Lynparza®
olaparib
tablets 150 mg

Combination Maintenance Therapy in Ovarian Cancer

In patients with newly diagnosed advanced ovarian cancer, **LYNPARZA® (olaparib) in combination with bevacizumab is a first-line maintenance treatment option** in patients with HRD.*†[1]

This infographic will explain the rationale for using combination maintenance therapy in advanced ovarian cancer, present the proposed mechanisms of action of LYNPARZA and bevacizumab, and outline the need for testing to identify patients with HRD who are eligible to receive the LYNPARZA plus bevacizumab combination.

Select to view.

*HRD-positive is defined as either a tumor *BRCA* mutation and/or an HRD score ≥42 by Myriad MyChoice® CDx.[2,3]

†Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA.[1]

CDx, companion diagnostic; FDA, US Food and Drug Administration; HRD, homologous recombination deficiency; PARP, poly (ADP-ribose) polymerase.

Select to view Indications and Important Safety Information.

Use to navigate.

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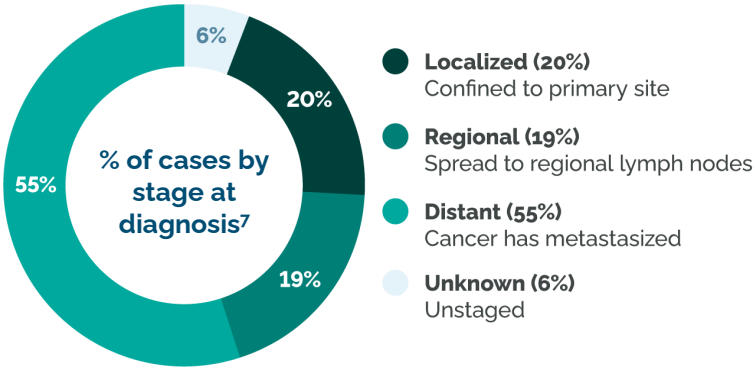
1 Why Use Maintenance Therapy in Ovarian Cancer?

Select to learn about PARPi indications in ovarian cancer.

Ovarian cancer is the **most common cause of death** among gynecologic cancers.[4]

Most patients with advanced ovarian cancer respond to first-line chemotherapy. However, in the absence of maintenance therapy, **70% of patients relapse within 3 years**.[5,6]

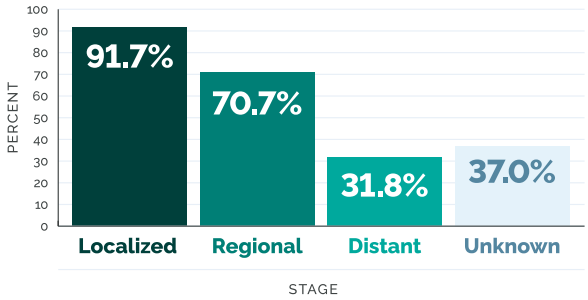
70% relapse after first-line chemotherapy[5,6]



The majority (55%) of patients are diagnosed with disease that has **spread to distant parts of the body.**[7]

According to SEER data, the **5-year survival rate** for patients diagnosed with distant disease is **approximately 32%**.[7]

5-year survival by stage[7]



Maintenance therapy should be offered to **all eligible patients with advanced ovarian cancer who respond to first-line chemotherapy**.[8]

PARPi, poly (ADP-ribose) polymerase inhibitor; SEER, Surveillance, Epidemiology, and End Results.

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PARPis as First-Line Maintenance Therapy in Advanced Ovarian Cancer

PARPis **require a positive *BRCA* and/or HRD test** for patients with advanced ovarian cancer to be eligible for first-line maintenance therapy.*[1,9]

Drug approved for patients with any of the following†:

	*gBRCA*m	*sBRCA*m	HRD+
LYNPARZA® (olaparib) monotherapy[1]	✓	✓	—
LYNPARZA + bevacizumab combination therapy[1]	✓	✓	✓
Zejula® (niraparib) monotherapy[9]	✓	✓	✓
Rubraca® (rucaparib) monotherapy[10]	—	—	—

LYNPARZA is indicated as monotherapy for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic *BRCA*-mutated (g*BRCA*m or s*BRCA*m) advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line, platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA.[1]

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 HRD-positive status defined by either[1]:

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

Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA.[1]

