer, prostate cancer and some other closely related cancers, there are mutations in genes such as the *BRCA* (breast cancer) or *ATM* genes. For breast cancer and pancreatic cancer, LYNPARZA works in patients with *BRCA* mutations. For cancer of the ovaries and some other closely related cancers, LYNPARZA works in patients with and without *BRCA* mutations. For prostate cancer, LYNPARZA works in patients with mutations in either the *BRCA* or *ATM* genes. A test is used to see if you have mutations of your *BRCA* or *ATM* genes.

What are the ingredients in LYNPARZA?
Medicinal ingredients: Olaparib

Non-medicinal ingredients: Colloidal silicon dioxide, copovidone, hypromellose, iron oxide black (150 mg tablet only), iron oxide yellow, macrogol 400, mannitol, sodium stearyl fumarate, titanium dioxide.

LYNPARZA comes in the following dosage forms:
Film-coated tablets: 100 mg and 150 mg

Do not use LYNPARZA if:

- You are allergic to olaparib or any of the other ingredients in this medicine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take LYNPARZA. Talk about any health conditions or problems you may have, including:
- If you have moderate or severe kidney disease.
- If you have severe liver disease.
- If you have clots in your blood vessels.

Other warnings you should know about:

Female Patients:
- If you are pregnant, or still able to get pregnant and/or breast-feed, there are specific risks you must discuss with your healthcare professional.
- Avoid becoming pregnant while taking LYNPARZA. It may harm your unborn baby or make you lose the pregnancy. You should use two effective methods of birth control while taking LYNPARZA.
- Keep using birth control for 6 months after taking your last dose of LYNPARZA. If you do become pregnant while taking LYNPARZA, tell your healthcare professional right away.
- It is not known if LYNPARZA causes hormonal birth control to not work as well. Please tell your healthcare professional if you are taking a hormonal birth control. They may recommend the addition of a non-hormonal birth control method. If you have hormone dependent cancer, they may recommend two non-hormonal birth control methods.
- **For women who can get pregnant:** a pregnancy test should be done: before you start to take LYNPARZA; regularly while you are taking it; and for 6 months after taking your last dose.
- LYNPARZA may pass into breast milk. Do not breast-feed while you are taking LYNPARZA and for 1 month after taking your last dose of LYNPARZA. If you are planning to breast-feed, tell your healthcare professional.

Male Patients:
- Use a condom when having sexual intercourse with a woman (even if she is pregnant). The condom must be used:
  - while you are taking LYNPARZA, and
  - for 3 months after you take your last dose of LYNPARZA.
- Your female partner must also use an effective method of birth control.
- Do not donate sperm while taking LYNPARZA and for 3 months after stopping LYNPARZA.

Driving and using machines: Before you do tasks which may require special attention, wait until you know how you respond to LYNPARZA. If you feel dizzy, weak, or tired, do not drive or use tools or machines.

Blood tests: LYNPARZA can cause abnormal blood test results. Your healthcare professional will test your blood every month for the first year of treatment and periodically thereafter. Your healthcare professional will tell you if your test results are abnormal and if you need treatment to correct these side effects.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.
Some medicines can affect the level of LYNPARZA in your body. Also, LYNPARZA can affect

the way some other medicines work. The medicines listed here may not be the only ones that could interact with LYNPARZA.

The following may interact with LYNPARZA:
- Itraconazole, fluconazole - used to treat fungal infections.
- Telithromycin, clarithromycin, erythromycin, ciprofloxacin - used to treat bacterial infections.
- Ritonavir, nelfinavir, indinavir, saquinavir, nevirapine, cobicistat, boceprevir, telaprevir, etravirine, efavirenz, amantadine - used to treat viral infections, primarily HIV.
- Rifampicin, rifapentine, rifabutin - used to treat bacterial infections, primarily tuberculosis.
- Phenytoin, carbamazepine, phenobarbital - used to treat seizures and epilepsy.
- St John's Wort (*Hypericum perforatum*) - an herbal remedy used mainly for depression.
- Bupropion - mainly used for depression and smoking cessation.
- Diltiazem, furosemide, valsartan, verapamil - used to treat heart conditions or high blood pressure.
- Bosentan - used to treat pulmonary artery hypertension.
- Statins e.g. simvastatin - used to lower blood cholesterol levels.
- Glibenclamide, metformin, repaglinide - used to treat diabetes.
- Ergot alkaloids - used to treat migraines and headaches.
- Fentanyl - used to treat cancer pain.
- Pimozide, quetiapine - used to treat mental health problems.
- Cisapride, cimetidine - used to treat stomach problems.
- Cyclosporine, sirolimus, tacrolimus - used to suppress the immune system.
- Cisplatin - used to treat cancer.
- Methotrexate - used to treat cancer, rheumatoid arthritis and psoriasis.
- Modafinil - used to treat a sleep disorder called narcolepsy.
- Midazolam - used to produce sleepiness and drowsiness.

Do not eat or drink any products or juices containing grapefruit, star fruit, pomegranate or Seville oranges while taking LYNPARZA. They can affect the way the medicine works.

