

Recurrent Ovarian Cancer, Germline *BRCA*m Advanced 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
- Advanced germline *BRCA*-mutated 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) analog 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 (CL_{cr} 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, oval, bi-convex, film-coated, with debossment ‘OP150’ on one side and plain on the reverse side.
- 100 mg: yellow to dark yellow, oval, bi-convex, film-coated, with debossment ‘OP100’ on one side and plain on the reverse side.

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 labeling:

- Myelodysplastic Syndrome/Acute Myeloid Leukemia [*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 2351 patients; 1585 patients with exposure to 300 mg twice daily tablet dose including five controlled, randomized, 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, 55% of patients were exposed for 6 months or longer and 31% were exposed for greater than one year in the Lynparza group.

In this pooled safety population, the most common adverse reactions in $\geq 10\%$ of patients were nausea (60%), fatigue (55%), anemia (37%), vomiting (34%), diarrhea (25%), decreased appetite (23%), headache (16%), neutropenia (15%), dysgeusia (15%), cough (15%), dyspnea (14%), dizziness (12%), dyspepsia (12%), leukopenia (11%), thrombocytopenia (11%), and abdominal pain upper (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.

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

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

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

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

Tables 4 and 5 summarize 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				
Anemia [‡]	41	17	10	0.4
Lymphopenia [§]	24	7	9	1.1
Leukopenia	18	1.9	10	1.5

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

[†] Includes asthenia, and fatigue.

[‡] Includes anemia, anemia macrocytic, erythropenia, haematocrit decreased, haemoglobin decreased, normochromic anemia, normochromic normocytic anemia, normocytic anemia, and red blood cell count decreased. Includes B-lymphocyte count decreased, lymphocyte count decreased, lymphopenia, and T-lymphocyte count decreased.

[§] Includes 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%), anemia (41%), lymphopenia, vomiting (22%), diarrhea (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%), dyspnea (8%), stomatitis (5%), dyspepsia (4.3%), erythema (3%), dizziness (2.6%), and hypersensitivity (1.7%).

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 hemoglobin	79	13	55	0.4
Decrease in lymphocytes	63	10	42	3.0
Increase in serum creatinine	61	0.4	36	0.4
Decrease in leukocytes	59	3.4	45	2.2
Decrease in absolute neutrophil count	35	7	30	3.7
Decrease in platelets	35	2.4	28	0.4

* Reported within 30 days of the last dose.

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

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

Maintenance Treatment of Recurrent Ovarian Cancer

SOLO-2

The safety of Lynparza for the maintenance treatment of patients with platinum sensitive *gBRCAm* 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 anemia (22%), neutropenia (9%), and fatigue/asthenia (8%). Discontinuation due to an adverse reaction occurred in 11% of patients receiving Lynparza.

Tables 6 and 7 summarize 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
Diarrhea	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				
Anemia [‡]	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 anemia, hematocrit decreased, hemoglobin 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%), edema (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 hemoglobin	83	17	69	0
Decrease in leukocytes	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 summarize 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
Diarrhea	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				
Anemia [†]	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%), dyspnea (13%), pyrexia (10%), stomatitis (9%), edema (9%), increase in creatinine (7%), neutropenia (5%), thrombocytopenia (4%), leukopenia (2%), 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 hemoglobin	82	8	58	1
Increase in mean corpuscular volume [‡]	82	-	51	-
Decrease in leukocytes	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.

Advanced Germline BRCA-mutated Ovarian Cancer After 3 or More Lines of Chemotherapy

Pooled Data

The safety of Lynparza was investigated in 223 patients (pooled from 6 studies) with gBRCAm advanced ovarian cancer who had received 3 or more prior lines of chemotherapy [see [Clinical Studies \(14.4\)](#)]. Patients received Lynparza capsules 400 mg orally twice daily until disease progression or unacceptable tolerability. The median exposure to Lynparza in these patients was 5.2 months.

There were 8 (4%) patients with adverse reactions leading to death, two were attributed to acute leukemia, and one each was attributed to COPD, cerebrovascular accident, intestinal perforation, pulmonary embolism, sepsis, and suture rupture. Adverse reactions led to dose interruption in 40% of patients, dose reduction in 4%, and discontinuation in 7%.

Tables 10 and 11 summarize the adverse reactions and laboratory abnormalities from the pooled studies.