In the PAOLA-1 clinical trial, HRD+ was defined as a tumor *BRCA* mutation and/or a GIS ≥42 by the Myriad MyChoice® HRD assay.[3]

Zejula is a PARPi indicated for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with HRD-positive status defined by either[9]:

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

Rubraca does not currently have an approved indication as a first-line maintenance therapy in advanced ovarian cancer.[10]

*No PARPis are approved for use in HRD-negative patients. Bevacizumab monotherapy may be a treatment option for these patients; Avastin® (bevacizumab) in combination with carboplatin and paclitaxel, followed by Avastin as a single agent, is indicated for the treatment of patients with stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer following initial surgical resection.[1,9-11]

†Only first-line maintenance indications in ovarian cancer are described. See Prescribing Information for full indications.

*BRCA*m, *BRCA* mutation; FDA, US Food and Drug Administration; g*BRCA*m, germline *BRCA* mutation; GIS, Genomic Instability Score; HRD, homologous recombination deficiency; HRD+, homologous recombination deficiency–positive; PARPis, poly (ADP-ribose) polymerase inhibitors; s*BRCA*m, somatic *BRCA* mutation.

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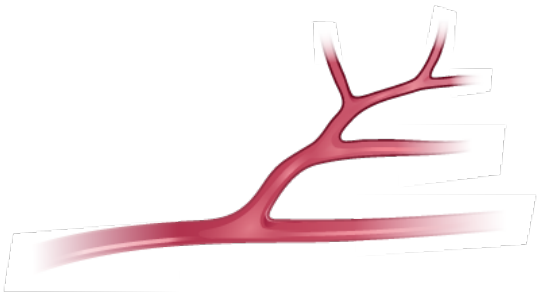
2 Why Consider Maintenance Therapy Combinations in Ovarian Cancer?

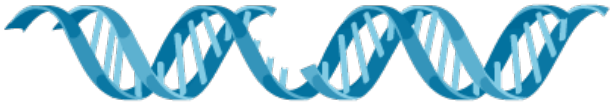
The PARPi LYNPARZA is indicated both as monotherapy and in combination with the angiogenesis inhibitor bevacizumab (a VEGF inhibitor) **as maintenance therapy in biomarker-selected patients with advanced ovarian cancer**.[1,11]

Cancer cells may rely on distinct and complementary mechanisms for survival. Combination therapy with LYNPARZA plus bevacizumab was designed to target two disease mechanisms present in ovarian tumors*[1,11,12]:

Angiogenesis



Genomic instability and mutation



PARPis and antiangiogenic agents are known to have limited overlapping toxicity profiles.[13]

*The exact mechanism of disease in the context of combination treatment strategies is yet to be elucidated, and the exact mechanism of action of LYNPARZA is unknown.