How to take LYNPARZA:
- Always take LYNPARZA exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- Swallow LYNPARZA tablets whole. Do NOT chew, crush, dissolve or divide the tablets. This may affect how quickly the drug gets into your body.
- Take LYNPARZA at about the same time each morning and evening.
- LYNPARZA can be taken with or without food.
- If you are taking LYNPARZA for prostate cancer:
    - You should also receive gonadotropin-releasing hormone (GnRH) analog therapy at the same time unless you had a surgery to lower testosterone in your body.
- If you are taking LYNPARZA for early breast cancer and you have hormone receptor-positive disease, you should continue to take hormonal therapy during your treatment with LYNPARZA.
- Never take more than 4 tablets in a day.
- Your healthcare professional will tell you when to start LYNPARZA after you finish your chemotherapy treatment.
- Your healthcare professional will decide how long you stay on LYNPARZA treatment.

Recommended Total Daily Dose:

Adult Daily Dose 600 mg: take two 150 mg tablets twice a day.
Your healthcare professional may interrupt or reduce your dose. This may happen if you:

- have problems with your kidneys.
- are taking medicines that may interact with LYNPARZA.
- have certain side effects while taking LYNPARZA.

Reduced Total Daily Doses:
Adult Daily Dose 500 mg: take one 150 mg tablet and one 100 mg tablet twice a day.
Adult Daily Dose 400 mg: take two 100 mg tablets twice a day.
Adult Daily Dose 300 mg: take one 150 mg tablet twice a day.
Adult Daily Dose 200 mg: take one 100 mg tablet twice a day.

Overdose:

If you think you, or a person you are caring for, have taken too much LYNPARZA, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to take LYNPARZA, take your next dose at its scheduled time. Do not take a double dose (two doses at the same time) to make up for forgotten tablets.

What are possible side effects from using LYNPARZA?
These are not all the possible side effects you may feel when taking LYNPARZA. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Headache
- Feeling dizzy
- Loss of appetite
- Feeling tired or weak
- Changes in the way food tastes
- Indigestion or heartburn
- Pain in the stomach area under the ribs
- Rash
- Itchy rash on swollen, reddened skin (dermatitis)
- Cough
- Fever
- Shortness of breath
- Constipation

It is common to experience nausea and vomiting at the start of your treatment. These side effects may improve over time. Ask your healthcare professional how to treat these side effects.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Anemia (low red blood cells): Being short of breath, feeling very tired, having pale skin, fast heartbeat, loss of energy, or weakness.		X	
Neutropenia or Leukopenia (low white blood cells: neutrophils and leukocytes): Fever or infection, fatigue, aches and pains, and flu-like symptoms.		X	
Nausea and Vomiting: Feeling sick. Being sick or throwing up.	X		
Urinary tract infection (infection in urinary system including kidneys, ureters, bladder and urethra): Pain or burning sensation while urinating, frequent urination, blood in urine, pain in the pelvis, strong smelling urine, cloudy urine.		X	
COMMON			
Stomatitis (mouth sores, inflammation of the mouth) **or Mucosal Inflammation** (inflammation of the moist body surfaces): Red, sore or swollen mouth, lips, gums, nose or eyes. Ulcers can occur.	X		
Diarrhea: Severe, at least 3 loose or liquid bowel movements in a day.	X		
Myelodysplastic Syndrome or **Acute Myeloid Leukemia** (a group of diseases in which the body produces large numbers of abnormal blood cells): Fever, infection, bruising or bleeding easily, breathlessness, blood in urine or stool.			X
Cystitis (inflammation of the bladder): Urge to urinate more often, uncomfortable or painful urination, cloudy, dark or strong smelling urine, blood in urine.	X		
Lymphopenia (low white blood cells: lymphocytes): Get infections more easily.		X	
Pneumonia (infection in the lungs): Cough which may produce phlegm, fever, chills, shortness of breath, difficult and painful breathing, nausea, vomiting or diarrhea, chest pain when you breathe or cough, confusion.		X	
Pulmonary embolism (blood clot in the lung): Shortness of breath, chest pain particularly on breathing in, breathing that is more rapid than normal or heart beats faster than normal and coughing up blood.			X

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Thrombosis (clot in a blood vessel): swelling and pain in one part of the body, usually in the leg (venous thrombosis).			X
Thrombocytopenia (low blood platelets): Bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness.		X	
UNCOMMON			
Allergic Reactions: Rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing.			X
Pneumonitis (lung inflammation): New or worsening shortness of breath, cough, wheezing or fever.			X
RARE			
Angioedema (swelling of the tissue under the skin or other body tissue).		X	
Erythema nodosum (painful inflammation in a part of the fatty layer of the skin): Red and painful lumps usually in the legs		X	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store between 2 - 30°C.
- Store in the original package in order to protect from moisture.
- Do not use after the expiry date stated on the bottle after EXP. The expiry date refers to the last day of that month.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

Keep out of reach and sight of children.

If you want more information about LYNPARZA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (www.astrazeneca.ca), or by calling 1-800-668-6000.
- This Patient Medication Information is current at the time of printing. The most up-to date version can be found at www.astrazeneca.ca.

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