Table 10 Adverse Reactions Reported in Pooled Data (≥20% of Patients Who Received Lynparza)

Adverse Reaction	Lynparza capsules n=223	
	Grades 1-4 (%)	Grades 3-4 (%)
General Disorders		
Fatigue/asthenia	66	8
Gastrointestinal Disorders		
Nausea	64	3
Vomiting	43	4
Diarrhea	31	1
Dyspepsia	25	0
Decreased appetite	22	1
Blood and Lymphatic Disorders		
Anemia	34	18
Infections and Infestations		
Nasopharyngitis/URI	26	0
Musculoskeletal and Connective Tissue Disorders		
Arthralgia/musculoskeletal pain	21	0
Myalgia	22	0

Table 11 Laboratory Abnormalities Reported in ≥25% of Patients in Pooled Data

Laboratory Parameter*	Lynparza capsules n [†] =223	
	Grades 1-4 (%)	Grades 3-4 (%)
Decrease in hemoglobin	90	15
Mean corpuscular volume elevation	57	-
Decrease in lymphocytes	56	17
Decrease in platelets	30	3
Increase in creatinine	30	2
Decrease in absolute neutrophil count	25	7

* 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.

The following adverse reactions and laboratory abnormalities have been identified in ≥10 to <20% of the 223 patients receiving Lynparza and not included in the table: cough (16%), constipation (16%), dysgeusia (16%), headache (15%), peripheral edema (14%), back pain (14%), urinary tract infection (14%), dyspnea (13%), and dizziness (11%).

The following adverse reactions and laboratory abnormalities have been identified in <10% of the 223 patients receiving Lynparza and not included in the table: leukopenia (9%), pyrexia (8%), peripheral neuropathy (5%), hypomagnesemia (5%), rash (5%), stomatitis (4%), and venous thrombosis (including pulmonary embolism) (1%).

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

OlympiAD

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

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

Tables 12 and 13 summarize the adverse reactions and laboratory abnormalities in OlympiAD.

Table 12 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
Diarrhea	21	1	22	0
Blood and Lymphatic Disorders				
Anemia [†]	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 anemia (anemia erythropenia, hematocrit decreased, hemoglobin 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 13 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 hemoglobin	82	17	66	3
Decrease in lymphocytes	73	21	63	3
Decrease in leukocytes	71	8	70	23
Increase in mean corpuscular volume [‡]	71	-	33	-
Decrease in absolute neutrophil count	46	11	65	38
Decrease in platelets	33	3	28	0

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

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

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

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

POLO

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

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

Tables 14 and 15 summarize the adverse reactions and laboratory abnormalities in patients in POLO.

Table 14 Adverse Reactions* in POLO (Occurring in ≥10% of Patients who Received Lynparza)

Adverse Reaction	Lynparza tablets (n=91) [†]		Placebo (n=60) [†]	
	All Grades (%)	Grades 3 – 4 (%)	All Grades (%)	Grades 3 – 4 (%)
General Disorders and Administration Site Conditions				
Fatigue [‡]	60	5	35	2
Gastrointestinal Disorders				
Nausea	45	0	23	2
Abdominal pain [^]	34	2	37	5
Diarrhea	29	0	15	0
Constipation	23	0	10	0
Vomiting	20	1	15	2
Stomatitis [§]	10	0	5	0
Blood and Lymphatic System Disorders				
Anemia	27	11	17	3
Thrombocytopenia	14	3	7	0
Neutropenia [¶]	12	4	8	3
Metabolism and Nutrition Disorders				
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 [#]	15	0	5	0
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea ^{**}	13	0	5	2
Infections and Infestations				
Nasopharyngitis	12	0	3	0
Nervous System Disorders				
Dysgeusia	11	0	5	0

* Graded according to NCI CTCAE, version 4.0

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

‡ Includes asthenia and fatigue

^ Includes abdominal pain, abdominal pain upper, abdominal pain lower

§ Includes stomatitis and mouth ulceration

|| Includes platelets count decreased and thrombocytopenia

¶ Includes neutropenia, febrile neutropenia and neutrophil count decreased

Includes rash erythematous, rash macular and rash maculo-papular

**Includes dyspnea and dyspnea 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 15 Laboratory Abnormalities Reported in ≥25% of Patients in POLO

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

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

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

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

HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

PROfound

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

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

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

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

Tables 16 and 17 summarize the adverse reactions and laboratory abnormalities, respectively, in patients in PROfound.