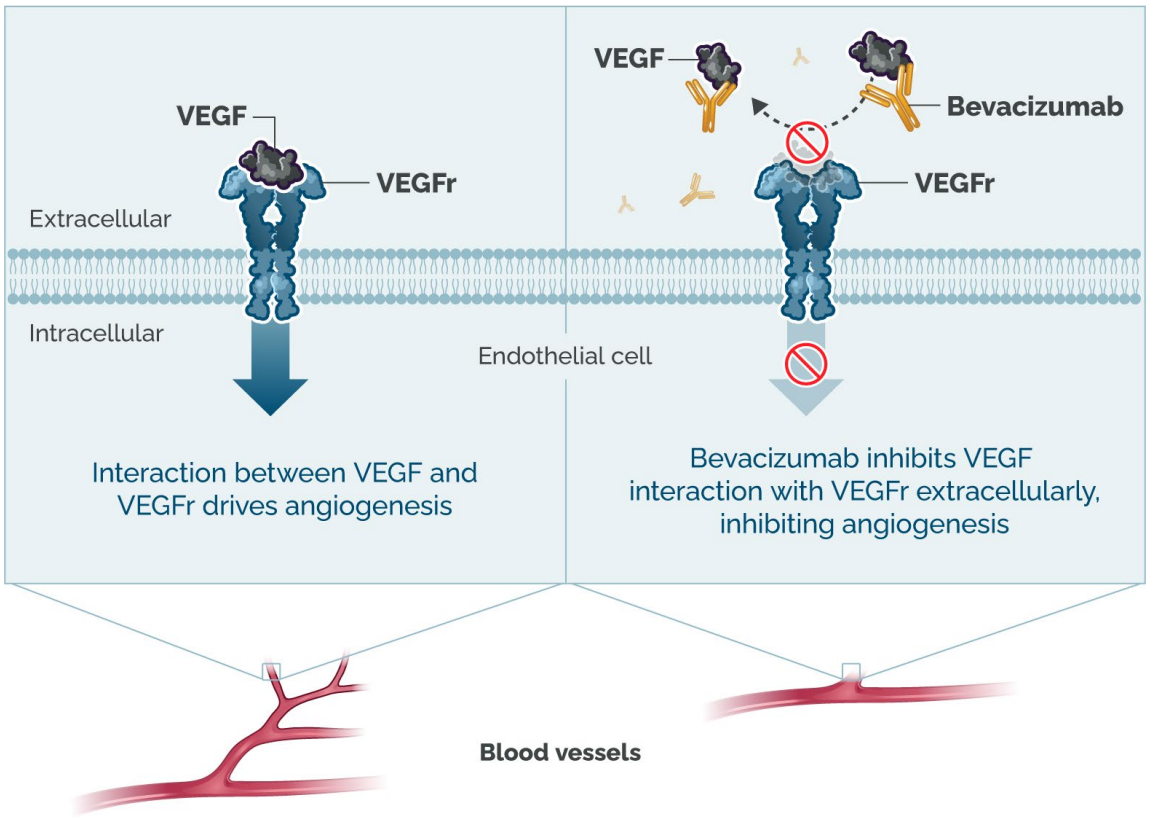
PARPi, poly (ADP-ribose) polymerase inhibitor; VEGF, vascular endothelial growth factor.

3 Mechanism of Action of Bevacizumab – Inhibition of Angiogenesis

Bevacizumab is a humanized anti-VEGF monoclonal antibody that[11]:

- Binds to VEGF, preventing its interaction with receptors
- Leads to reduced growth of vascular endothelial cells, **inhibiting tumor vascularization (angiogenesis)**

Proposed mechanism of action of bevacizumab*[11,14,15]



*The mechanism of action of bevacizumab has been elucidated in preclinical models. Its clinical significance is unknown.[14]

VEGF, vascular endothelial growth factor; VEGFr, vascular endothelial growth factor receptor.

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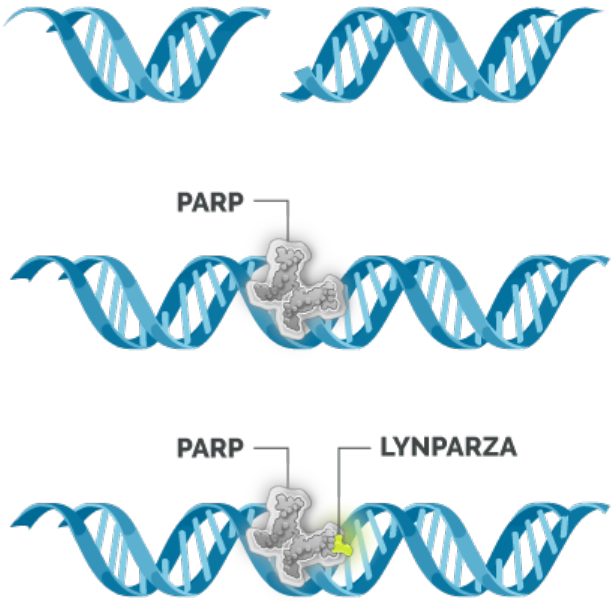
4 Mechanism of Action of LYNPARZA – PARP Inhibition

LYNPARZA, a PARP enzyme inhibitor, works by disrupting the internal DNA repair process in tumors, thereby inhibiting their growth.[1]

Proposed mechanism of action of LYNPARZA*[1,16,17]



Cells accumulate DNA damage.[16]

Tumor cells survive by repairing their damaged DNA via the PARP enzyme, among other cellular processes.[16,17]

LYNPARZA inhibits PARP to disrupt the DNA repair process and potentially kill tumor cells.[1,17]

*The exact mechanism of action of LYNPARZA remains a subject of research.

Note that any treatment benefit from the combination of LYNPARZA plus bevacizumab is believed to be additive, not synergistic.[5,18]

PARP, poly (ADP-ribose) polymerase.

