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

1 INDICATIONS AND USAGE

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

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

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

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

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

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

1.3 Maintenance Treatment of Recurrent Ovarian Cancer

Lynparza is indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy.

1.4 Germline BRCA-mutated HER2-negative Metastatic Breast Cancer

Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer, who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Selection of patients for therapy should be determined by an experienced laboratory using a validated test method *[see Dosage and Administration (2.1)]*.

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

Lynparza is indicated for the maintenance treatment of adult patients with deleterious or suspected deleterious gBRCAm metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen. Selection of patients for therapy should be

determined by an experienced laboratory using a validated test method *[see Dosage and Administration (2.1)]*.

1.6 HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

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

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

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

Table 1 Biomarker Testing for Patient Selection*

Indication	Biomarker	Sample type		
		Tumour	**Blood**	**Plasma (ctDNA)**
First-line maintenance treatment of germline or somatic *BRCA*m advanced ovarian cancer	*BRCA1*m, *BRCA2*m	X	X	
First-line maintenance treatment of HRD-positive advanced ovarian cancer in combination with bevacizumab	*BRCA1*m, *BRCA2*m, and/or genomic instability	X		
Maintenance treatment of recurrent ovarian cancer	No requirement for biomarker testing			
g*BRCA*m HER2-negative metastatic breast cancer	*gBRCA1*m, *gBRCA2*m		X	
First-line maintenance treatment of germline *BRCA*-mutated metastatic pancreatic adenocarcinoma	*gBRCA1*m, *gBRCA2*m		X	

Germline or somatic HRR gene-mutated metastatic castration-resistant prostate cancer	*ATM*m, *BRCA1*m, *BRCA2*m, *BARD1*m, *BRIP1*m, *CDK12*m, *CHEK1*m, *CHEK2*m, *FANCL*m, *PALB2*m, *RAD51B*m, *RAD51C*m, *RAD51D*m, *RAD54L*m	X		
	g*BRCA1*m, g*BRCA2*m		X	
	*ATM*m, *BRCA1*m, *BRCA2*m			X

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

2.2 Recommended Dosage

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

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

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

Continue treatment until disease progression, unacceptable toxicity, or completion of 2 years of treatment. Patients with a complete response (no radiological evidence of disease) at 2 years should stop treatment. Patients with evidence of disease at 2 years, who in the opinion of the treating healthcare provider can derive further benefit from continuous treatment, can be treated beyond 2 years.

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

Continue Lynparza treatment until disease progression, unacceptable toxicity, or completion of 2 years of treatment. Patients with a complete response (no radiological evidence of disease) at 2 years should stop treatment. Patients with evidence of disease at 2 years, who in the opinion of the treating healthcare provider can derive further benefit from continuous Lynparza treatment, can be treated beyond 2 years.

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

Recurrent Ovarian Cancer, HER2-negative Metastatic Breast Cancer, Metastatic Pancreatic Adenocarcinoma, and HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

Continue treatment until disease progression or unacceptable toxicity for:

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

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

2.3 Dosage Modifications for Adverse Reactions

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

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

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

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

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

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

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

2.5 Dosage Modifications for Renal Impairment

Moderate Renal Impairment

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

3 DOSAGE FORMS AND STRENGTHS

Tablets:

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Myelodysplastic Syndrome/Acute Myeloid Leukaemia

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

In clinical studies enrolling 2901 patients with various cancers who received Lynparza as a single agent *[see Adverse Reactions (6.1)]*, the cumulative incidence of MDS/AML was approximately 1.5% (43/2901). Of these, 51% (22/43) had a fatal outcome. The median duration of therapy with Lynparza in patients who developed MDS/AML was 2 years (range: < 6 months to > 10 years). All of these patients had received previous chemotherapy with platinum agents and/or other DNA damaging agents including radiotherapy.

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

5.2 Pneumonitis

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

5.3 Embryo-Foetal Toxicity

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

5.4 Venous Thromboembolic Events

Venous thromboembolic events, including pulmonary embolism, occurred in 7% of patients with metastatic castration resistant prostate cancer who received Lynparza plus androgen deprivation therapy (ADT) compared to 3.1% of patients receiving enzalutamide or abiraterone plus ADT in the PROfound

study. Patients receiving Lynparza and ADT had a 6% incidence of pulmonary embolism compared to 0.8% of patients treated with ADT plus either enzalutamide or abiraterone. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate, which may include long-term anticoagulation as clinically indicated.

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labelling:

- Myelodysplastic Syndrome/Acute Myeloid Leukaemia *[see Warnings and Precautions (5.1)]*
- Pneumonitis *[see Warnings and Precautions (5.2)]*
- Venous Thromboembolic Events *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trial Experience

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

The data described in the WARNINGS AND PRECAUTIONS reflect exposure to Lynparza as a single agent in 2901 patients; 2135 patients with exposure to 300 mg twice daily tablet dose including five controlled, randomised, trials (SOLO-1, SOLO-2, OlympiAD, POLO, and PROfound) and to 400 mg twice daily capsule dose in 766 patients in other trials that were pooled to conduct safety analyses. In these trials, 56% of patients were exposed for 6 months or longer and 28% were exposed for greater than one year in the Lynparza group.