Table 16 Adverse Reactions* Reported in ≥10% of Patients in PROfound

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

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

[†] Includes anemia and hemoglobin decreased

[‡] Includes platelet count decreased and thrombocytopenia

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 17 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 hemoglobin	242 (98)	33 (13)	91 (73)	5 (4)
Decrease in lymphocytes	154 (62)	57 (23)	42 (34)	16 (13)
Decrease in leukocytes	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 (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 fetal 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-fetal 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 fetus 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. The estimated background risk in the U.S. general population of major birth defects is 2-4%; and the risk for spontaneous abortion is approximately 15-20% in clinically recognized pregnancies.

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_{0-24h}) at the recommended dose).

In an embryo-fetal development study, pregnant rats received oral doses of 0.05 and 0.5 mg/kg/day olaparib during the period of organogenesis. A dose of 0.5 mg/kg/day (with maternal systemic exposures approximately 0.18% of human exposure (AUC_{0-24h}) at the recommended dose) caused embryo-fetal toxicities including increased post-implantation loss and major malformations of the eyes (anophthalmia, microphthalmia), vertebrae/ribs (extra rib or ossification center; 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 fetal 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 Pediatric Use

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

8.5 Geriatric Use

Of the 2351 patients with advanced solid tumors 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 [see [Adverse Reactions \(6.1\)](#)].

Of the 535 patients with advanced solid tumors 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 \(12.3\)](#)].

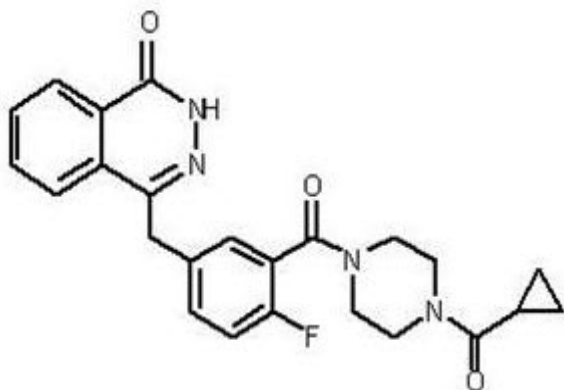
8.7 Hepatic Impairment

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(2H)-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 ferrousferrous 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 tumor cell lines in vitro and decrease tumor growth in mouse xenograft models of human cancer, both as monotherapy or following platinum-based chemotherapy. Increased cytotoxicity and anti-tumor activity following treatment with olaparib were noted in cell lines and mouse tumor models with deficiencies in *BRCA1/2*, *ATM*, or other genes involved in the homologous recombination repair (HRR) of DNA damage and correlated with platinum response. In vitro studies have shown that olaparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes, resulting in DNA damage and cancer cell death.

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 $\mu\text{g}/\text{mL}$ (32%) and AUC is 39.2 $\mu\text{g}\cdot\text{h}/\text{mL}$ (44%) following a single 300 mg dose. The mean steady state olaparib C_{max} and AUC is 7.6 $\mu\text{g}/\text{mL}$ (35%) and 49.2 $\mu\text{g}\cdot\text{h}/\text{mL}$ (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 (\pm 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 (\pm 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 metabolized by cytochrome P450 (CYP) 3A in vitro.

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

Excretion

Following a single dose of radiolabeled 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.

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 ($CL_{Cr}=51-80$ 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 ($CL_{Cr}=31-50$ mL/min; $n=13$), compared to those with normal renal function ($CL_{Cr} \geq 81$ 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 ($CL_{Cr} \leq 30$ mL/min).

Patients with Hepatic Impairment

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

Drug Interaction Studies

Clinical Studies

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

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

In vitro Studies

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

UGT Enzymes: Olaparib is an inhibitor of UGT1A1.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with olaparib.

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

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

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

14 CLINICAL STUDIES

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

The efficacy of Lynparza was evaluated in SOLO-1 (NCT01844986), a randomized (2:1), double-blind, placebo-controlled, multi-center trial in patients with *BRCA*-mutated advanced ovarian, fallopian tube, or primary peritoneal cancer following first-line platinum-based chemotherapy. Patients were randomized 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. Randomization 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 Tumors (RECIST), version 1.1.

A total of 391 patients were randomized, 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*BRCAM*), and 2 patients had somatic *BRCAM* (s*BRCAM*).