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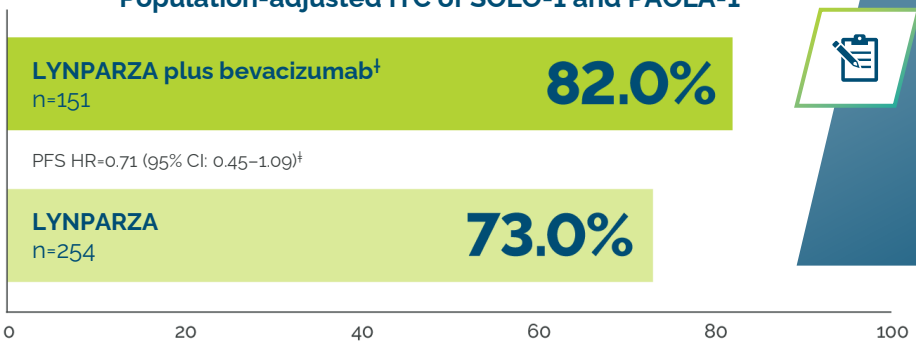
5 Has LYNPARZA Plus Bevacizumab Combination Maintenance Therapy Been Compared to LYNPARZA Maintenance Monotherapy?

There is no randomized controlled trial of maintenance LYNPARZA plus bevacizumab vs LYNPARZA or maintenance bevacizumab vs LYNPARZA in the first-line setting.[18]

A hypothesis-generating, population-adjusted **indirect treatment comparison (ITC)** of the *BRCA*-mutated populations of the SOLO-1 (LYNPARZA) and PAOLA-1 (LYNPARZA plus bevacizumab) trials reported a numerical, nonsignificant improvement in PFS for LYNPARZA plus bevacizumab vs LYNPARZA alone in patients with newly diagnosed, advanced ovarian cancer and a *BRCA* mutation.[18]

Population-adjusted ITC of SOLO-1 and PAOLA-1*[18]



Proportion of patients with *BRCA*m free from disease progression and death at 24 months

These results should be interpreted with caution as **this analysis was not a randomized, controlled trial and the outcomes of the ITC were the result of statistical modeling.[18]**

Limitations of the ITC model[18]:

This ITC is for descriptive purposes only. The outcomes of this ITC are the results of statistical modeling and should therefore be interpreted with caution.

This analysis uses patient-level data to provide additional context to the role of olaparib and bevacizumab in the treatment of newly diagnosed advanced ovarian cancer. The results of this cross-trial comparison rely on matching of observed prognostic and effect-modifying factors across the studies to minimize differences in patient characteristics and are therefore subject to assumptions around the absence of unobserved confounding variables.

Although this ITC analysis is based on an accepted methodology, it is not possible to address all differences in baseline characteristics as the analysis was non-randomized.

This analysis is not meant to replace a randomized controlled trial. It was conducted because currently there is no randomized controlled trial that investigates maintenance PARP inhibitor monotherapy, bevacizumab monotherapy, PARP inhibitor + bevacizumab combination therapy, and watch-and-wait placebo.

*In SOLO-1, median follow-up was 40.7 months in the olaparib arm and 41.2 months in the placebo arm. In PAOLA-1, median follow-up was 22.7 months in the olaparib + bevacizumab arm and 24.0 months in the placebo + bevacizumab arm.[18] The PAOLA-1 *BRCA*m cohort was adjusted to match the SOLO-1 patient population using a propensity score weighting method. All analyses were performed in patients with complete baseline data.[18]

‡These results are based on weighted outcomes after matching tumor location status, ECOG status, FIGO stage, type of surgery (interval vs upfront), residual disease status after surgery, response to first-line treatment and to those in SOLO-1.[18]

‡Confidence intervals were generated via bootstrapping.[18]

*BRCA*m, *BRCA* mutation; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; ITC, indirect treatment comparison; PARP, poly (ADP-ribose) polymerase; PFS, progression-free survival.