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

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

SOLO-1

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

receiving Lynparza. The most frequent adverse reactions that led to discontinuation of Lynparza were fatigue (3.1%), anaemia (2.3%), and nausea (2.3%).

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

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

Adverse Reaction	Lynparza tablets n=260		Placebo n=130	
	All Grades (%)	Grades 3 – 4 (%)	All Grades (%)	Grades 3 – 4 (%)
Gastrointestinal Disorders				
Nausea	77	1	38	0
Abdominal pain†	45	2	35	1
Vomiting	40	0	15	1
Diarrhoea‡	37	3	26	0
Constipation	28	0	19	0
Dyspepsia	17	0	12	0
Stomatitis§	11	0	2	0
General Disorders and Administration Site Conditions				
Fatigue¶	67	4	42	2
Blood and Lymphatic System Disorders				
Anaemia	38	21	9	2
Neutropenia#	17	6	7	3
Leukopeniaᵇ	13	3	8	0
Thrombocytopeniaß	11	1	4	2
Infections and Infestations				
Upper respiratory tract infection/ influenza/nasopharyngitis/bronchitis	28	0	23	0
UTIà	13	1	7	0
Nervous System Disorders				
Dysgeusia	26	0	4	0
Dizziness	20	0	15	1
Metabolism and Nutrition Disorders				
Decreased appetite	20	0	10	0
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnoeaè	15	0	6	0

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

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

‡ Includes colitis, diarrhoea, and gastroenteritis.

§ Includes stomatitis, aphthous ulcer, and mouth ulceration.
¶ Includes: asthenia, fatigue, lethargy, and malaise.
# Includes neutropenia and febrile neutropenia.
Þ Includes leukopenia and white blood cell count decreased.
ß Includes platelet count decreased and thrombocytopenia.
à Includes urosepsis, urinary tract infection, urinary tract pain, and pyuria.
è Includes dyspnoea and dyspnoea exertional.

In addition, the adverse reactions observed in SOLO-1 that occurred in <10% of patients receiving Lynparza were increased blood creatinine (8%), lymphopenia (6%), hypersensitivity (2%), MDS/AML (1%), dermatitis (1%), and increased mean cell volume (0.4%).

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

Laboratory Parameter*	**Lynparza tablets n†=260**		**Placebo n†=130**	
	Grades 1-4 (%)	**Grades 3-4 (%)**	**Grades 1-4 (%)**	**Grades 3-4 (%)**
Decrease in haemoglobin	87	19	63	2
Increase in mean corpuscular volume	87	-	43	-
Decrease in leucocytes	70	7	52	1
Decrease in lymphocytes	67	14	29	5
Decrease in absolute neutrophil count	51	9	38	6
Decrease in platelets	35	1	20	2
Increase in serum creatinine	34	0	18	0

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

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

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

PAOLA-1

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

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

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

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

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

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

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

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

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

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

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

In addition, venous thromboembolic events occurred more commonly in patients receiving Lynparza/bevacizumab (5%) than in those receiving placebo/bevacizumab (1.9%).

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

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

* Reported within 30 days of the last dose.

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

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

Maintenance Treatment of Recurrent Ovarian Cancer

SOLO-2

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

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

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

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

Adverse Reaction	Lynparza tablets n=195		Placebo n=99	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)

Gastrointestinal Disorders				
Nausea	76	3	33	0
Vomiting	37	3	19	1
Diarrhoea	33	2	22	0
Stomatitis†	20	1	16	0
General Disorders and Administration Site Conditions				
Fatigue including asthenia	66	4	39	2
Blood and Lymphatic Disorders				
Anaemia‡	44	20	9	2
Infections and Infestations				
Nasopharyngitis/URI/sinusitis/ rhinitis/influenza	36	0	29	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia/myalgia	30	0	28	0
Nervous System Disorders				
Dysgeusia	27	0	7	0
Headache	26	1	14	0
Metabolism and Nutrition Disorders				
Decreased appetite	22	0	11	0

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

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

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

In addition, the adverse reactions observed in SOLO-2 that occurred in <20% of patients receiving Lynparza were neutropenia (19%), cough (18%), leukopenia (16%), hypomagnesemia (14%), thrombocytopenia (14%), dizziness (13%), dyspepsia (11%), increased creatinine (11%), MDS/AML (8%), oedema (8%), rash (6%), and lymphopenia (1%).