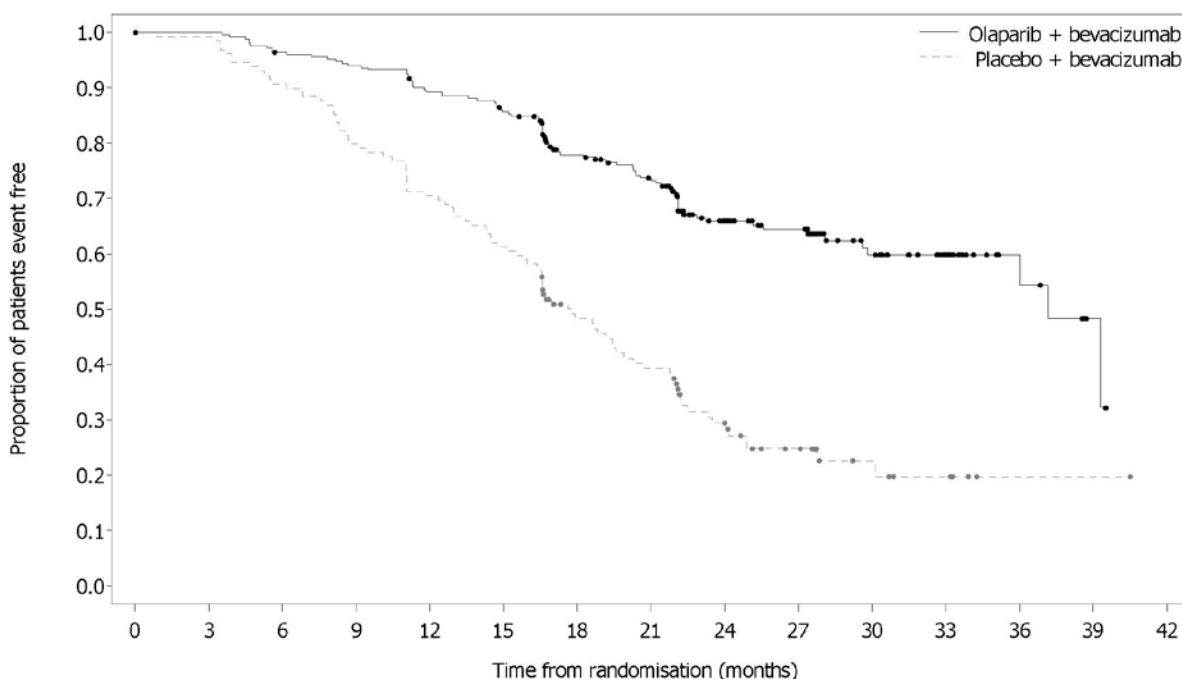
Of the 391 patients randomized in SOLO-1, 386 were retrospectively or prospectively tested with a Myriad BRACAnalysis test and 383 patients were confirmed to have deleterious or suspected deleterious

* Median follow-up of 27.4 months in Lynparza/bevacizumab arm and 27.5 months in placebo/bevacizumab arm.

^a The analysis was performed using an unstratified Cox proportional hazards model.

CI Confidence interval

Figure 2 Kaplan-Meier Curves of Investigator-Assessed Progression-Free Survival – PAOLA-1 (HRD-positive status)



Number of patients at risk:

Olaparib + bevacizumab	255	252	242	236	223	213	169	155	103	85	46	29	11	3	0
Placebo + bevacizumab	132	128	117	103	91	79	54	44	28	18	8	5	1	1	0