6 Why Test for HRD in Patients With Advanced Ovarian Cancer?

Testing for HRD is required to identify patients eligible for treatment with LYNPARZA plus bevacizumab.[1]

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 HRD-positive status defined by either[1]:

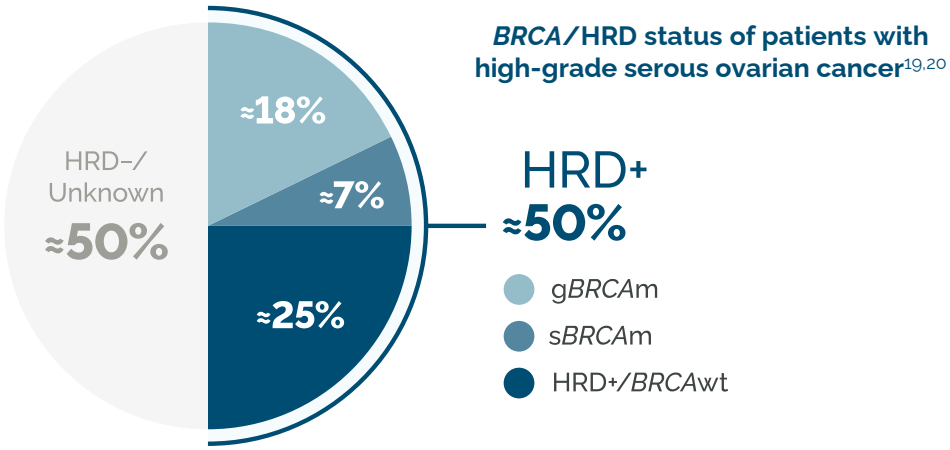
- a deleterious or suspected deleterious *BRCA* mutation, and/or
- genomic instability

Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA.[1]

In the PAOLA-1 clinical trial, HRD-positive was defined as a tumor *BRCA* mutation and/or a GIS ≥42 by the Myriad MyChoice® HRD assay.[3]

About **half** of high-grade serous ovarian cancers exhibit HRD.[19,20]

Testing for HRD, including genomic instability tests, **identifies more patients** than testing for *BRCA* mutations alone.[19,20]



To identify patients eligible for LYNPARZA plus bevacizumab, **use an FDA-approved CDx test that includes genomic instability tests for all patients with advanced ovarian cancer.**[2]

*BRCA*wt, *BRCA* wild type; CDx, companion diagnostic; FDA, US Food and Drug Administration; g*BRCA*m, germline *BRCA* mutation; GIS, Genomic Instability Score; HRD, homologous recombination deficiency; HRD+, homologous recombination deficiency–positive; HRD−, homologous recombination deficiency–negative; s*BRCA*m, somatic *BRCA* mutation.

7 What Is the Take-Home Message?

- In the absence of maintenance therapy, most patients with advanced ovarian cancer relapse within 3 years; maintenance therapy should be offered to all eligible patients with advanced ovarian cancer who respond to first-line chemotherapy[5,6,8]

- The combination of LYNPARZA plus bevacizumab allows the targeting of two disease mechanisms present in ovarian tumors, with limited overlapping toxicity[12,13]
  - Bevacizumab binds to VEGF, preventing its interaction with receptors and leading to reduced growth of vascular endothelial cells, inhibiting tumor vascularization (angiogenesis)[11]
  - LYNPARZA disrupts the internal DNA repair process in tumors, thereby inhibiting their growth[1]

- The combination of LYNPARZA plus bevacizumab is approved for use in select patients with advanced ovarian cancer who are HRD+, based on an FDA-approved test*[1]

- A population-adjusted ITC of the SOLO-1 (olaparib) and PAOLA-1 (olaparib plus bevacizumab) trials reported a numerical, nonsignificant improvement in PFS for olaparib plus bevacizumab vs olaparib alone (HR=0.71 [95% CI: 0.45–1.09]) in patients with newly diagnosed, advanced ovarian cancer and a *BRCA* mutation. These results should be interpreted with caution as this analysis was not a randomized, controlled trial and the outcomes of the ITC were the result of statistical modeling[18]

- Testing for HRD is required to identify patients eligible for treatment with LYNPARZA plus bevacizumab[1]

- About half of high-grade serous ovarian cancers exhibit HRD; testing for HRD, including genomic instability tests, identifies more patients than testing for *BRCA* mutations alone[19,20]

- To identify patients eligible for LYNPARZA plus bevacizumab, use an FDA-approved CDx test that includes genomic instability tests for all patients with advanced ovarian cancer[2]

*In the PAOLA-1 clinical trial, HRD-positive was defined as a tumor *BRCA* mutation and/or a GIS ≥42 by the Myriad MyChoice® HRD assay.[3] Zejula®, Rubraca®, and Avastin® are trademarks of GlaxoSmithKline, pharma&, and Genentech Inc., respectively.