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

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

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

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

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

Study 19

The safety of Lynparza as maintenance monotherapy was evaluated in patients with platinum sensitive ovarian cancer who had received 2 or more previous platinum containing regimens in Study 19 *[see Clinical Studies (14.3)]*. Patients received Lynparza capsules 400 mg orally twice daily (n=136) or placebo (n=128). At the time of final analysis, the median duration of exposure was 8.7 months in patients who received Lynparza and 4.6 months in patients who received placebo.

Adverse reactions led to dose interruptions in 35% of patients receiving Lynparza; dose reductions in 26% and discontinuation in 6% of patients receiving Lynparza.

Tables 8 and 9 summarise adverse reactions and laboratory abnormalities in Study 19.

Table 8 Adverse Reactions* in Study 19 (≥20% of Patients Who Received Lynparza)

Adverse Reaction	Lynparza capsules n=136		Placebo n=128	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Gastrointestinal Disorders				
Nausea	71	2	36	0
Vomiting	35	2	14	1
Diarrhoea	28	2	25	2
Constipation	22	1	12	0
Dyspepsia	20	0	9	0
General Disorders and Administration Site Conditions				
Fatigue (including asthenia)	63	9	46	3
Blood and Lymphatic Disorders				
Anaemia†	23	7	7	1
Infections and Infestations				
Respiratory tract infection	22	2	11	0
Metabolism and Nutrition Disorders				
Decreased appetite	21	0	13	0
Nervous System Disorders				
Headache	21	0	13	1

* Graded according to NCI CTCAE v4.0.
† Represents grouped terms of related terms that reflect the medical concept of the adverse reaction.

In addition, the adverse reactions in Study 19 that occurred in <20% of patients receiving Lynparza were dysgeusia (16%), dizziness (15%), dyspnoea (13%), pyrexia (10%), stomatitis (9%), oedema (9%), increase in creatinine (7%), neutropenia (5%), thrombocytopenia (4%), leukopenia (2%), MDS/AML (1%), and lymphopenia (1%).

Table 9 Laboratory Abnormalities Reported in ≥25% of Patients in Study 19

Laboratory Parameter*	Lynparza capsules n†=136	Placebo n†=129

	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Decrease in haemoglobin	82	8	58	1
Increase in mean corpuscular volume‡	82	-	51	-
Decrease in leucocytes	58	4	37	2
Decrease in lymphocytes	52	10	32	3
Decrease in absolute neutrophil count	47	7	40	2
Increase in serum creatinine	45	0	14	0
Decrease in platelets	36	4	18	0

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

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

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

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

OlympiAD

The safety of Lynparza was evaluated in g*BRCA*m patients with HER2-negative metastatic breast cancer who had previously received up to two lines of chemotherapy for the treatment of metastatic disease in OlympiAD *[see Clinical Studies (14.4)]*. Patients received either Lynparza tablets 300 mg orally twice daily (n=205) or a chemotherapy (capecitabine, eribulin, or vinorelbine) of the healthcare provider's choice (n=91) until disease progression or unacceptable toxicity. The median duration of study treatment was 8.2 months in patients who received Lynparza and 3.4 months in patients who received chemotherapy.

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

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

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

Adverse Reaction	Lynparza tablets n=205		Chemotherapy n=91	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Gastrointestinal Disorders				
Nausea	58	0	35	1
Vomiting	30	0	15	1
Diarrhoea	21	1	22	0
Blood and Lymphatic Disorders				
Anaemia†	40	16	26	4
Neutropenia‡	27	9	50	26
Leukopenia§	25	5	31	13
General Disorders and Administration Site Conditions				

Fatigue (including asthenia)	37	4	36	1
Infections and Infestations				
Respiratory tract infection¶	27	1	22	0
Nervous System Disorders				
Headache	20	1	15	2

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

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

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

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

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

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

POLO

The safety of Lynparza as maintenance treatment of germline *BRCA*-mutated metastatic pancreatic adenocarcinoma following first-line treatment with platinum-based chemotherapy was evaluated in POLO *[see Clinical Studies (14.5)]*. Patients received Lynparza tablets 300 mg orally twice daily (n=90) or placebo (n=61) until disease progression or unacceptable toxicity. Among patients receiving Lynparza, 34% were exposed for 6 months or longer and 25% were exposed for greater than one year.

Among patients who received Lynparza, dosage interruptions due to an adverse reaction of any grade occurred in 35% and dosage reductions due to an adverse reaction occurred in 17%. The most frequent adverse reactions leading to dosage interruption or reduction in patients who received Lynparza were

anaemia (11%), vomiting (5%), abdominal pain (4%), asthenia (3%), and fatigue (2%). Discontinuation due to adverse reactions occurred in 6% of patients receiving Lynparza. The most frequent adverse reaction that led to discontinuation of Lynparza was fatigue (2.2%).