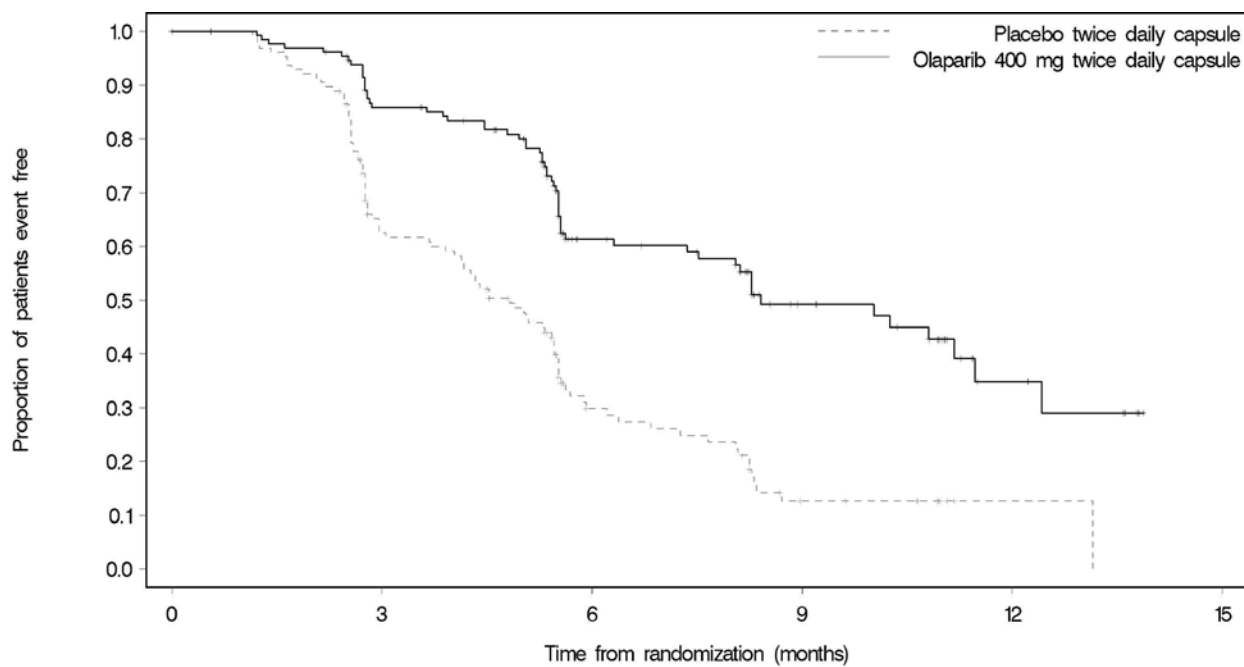
14.3 Maintenance Treatment of Recurrent Ovarian Cancer

The efficacy of Lynparza was investigated in two randomized, placebo-controlled, double-blind, multi-center 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 randomized (2:1) double-blind, placebo-controlled trial in patients with *gBRCAm* ovarian, fallopian tube, or primary peritoneal cancer. Patients were randomized to Lynparza tablets 300 mg orally twice daily or placebo until unacceptable toxicity or progressive disease. Randomization 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-

Figure 4 Kaplan-Meier Curves of Investigator-Assessed Progression-Free Survival – Study 19



Number of patients at risk:

Time (months)	0	3	6	9	12	15
Olaparib 400 mg twice daily capsule	136	106	53	24	7	0
Placebo twice daily capsule	129	72	24	7	1	0

14.4 Advanced Germline *BRCA*-mutated Ovarian Cancer Treated with 3 or More Prior Lines of Chemotherapy

The efficacy of Lynparza was investigated in a single-arm study of patients with deleterious or suspected deleterious *gBRCAm* advanced cancers. A total of 137 patients with measurable, advanced *gBRCAm* ovarian cancer treated with three or more prior lines of chemotherapy were enrolled. All patients received Lynparza capsules 400 mg orally twice daily until disease progression or intolerable toxicity. The efficacy outcome measures were objective response rate (ORR) and duration of response (DOR) as assessed by the investigator according to RECIST, version 1.0.

The median age of the patients was 58 years, the majority were White (94%) and 93% had an ECOG PS of 0 or 1. Deleterious or suspected deleterious *gBRCAm* status was verified retrospectively in 97% (59/61) of the patients for whom blood samples were available by the BRACAnalysis CDx™.

Efficacy results are summarized in Table 22.

Table 22 Overall Response and Duration of Response in Patients with gBRCA-mutated Advanced Ovarian Cancer Who Received 3 or More Lines of Chemotherapy

	Lynparza Capsules n=137
Objective Response Rate (95% CI)	34% (26, 42)
Complete response	2%
Partial response	32%
Median DOR in months (95% CI)	7.9 (5.6, 9.6)