CDx, companion diagnostic; FDA, US Food and Drug Administration; HRD, homologous recombination deficiency; HRD+, homologous recombination deficiency–positive; ITC, indirect treatment comparison; PFS, progression-free survival; VEGF, vascular endothelial growth factor.

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Indications and Important Safety Information

See Important Safety Information, including Warnings and Precautions for MDS/AML, pneumonitis, venous thromboembolism, hepatotoxicity, including drug-induced liver injury, and embryo-fetal toxicity below.

INDICATIONS
LYNPARZA is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated:

First-Line Maintenance *BRCA*m Advanced Ovarian Cancer
For the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic *BRCA*-mutated (g*BRCA*m or s*BRCA*m) advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA.

First-Line Maintenance HRD-Positive Advanced Ovarian Cancer in Combination with Bevacizumab
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

Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA.

Maintenance *BRCA*-mutated Recurrent Ovarian Cancer
For the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic *BRCA*-mutated (g*BRCA*m or s*BRCA*m) recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS
There are no contraindications for LYNPARZA.

WARNINGS AND PRECAUTIONS
Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML): Occurred in approximately 1.2% of patients (26/2219) with various *BRCA*m, g*BRCA*m, HRR gene-mutated or HRD-positive cancers who received LYNPARZA in clinical studies as a single agent or as part of a combination regimen, consistent with the approved indications, and the majority of events had a fatal outcome. The median duration of therapy in patients who developed MDS/AML was approximately 2 years (range: <6 months to >4 years). All of these patients had previous chemotherapy with platinum agents and/or other DNA-damaging agents, including radiotherapy.

In SOLO-1, patients with newly diagnosed advanced *BRCA*m ovarian cancer, the incidence of MDS/AML was 1.9% (5/260) in patients who received LYNPARZA and 0.8% (1/130) in patients who received placebo based on an updated analysis. In PAOLA-1, of patients with newly diagnosed advanced ovarian cancer with HRD-positive status, the incidence of MDS/AML was 1.6% (4/255) in patients who received LYNPARZA and 2.3% (3/131) in the control arm.

In SOLO-2, patients with *BRCA*m platinum-sensitive relapsed ovarian cancer, the incidence of MDS/AML was 8% (15/195) in patients who received LYNPARZA and 4% (4/99) in patients who received placebo. The duration of LYNPARZA treatment prior to the diagnosis of MDS/AML ranged from 0.6 years to 4.5 years.

Do not start LYNPARZA until patients have recovered from hematological 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 hematological 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 hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. Discontinue LYNPARZA if MDS/AML is confirmed.

Pneumonitis: Including severe and fatal cases, has occurred in patients treated with LYNPARZA. In clinical studies, among patients who received LYNPARZA as a single agent or as part of a combination regimen, the incidence of pneumonitis, including fatal cases, was 1.0% (29/2851). If patients present with new or worsening respiratory symptoms such as dyspnea, 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.

Indications and Important Safety Information

Venous Thromboembolism (VTE): Including severe or fatal pulmonary embolism (PE), occurred in patients treated with LYNPARZA. 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.

Hepatotoxicity, including Drug-Induced Liver Injury (DILI): Hepatotoxicity, including severe and potentially fatal cases of DILI has occurred in patients treated with LYNPARZA. Evaluate bilirubin and transaminases at baseline and throughout treatment with LYNPARZA. For patients who develop abnormal liver tests after LYNPARZA, monitor more frequently for liver test abnormalities and clinical signs and symptoms of hepatic toxicity. If DILI is suspected, withhold LYNPARZA. Upon confirmation of DILI, discontinue LYNPARZA.

Embryo-Fetal Toxicity: Based on its mechanism of action and findings in animals, LYNPARZA can cause fetal harm. Verify pregnancy status in females of reproductive potential prior to initiating treatment.

Females
Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for 6 months following the last dose.

ADVERSE REACTIONS—First-Line Maintenance *BRCA*m Advanced Ovarian Cancer
Most common adverse reactions (all Grades) in ≥10% of patients who received LYNPARZA in the **first-line maintenance setting** for **SOLO-1** were: nausea (77%), fatigue (67%), abdominal pain (45%), vomiting (40%), anemia (38%), diarrhea (37%), constipation (28%), upper respiratory tract infection/influenza/nasopharyngitis/bronchitis (28%), dysgeusia (26%), decreased appetite (20%), dizziness (20%), neutropenia (17%), dyspepsia (17%), dyspnea (15%), leukopenia (13%), urinary tract infection (13%), thrombocytopenia (11%), and stomatitis (11%).