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

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

Adverse Reaction	Lynparza tablets (n=91)[†]		Placebo (n=60)[†]	
	All Grades (%)	Grades 3 – 4 (%)	All Grades (%)	Grades 3 – 4 (%)
General Disorders and Administration Site Conditions				
Fatigue[‡]	60	5	35	2
Gastrointestinal Disorders				
Nausea	45	0	23	2
Abdominal pain[§]	34	2	37	5
Diarrhoea	29	0	15	0
Constipation	23	0	10	0
Vomiting	20	1	15	2
Stomatitis[¶]	10	0	5	0
Blood and Lymphatic System Disorders				
Anaemia	27	11	17	3
Thrombocytopenia[#]	14	3	7	0
Neutropenia[Þ]	12	4	8	3
Metabolism and Nutrition Disorders				
Decreased appetite	25	3	7	0
Musculoskeletal and Connective Tissue Disorders				
Back pain	19	0	17	2
Arthralgia	15	1	10	0
Skin and Subcutaneous Tissue Disorder				
Rash[ß]	15	0	5	0
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnoea[à]	13	0	5	2
Infections and Infestations				
Nasopharyngitis	12	0	3	0
Nervous System Disorders				
Dysgeusia	11	0	5	0

* Graded according to NCI CTCAE, version 4.0.

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

‡ Includes asthenia and fatigue.

§ Includes abdominal pain, abdominal pain upper, abdominal pain lower.

¶ Includes stomatitis and mouth ulceration.

Includes platelets count decreased and thrombocytopenia.
Þ Includes neutropenia, febrile neutropenia, and neutrophil count decreased.
ß Includes rash erythematous, rash macular, and rash maculo-papular.
à Includes dyspnoea and dyspnoea exertional.

In addition, the adverse reactions observed in POLO that occurred in <10% of patients receiving Lynparza were cough (9%), abdominal pain upper (7%), blood creatinine increased (7%), dizziness (7%), headache (7%), dyspepsia (5%), leukopenia (5%), hypersensitivity (2%), and lymphopenia (2%).

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

Laboratory Parameter*	**Lynparza tablets n†=91**		**Placebo n†=60**	
	Grades 1-4 (%)	**Grades 3-4 (%)**	**Grades 1-4 (%)**	**Grades 3-4 (%)**
Increase in serum creatinine	99	2	85	0
Decrease in haemoglobin	86	11	65	0
Increase in mean corpuscular volume‡	71	-	30	-
Decrease in lymphocytes	61	9	27	0
Decrease in platelets	56	2	39	0
Decrease in leucocytes	50	3	23	0
Decrease in absolute neutrophil count	25	3	10	0

* Patients were allowed to enter POLO with haemoglobin ≥9 g/dL (CTCAE Grade 2) and other laboratory values of CTCAE Grade 1.
† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.
‡ Represents the proportion of subjects whose mean corpuscular volume was > ULN.

HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

PROfound

The safety of Lynparza as monotherapy was evaluated in patients with mCRPC and HRR gene mutations who have progressed following prior treatment with enzalutamide or abiraterone in PROfound *[see Clinical Studies (14.6)]*. This study was a randomised, open-label, multicentre study in which 386 patients received either Lynparza tablets 300 mg orally twice daily (n=256) or investigator's choice of enzalutamide or abiraterone acetate (n=130) until disease progression or unacceptable toxicity. Among patients receiving Lynparza, 62% were exposed for 6 months or longer and 20% were exposed for greater than one year.

Fatal adverse reactions occurred in 4% of patients treated with Lynparza. These included pneumonia (1.2%), cardiopulmonary failure (0.4%), aspiration pneumonia (0.4%), intestinal diverticulum (0.4%),

septic shock (0.4%), Budd-Chiari Syndrome (0.4%), sudden death (0.4%), and acute cardiac failure (0.4%).

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

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

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

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

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

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

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

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

Laboratory Parameter*	Lynparza tablets n†= 256		Enzalutamide or abiraterone n†=130	
	Grades 1-4 n= 247 (%)	Grades 3-4 n=247 (%)	Grades 1-4 n=124 (%)	Grades 3-4 n=124 (%)
Decrease in haemoglobin	242 (98)	33 (13)	91 (73)	5 (4)
Decrease in lymphocytes	154 (62)	57 (23)	42 (34)	16 (13)
Decrease in leucocytes	130 (53)	9 (4)	26 (21)	0
Decrease in absolute neutrophil count	83 (34)	8 (3)	11 (9)	0

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

6.2 Postmarketing Experience

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

Immune System Disorders: Hypersensitivity including angioedema.