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

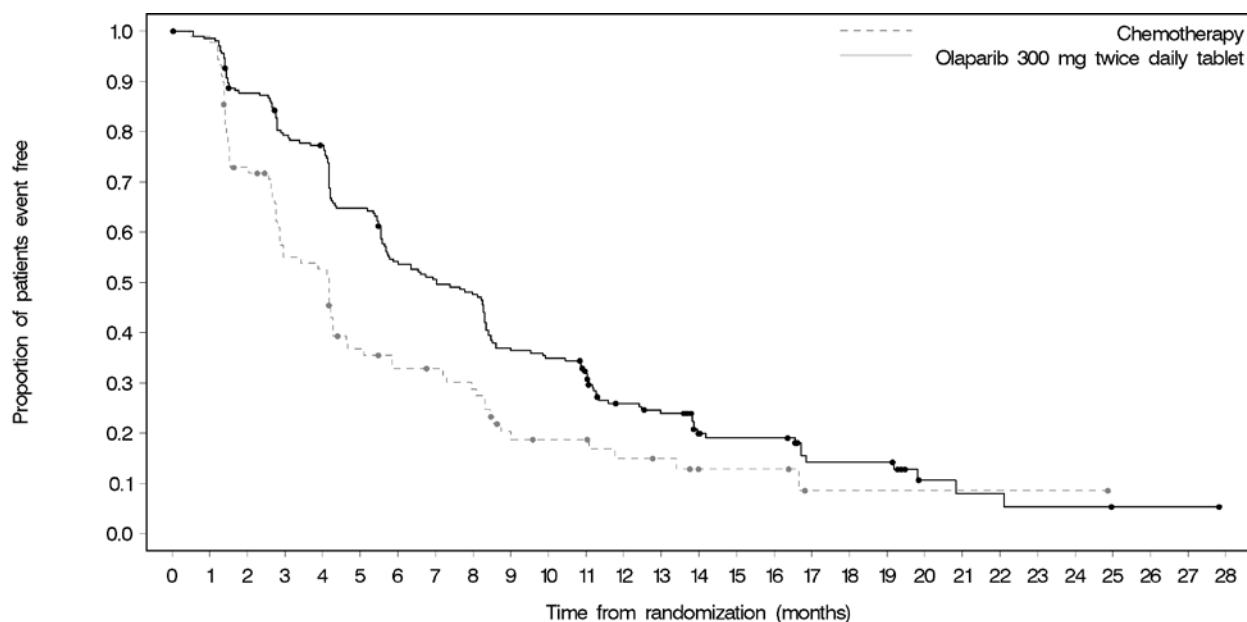
The efficacy of Lynparza was evaluated in OlympiAD (NCT02000622), an open-label randomized (2:1) study in patients with gBRCAm HER2-negative metastatic breast cancer. Patients were required to have received treatment with an anthracycline (unless contraindicated) and a taxane, in the neoadjuvant, adjuvant 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 randomized 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. 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 major efficacy outcome measure was PFS assessed by blinded independent central review (BICR) using RECIST version 1.1.

A total of 302 patients were randomized, 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 tumors and 50% had estrogen receptor and/or progesterone receptor positive tumors 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 percent of patients in the Lynparza arm and 14% in the chemotherapy arm had received platinum therapy for metastatic disease. Seven percent of patients in each treatment arm had received platinum therapy for localized disease.

Of the 302 patients randomized onto OlympiAD, 299 were tested with the BRACAnalysis CDx[®] and 297 were confirmed to have deleterious or suspected deleterious gBRCAm status; 202 were randomized to the Lynparza arm and 95 to the healthcare provider’s choice of chemotherapy arm.

A statistically significant improvement in PFS was demonstrated for the Lynparza arm compared to the chemotherapy arm. Efficacy data for OlympiAD are displayed in Table 23 and Figure 5. 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.

Figure 5 Kaplan-Meier Curves of Progression-Free Survival – OlympiAD



Number of patients at risk:

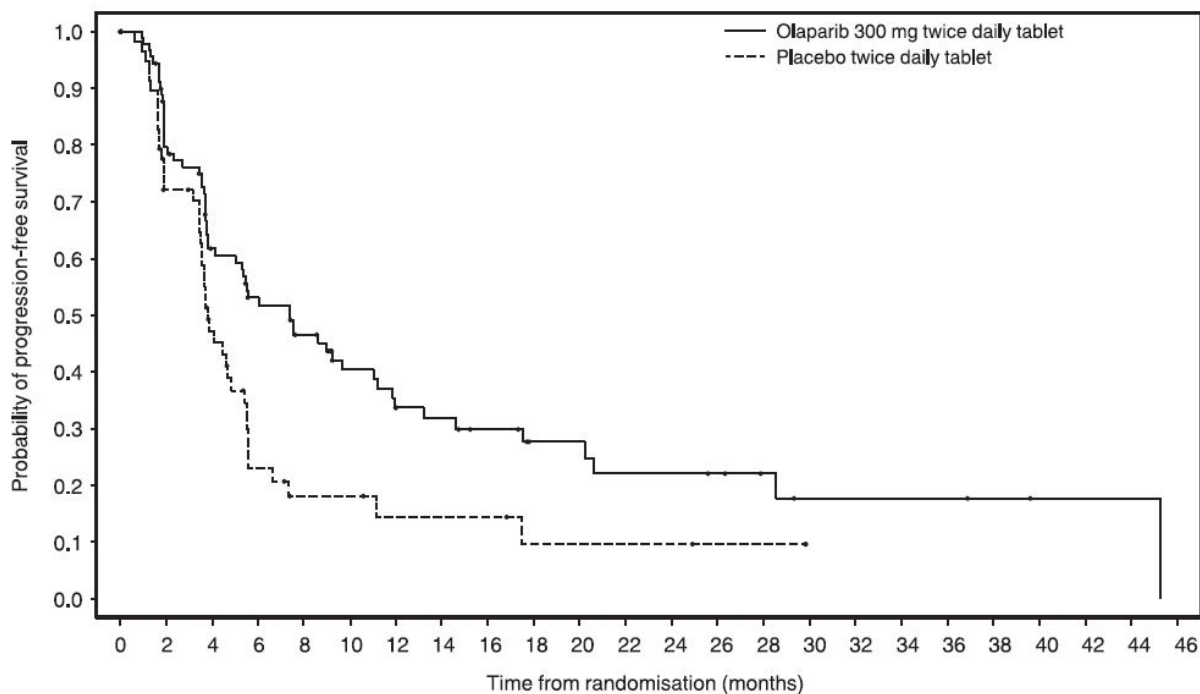
Time (months)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Olaparib 300 mg twice daily tablet	205	201	177	159	154	129	107	100	94	73	69	61	40	36	23	21	21	11	11	11	4	3	3	2	2	1	1	1	0
Chemotherapy	97	88	63	46	44	29	25	24	21	13	11	11	8	7	4	4	4	1	1	1	1	1	1	1	1	0	0	0	0

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

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

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

Figure 6 Kaplan-Meier Curves of BICR-Assessed Progression-Free Survival - POLO



Number of patients at risk:

Olaparib 300 mg twice daily tablet

92 69 50 41 34 24 18 17 14 10 10 8 8 7 5 3 3 3 3 2 1 1 1 0

Placebo twice daily tablet

62 39 23 10 6 6 4 4 4 2 2 2 2 1 1 0 0 0 0 0 0 0 0 0

14.7 HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

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

Patients were divided into two cohorts based on HRR gene mutation status. Patients with mutations in either *BRCA1*, *BRCA2*, or *ATM* were randomized in Cohort A; patients with mutations among 12 other genes involved in the HRR pathway (*BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L*) were randomized in Cohort B; patients with co-mutations (*BRCA1*, *BRCA2*, or *ATM* plus a Cohort B gene) were assigned to Cohort A. Although patients with *PPP2R2A* gene mutations were enrolled in the trial, Lynparza is not indicated for the treatment of patients with this gene mutation due to unfavorable risk-benefit. Patients were randomized (2:1), 256 to Lynparza arm and 131 to enzalutamide or abiraterone acetate arm; in Cohort A there were 245 (162 Lynparza arm and 83 in enzalutamide or abiraterone acetate arm) and in Cohort B there were 142 patients

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 hematological toxicity or a more serious uncommon bone marrow problem called ‘myelodysplastic syndrome’ (MDS) or ‘acute myeloid leukemia’ (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-Fetal Toxicity

Inform pregnant women of the risk to a fetus 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 Populations \(8.3\)](#)].

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, tachypnea, 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 \(6.1\)](#)].

What are the ingredients in Lynparza?

Active ingredient: olaparib

Inactive ingredients:

Tablet contains: copovidone, mannitol, colloidal silicon dioxide and sodium stearyl fumarate

Tablet coating contains: hypromellose, polyethylene glycol 400, titanium dioxide, ferric oxide yellow and ferrousferrous oxide (150 mg tablet only)

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For more information, call 1-800-236-9933 or go to www.Lynparza.com.

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