Most common laboratory abnormalities (Grades 1-4) in ≥25% of patients who received LYNPARZA in the **first-line maintenance setting** for **SOLO-1** were: decrease in hemoglobin (87%), increase in mean corpuscular volume (87%), decrease in leukocytes (70%), decrease in lymphocytes (67%), decrease in absolute neutrophil count (51%), decrease in platelets (35%), and increase in serum creatinine (34%).

ADVERSE REACTIONS—First-Line Maintenance Advanced Ovarian Cancer in Combination with Bevacizumab
Most common adverse reactions (Grades 1-4) in ≥10% of patients treated with LYNPARZA/bevacizumab and at a ≥5% frequency compared to placebo/bevacizumab in the **first-line maintenance setting** for **PAOLA-1** were: nausea (53%), fatigue (including asthenia) (53%), anemia (41%), lymphopenia (24%), vomiting (22%), and leukopenia (18%). In addition, the most common adverse reactions (≥10%) for patients receiving LYNPARZA/bevacizumab irrespective of the frequency compared with the placebo/bevacizumab arm were: diarrhea (18%), neutropenia (18%), urinary tract infection (15%), and headache (14%).

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

Most common laboratory abnormalities (Grades 1-4) in ≥25% of patients for LYNPARZA in combination with bevacizumab in the **first-line maintenance setting** for **PAOLA-1** were: decrease in hemoglobin (79%), decrease in lymphocytes (63%), increase in serum creatinine (61%), decrease in leukocytes (59%), decrease in absolute neutrophil count (35%), and decrease in platelets (35%).

ADVERSE REACTIONS—Maintenance g*BRCA*m Recurrent Ovarian Cancer
Most common adverse reactions (Grades 1-4) in ≥20% of patients who received LYNPARZA in the **maintenance setting** for **SOLO-2** were: nausea (76%), fatigue (including asthenia) (66%), anemia (44%), vomiting (37%), nasopharyngitis/upper respiratory tract infection (URI)/sinusitis/rhinitis/influenza (36%), diarrhea (33%), arthralgia/myalgia (30%), dysgeusia (27%), headache (26%), decreased appetite (22%), and stomatitis (20%).

Most common laboratory abnormalities (Grades 1-4) in ≥25% of patients who received LYNPARZA in the **maintenance setting** for **SOLO-2** were: increase in mean corpuscular volume (89%), decrease in hemoglobin (83%), decrease in leukocytes (69%), decrease in lymphocytes (67%), decrease in absolute neutrophil count (51%), increase in serum creatinine (44%), and decrease in platelets (42%).

Indications and Important Safety Information

DRUG INTERACTIONS

Anticancer Agents: Clinical studies of LYNPARZA with other myelosuppressive anticancer agents, including DNA-damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity.

CYP3A Inhibitors: Avoid coadministration of strong or moderate CYP3A inhibitors when using LYNPARZA. If a strong or moderate CYP3A inhibitor must be coadministered, reduce the dose of LYNPARZA. Advise patients to avoid grapefruit, grapefruit juice, Seville oranges, and Seville orange juice during LYNPARZA treatment.

CYP3A Inducers: Avoid coadministration of strong or moderate CYP3A inducers when using LYNPARZA.

USE IN SPECIFIC POPULATIONS

Lactation: No data are available regarding the presence of olaparib in human milk, its effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in the breastfed infant, advise a lactating woman not to breastfeed during treatment with LYNPARZA and for 1 month after receiving the final dose.

Pediatric Use: The safety and efficacy of LYNPARZA have not been established in pediatric patients.

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).

Renal Impairment: No dosage modification is recommended in patients with mild renal impairment (CLcr 51-80 mL/min estimated by Cockcroft-Gault). In patients with moderate renal impairment (CLcr 31-50 mL/min), reduce the dose of LYNPARZA to 200 mg twice daily. There are no data in patients with severe renal impairment or end-stage renal disease (CLcr ≤30 mL/min).

Please see complete Prescribing Information, including Medication Guide for LYNPARZA.

You may report side effects related to AstraZeneca products.