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

7 DRUG INTERACTIONS

7.1 Use with Anticancer Agents

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

7.2 Effect of Other Drugs on Lynparza

Strong and Moderate CYP3A Inhibitors

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

Strong and Moderate CYP3A Inducers

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

Data

Animal Data

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

In an embryo-foetal development study, pregnant rats received oral doses of 0.05 and 0.5 mg/kg/day olaparib during the period of organogenesis. A dose of 0.5 mg/kg/day (with maternal systemic exposures approximately 0.18% of human exposure ($AUC_{0\text{-}24h}$) at the recommended dose) caused embryo-foetal toxicities including increased post-implantation loss and major malformations of the eyes (anophthalmia, microphthalmia), vertebrae/ribs (extra rib or ossification centre; fused or absent neural arches, ribs, and sternebrae), skull (fused exoccipital), and diaphragm (hernia). Additional abnormalities or variants included incomplete or absent ossification (vertebrae/sternebrae, ribs, limbs) and other findings in the vertebrae/sternebrae, pelvic girdle, lung, thymus, liver, ureter, and umbilical artery. Some findings noted above in the eyes, ribs and ureter were observed at a dose of 0.05 mg/kg/day olaparib at lower incidence.

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Recommend pregnancy testing for females of reproductive potential prior to initiating treatment with Lynparza.

Contraception

Females

Lynparza can cause foetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with Lynparza and for at least 6 months following the last dose.

Males

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

8.4 Paediatric Use

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

8.5 Geriatric Use

Of the 2351 patients with advanced solid tumours who received Lynparza tablets 300 mg orally twice daily as monotherapy, 596 (25%) patients were aged ≥65 years, and this included 137 (6%) patients who were aged ≥75 years. Seven (0.3%) patients were aged ≥85 years.

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

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

8.6 Renal Impairment

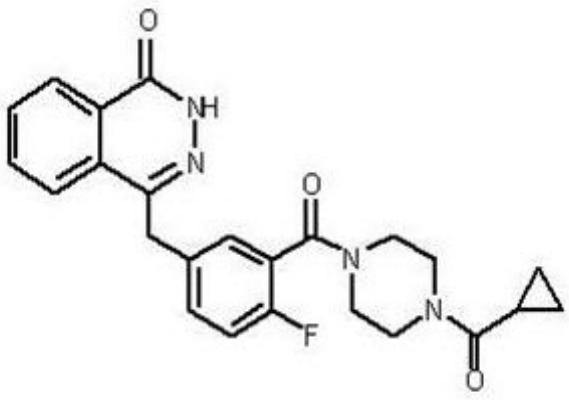
No dosage modification is recommended in patients with mild renal impairment (CLcr 51 to 80 mL/min estimated by Cockcroft-Gault). Reduce Lynparza dosage to 200 mg twice daily in patients with moderate renal impairment (CLcr 31 to 50 mL/min) *[see Dosage and Administration (2.5)]*. There are no data in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

8.7 Hepatic Impairment

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

11 DESCRIPTION

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



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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

Cardiac Electrophysiology

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

12.3 Pharmacokinetics

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

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

Absorption

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

Effect of Food

Co-administration of a high fat and high calorie meal (800-1000 kcal, 50% of the calorie content made up from fat) with olaparib slowed the rate (t_{max} delayed by 2.5 hours) of absorption, but did not significantly alter the extent of olaparib absorption (mean AUC increased by approximately 8%).

Distribution

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

Elimination

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

Metabolism

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

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

Excretion

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

Specific Populations

Patients with Renal Impairment

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

Patients with Hepatic Impairment

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

Drug Interaction Studies

Clinical Studies

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

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

In vitro Studies

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

UGT Enzymes: Olaparib is an inhibitor of UGT1A1.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with olaparib.

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

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

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

14 CLINICAL STUDIES

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

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

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

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

SOLO-1 demonstrated a statistically significant improvement in investigator-assessed PFS for Lynparza compared to placebo. Results from a blinded independent review were consistent. At the time of the analysis of PFS, overall survival (OS) data were not mature (21% of patients had died). Efficacy results are presented in Table 16.

Table 16 Efficacy Results – SOLO-1 (Investigator Assessment)

	Lynparza tablets (n=260)	**Placebo (n=131)**
Progression-Free Survival*		
Number of events (%)	102 (39%)	96 (73%)
Median, months	NR	13.8
Hazard ratio† (95% CI)	0.30 (0.23, 0.41)	
p-value‡	<0.0001	

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

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

PAOLA-1 (NCT02477644) was a randomised, double-blind, placebo-controlled, multicentre trial that compared the efficacy of Lynparza in combination with bevacizumab versus placebo/bevacizumab for the maintenance treatment of advanced high-grade epithelial ovarian cancer, fallopian tube or primary peritoneal cancer following first-line platinum-based chemotherapy and bevacizumab. Randomisation was stratified by first-line treatment outcome (timing and outcome of cytoreductive surgery and response to platinum-based chemotherapy) and t*BRCAm* status, determined by prospective local testing. All available clinical samples were retrospectively tested with Myriad myChoice® CDx. Patients were required to have no evidence of disease (NED) due to complete surgical resection, or who were in complete response (CR), or partial response (PR) following completion of first-line platinum-containing chemotherapy and bevacizumab. Patients were randomised (2:1) to receive Lynparza tablets 300 mg orally twice daily in combination with bevacizumab (n=537) 15 mg/kg every three weeks or placebo/bevacizumab (n=269). Patients continued bevacizumab in the maintenance setting and started treatment with Lynparza after a minimum of 3 weeks and up to a maximum of 9 weeks following completion of their last dose of chemotherapy. Lynparza treatment was continued for up to 2 years or until progression of the underlying disease or unacceptable toxicity. Patients who in the opinion of the treating physician could derive further benefit from continuous treatment could be treated beyond 2 years. Treatment with bevacizumab was for a total of up to 15 months, including the period given with chemotherapy and given as maintenance.

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

The median age of patients in both arms was 61 years overall (range 26 to 87). Ovarian cancer was the primary tumour type in 86% of patients in both arms. Ninety six per cent (96%) were serous histological type. The ECOG performance score was 0 in 70% of patients and 1 in 28% of patients, overall. All patients had received first-line platinum-based therapy and bevacizumab. First-line treatment outcomes at screening indicated that patients had no evidence of disease with complete macroscopic resection at initial debulking surgery (32%, both arms), no evidence of disease/ CR with complete macroscopic resection at interval debulking surgery (31%, both arms), no evidence of disease/ CR in patients who had either incomplete resection (at initial or interval debulking surgery) or no debulking surgery (15%, both arms) and patients with a partial response (22%, both arms). Thirty per cent (30%) of patients in both arms had a deleterious mutation. Patients were not restricted by the surgical outcome with 65% having complete cytoreduction at initial or interval debulking surgery and 35% having residual macroscopic disease. Demographics and baseline disease characteristics were balanced and comparable between the study and placebo arms in the Intention to Treat (ITT) population and also in the HRD-positive subgroup.

Efficacy results from a biomarker subgroup analysis of 387 patients with HRD-positive tumours, identified post-randomisation using the Myriad myChoice® HRD Plus tumour test, who received Lynparza/bevacizumab (n=255) or placebo/bevacizumab (n=132), are summarised in Table 17. Results from a blinded independent review of PFS were consistent. Overall survival data in this subpopulation were immature with 16% deaths.

Table 17 Efficacy Results – PAOLA-1 (HRD-positive status*, Investigator Assessment)

	Lynparza/bevacizumab (n=255)	**Placebo/bevacizumab (n=132)**
Progression-Free Survival		
Number of events (%)	87 (34%)	92 (70%)
Median, months	37.2	17.7
Hazard ratio† (95% CI)	0.33 (0.25, 0.45)	

* Median follow-up of 27.4 months in Lynparza/bevacizumab arm and 27.5 months in placebo/bevacizumab arm.
† The analysis was performed using an unstratified Cox proportional hazards model.
CI Confidence interval

14.3 Maintenance Treatment of Recurrent Ovarian Cancer

The efficacy of Lynparza was investigated in two randomised, placebo-controlled, double-blind, multicentre studies in patients with recurrent ovarian cancers who were in response to platinum-based therapy.

SOLO-2

The efficacy of Lynparza was evaluated in SOLO-2 (NCT01874353), a randomised (2:1) double-blind, placebo-controlled trial in patients with g*BRCA*m ovarian, fallopian tube, or primary peritoneal cancer. Patients were randomised to Lynparza tablets 300 mg orally twice daily or placebo until unacceptable toxicity or progressive disease. Randomisation was stratified by response to last platinum chemotherapy (complete versus partial) and time to disease progression in the penultimate platinum-based chemotherapy prior to enrollment (6-12 months versus >12 months). All patients had received at least two prior platinum-containing regimens and were in response (complete or partial) to their most recent platinum-based regimen. The major efficacy outcome measure was investigator-assessed PFS evaluated according to RECIST, version 1.1. An additional efficacy outcome measure was OS.

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

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

SOLO-2 demonstrated a statistically significant improvement in investigator-assessed PFS in patients randomised to Lynparza as compared with placebo. Results from a blinded independent review were consistent. The final analysis of OS did not reach statistical significance. Efficacy results are presented in Table 18.

Table 18 Efficacy Results – SOLO-2 (Investigator Assessment)

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

	Lynparza tablets (n=196)	**Placebo (n=99)**
Number of events (%)	116 (59)	65(66)
Median, months	51.7	38.8
Hazard ratio* (95% CI)	0.74 (0.54, 1.00)	
p-value†	0.0537	

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

Study 19

The efficacy of Lynparza was evaluated in Study 19 (NCT00753545), a randomised (1:1) double-blind, placebo-controlled trial in patients with platinum-sensitive ovarian cancer who had received 2 or more previous platinum-containing regimens. Patients were randomised to Lynparza capsules 400 mg orally twice daily or placebo until unacceptable toxicity or progressive disease. Randomisation was stratified by response to last platinum chemotherapy (complete response versus partial response), time to disease progression in the penultimate platinum-based chemotherapy (6-12 months versus >12 months), and descent (Jewish versus non-Jewish). The major efficacy outcome measure was investigator-assessed PFS according to RECIST, version 1.0.

A total of 265 patients were randomised, 136 to Lynparza and 129 to placebo. The median age of patients treated with Lynparza was 58 years (range: 21 to 89) and 59 years (range 33 to 84) among patients treated with placebo. ECOG PS was 0 in 81% of patients receiving Lynparza and 74% of patients receiving placebo. Of all patients, 97% were White, 19% were enrolled in the US or Canada, 45% were in complete response following their most recent platinum chemotherapy regimen, and 40% had a progression-free interval of 6-12 months since their penultimate platinum. Prior bevacizumab therapy was reported for 13% of patients receiving Lynparza and 16% of patients receiving placebo.

A retrospective analysis for germline *BRCA* mutation status, some performed using the Myriad test, indicated that 36% (n=96) of patients from the ITT population had deleterious g*BRCA* mutation, including 39% (n=53) of patients on Lynparza and 33% (n=43) of patients on placebo.

Efficacy results are presented in Table 19. Study 19 demonstrated a statistically significant improvement in investigator-assessed PFS in patients treated with Lynparza versus placebo.

Table 19 Efficacy Results - Study 19 (Investigator Assessment)

	Lynparza capsules (n=136)	Placebo (n=129)
Progression-Free Survival		
Number of events (%)	60 (44%)	94 (73%)
Median, months	8.4	4.8
Hazard ratio* (95% CI)	0.35 (0.25, 0.49)	
p-value†	<0.0001	
Overall Survival‡		
Number of events (%)	98 (72%)	112 (87%)
Median, months	29.8	27.8
Hazard ratio (95% CI)	0.73 (0.55, 0.95)	

* Hazard ratio from a Cox proportional hazards model including response to last platinum chemotherapy (complete response versus partial response), time to disease progression in the penultimate platinum-based chemotherapy (6-12 months versus >12 months), and Jewish descent (yes versus no) as covariates.
† The p-value is derived from a Cox proportional hazards model.
‡ Without adjusting for multiple analyses.

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

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

A total of 302 patients were randomised, 205 to Lynparza and 97 to chemotherapy. Among the 205 patients treated with Lynparza, the median age was 44 years (range: 22 to 76), 65% were White, 4% were males, and all the patients had an ECOG PS of 0 or 1. Approximately 50% of patients had triple-negative

tumours and 50% had oestrogen receptor and/or progesterone receptor positive tumours and the proportions were balanced across treatment arms. Patients in each treatment arm had received a median of 1 prior chemotherapy regimen for metastatic disease; approximately 30% had not received a prior chemotherapy regimen for metastatic breast cancer. Twenty-one per cent of patients in the Lynparza arm and 14% in the chemotherapy arm had received platinum therapy for metastatic disease. Seven per cent of patients in each treatment arm had received platinum therapy for localised disease.

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

A statistically significant improvement in PFS was demonstrated for the Lynparza arm compared to the chemotherapy arm. Efficacy data for OlympiAD are displayed in Table 20. Consistent results were observed across patient subgroups defined by study stratification factors. An exploratory analysis of investigator-assessed PFS was consistent with the BICR-assessed PFS results.

Table 20 Efficacy Results - OlympiAD (BICR-assessed)

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

* Hazard ratio is derived from a stratified log-rank test, stratified by ER, PgR negative versus ER and or PgR positive and prior chemotherapy (yes versus no).

† For PFS, p-value (2-sided) was compared to 0.05.
‡ Response based on confirmed responses. The confirmed complete response rate was 7.8% for Lynparza compared to 1.5% for chemotherapy arm.

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

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

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

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

Efficacy results of POLO are provided in Table 21.

Table 21 Efficacy Results - POLO (BICR-assessed)

	Lynparza tablets (n=92)	**Placebo (n=62)**
Progression-Free Survival		
Number of events (%)*	60 (65%)	44 (71%)
Median, months (95% CI)	7.4 (4.1, 11.0)	3.8 (3.5, 4.9)
Hazard ratio† (95% CI)	0.53 (0.35, 0.81)	
p-value	0.0035	

Patients with Measurable Disease	n=78	n=52
Objective Response Rate (95% CI)	23% (14, 34)	12% (4, 23)
Complete response (%)	2 (2.6)	0
Partial response (%)	16 (21)	6 (12)
Duration of Response (DOR)		
Median time in months (95% CI)	25 (15, NC)	4 (2, NC)

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

The result of an OS interim analysis conducted based on 67% information fraction did not show a statistically significant improvement in OS for Lynparza compared to placebo.

14.6 HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

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

Patients were divided into two cohorts based on HRR gene mutation status. Patients with mutations in either *BRCA1*, *BRCA2*, or *ATM* were randomised in Cohort A; patients with mutations among 12 other genes involved in the HRR pathway (*BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L*) were randomised in Cohort B; patients with co-mutations (*BRCA1*, *BRCA2*, or *ATM* plus a Cohort B gene) were assigned to Cohort A. Although patients with *PPP2R2A* gene mutations were enrolled in the trial, Lynparza is not indicated for the treatment of patients with this gene mutation due to unfavourable risk-benefit. Patients were randomised (2:1), 256 to Lynparza arm and 131 to enzalutamide or abiraterone acetate arm; in Cohort A there were 245 (162 Lynparza arm and 83 in enzalutamide or abiraterone acetate arm) and in Cohort B there were 142 patients (94 in Lynparza arm and 48 in enzalutamide or abiraterone acetate arm). Randomisation was stratified by prior receipt of taxane chemotherapy and presence of measurable disease by RECIST 1.1. Treatment was continued until objective radiological disease progression determined by BICR. Upon radiological progression confirmed by BICR, patients randomised to enzalutamide or abiraterone acetate were given the option to switch to olaparib. Patients with HRR gene mutations were identified by tissue-based testing using the Foundation Medicine FoundationOne® clinical trial HRR assay performed at a central laboratory.

Determination of deleterious or suspected deleterious somatic or germline HRR mutation status in line with the FDA approved mutation classification and testing criteria for the Foundation Medicine F1CDx tissue-based assay and assessment of the germline-*BRCA* status using the Myriad BRACAnalysis CDx blood-based assay was performed retrospectively. Representation of individual gene mutations by cohort is provided in Table 22. No patients were enrolled who had mutations in two of the 15 pre-specified HRR genes: *FANCL* and *RAD51C*.

Table 22 Frequency of Patients with HRR Mutations Enrolled in PROfound

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

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

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

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

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

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

PROfound demonstrated a statistically significant improvement in BICR-assessed rPFS for Lynparza compared to investigator's choice of enzalutamide or abiraterone acetate in Cohort A and Cohort A+B. In

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

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

Efficacy results of PROfound are provided in Tables 23 and 24.

Table 23 Efficacy Results - PROfound (BICR-assessed)

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

Median (95% CI), in months	19.1 (17.4, 23.4)	14.7 (11.9, 18.8)	-	-
Hazard ratio (95% CI)†	0.69 (0.50, 0.97)		-	
p-value‡	0.0175		-	

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

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

Response data by HRR mutations for patients in the Lynparza arm are presented in Table 24. In the comparator arm of Cohorts A and B, a total of three patients achieved a partial response, including one patient with an *ATM* mutation alone and 2 patients with co-occurring mutations (one with *PALB2*+*PPP2R2A* and one with *CDK12*+*PALB2*).

Table 24 Response Rate and Duration of Response by HRR Mutation in Patients with Measurable Disease at Baseline on the Lynparza Arm – PROfound (BICR-assessed)

HRR mutation*	**Patients (N=138)**	**Confirmed ORR†**	
		n (%)	**95% CI**
Single mutation			
BRCA2	43	24 (56)	(40, 71)
ATM	30	3 (10)	(2, 27)
CDK12	34	2 (6)	(1, 20)
BRCA1	6	SD, PD (4), NE	NA
CHEK2	4	SD (2), PD (2)	NA
BRIP1	2	SD, PD	NA
PALB2	2	SD, PD	NA
CHEK1	1	PD	NA
RAD51B	1	SD	NA
RAD51D	1	PD	NA
RAD54L	1	SD	NA
Co-occurring mutations			
BRCA2/CDK12	2	PR, SD	NA
BRCA2/ATM	2	SD, SD	NA
BRCA2/BARD1	1	PD	NA
BRCA2/CHEK2	1	SD	NA
CDK12/CHEK1	1	SD	NA

CDK12/PALB2	1	PD	NA
BRCA2/CDK12/CHEK2	1	PD	NA
BRCA2/CHEK2/RAD51D	1	SD	NA

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

16 HOW SUPPLIED/STORAGE AND HANDLING

Lynparza is available as 150 mg and 100 mg tablets.

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

Do not store above 30°C.

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

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

17 PATIENT COUNSELING INFORMATION

MDS/AML

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

Pneumonitis

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

Embryo-Foetal Toxicity

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

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

Advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months after receiving the last dose of Lynparza. Advise male patients not to donate sperm during therapy and for 3 months following the last dose of Lynparza *[see Warnings and Precautions (5.3) and Use in Specific Population (8.3)]*.

Venous Thromboembolic Events

Advise patients with metastatic castration-resistant prostate cancer to immediately report any signs or symptoms of thromboembolism such as pain or swelling in an extremity, shortness of breath, chest pain, tachypnoea, and tachycardia *[see Warnings and Precautions (5.4)]*.

Lactation

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

Drug Interactions

Advise patients and caregivers to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Inform patients to avoid grapefruit, grapefruit juice, Seville oranges, and Seville orange juice while taking Lynparza *[see Drug Interactions (7.2)]*.

Nausea/Vomiting

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

Manufactured by

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

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