LYNPARZA® (olaparib) Fact Sheet

LYNPARZA'S INDICATION IN Metastatic Breast Cancer

On January 12, LYNPARZA (olaparib) tablets (300 mg twice daily) were approved for use in patients with deleterious or suspected deleterious germline *BRCA*-mutated (g*BRCA*m), human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer (MBC) who have been previously treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor positive (HR+) breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine treatment. Patients are selected for therapy based on an FDA-approved companion diagnostic for LYNPARZA.[1]

LYNPARZA'S INDICATIONS IN Ovarian Cancer

On August 17th 2017, LYNPARZA was approved for use as a maintenance treatment for adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy, regardless of *BRCA* status.[1,7]

On December 19th 2014, LYNPARZA was approved for use in adult patients with deleterious or suspected deleterious germline *BRCA*-mutated (g*BRCA*m) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy; patients for this indication are selected for therapy based on an FDA-approved companion diagnostic.[8,9]

ABOUT METASTATIC BREAST CANCER

MBC is the most advanced stage of breast cancer (Stage IV), and occurs when cancer cells have spread beyond the initial tumor site to other parts of the body outside of the breast.[2,3,4]

It is estimated that in 2018, **there will be approximately 155,000 women in the US living with MBC**, and this number is projected to increase to approximately 160,000 by the year 2020. A portion of these patients will be diagnosed with g*BRCA*m, HER2-negative MBC.[5]

Despite the increase in treatment options during the past three decades, there is currently no cure for patients diagnosed with MBC and the goal of current treatment is to delay disease progression.[2,3,4] **The five-year survival rate for breast cancer that has metastasized is approximately 27%.[6]**

ABOUT OVARIAN CANCER

Approximately **20,000 women** in the US are diagnosed with ovarian cancer each year.[10]

Among US women, ovarian cancer is the **9th most common cancer** and the **5th leading cause of cancer death.**[10]

Symptoms are often non-specific and include:[11]

- Bloating
- Difficulty eating
- Pelvic/Abdominal pain
- Urinary issues

60% of ovarian cancers are diagnosed in the distant phase, when the cancer has metastasized. **The 5-year relative survival rate in this stage is approximately 29%.[12]**

LYNPARZA is associated with a number of serious risks, including Myelodysplastic Syndrome (MDS) / Acute Myeloid Leukemia (AML), Pneumonitis, and Embryo-Fetal Toxicity. Please see Important Safety Information on Page 3

ABOUT PARP INHIBITORS

LYNPARZA 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.[1]

LYNPARZA targets PARP-mediated DNA damage repair mechanisms, providing an alternative pathway to control the disease.[1,13,14]

- Germline *BRCA*m breast tumor cells accumulate DNA damage[15]
- Tumor cells survive by repairing their damaged DNA via the PARP enzyme, among other cellular processes[13]
- Germline *BRCA*m cells are especially reliant on PARP for survival due to their deficiencies in repairing DNA[13,14]
- LYNPARZA can affect normal/healthy cells as well

LYNPARZA was the first FDA-approved oral poly ADP-ribose polymerase (PARP) inhibitor that may exploit tumor DNA damage response (DDR) pathway deficiencies to potentially kill cancer cells.[16,17,18]

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 cell death.[1]

LYNPARZA CLINICAL TRIAL PROGRAM IN MBC[1]

Phase III OlympiAD Trial: LYNPARZA tablets demonstrated a significantly prolonged progression free survival (PFS) in patients with HER2-negative metastatic breast cancer. Patients had a confirmed deleterious or suspected deleterious germline *BRCA* mutation.

- LYNPARZA significantly prolonged PFS as assessed by Blinded Independent Central Review (BICR) and reduced the risk of disease progression or death by 42% (HR 0.58; 95% CI 0.43-0.80; P=0.0009 median 7.0 vs 4.2 months) compared to those who received physician's choice chemotherapy (capecitabine, eribulin, or vinorelbine)
- Additionally, patients with measurable disease taking LYNPARZA (n=167) experienced a confirmed objective response rate of 52% (95% CI 44-60), double the response rate of those in the chemotherapy arm (n=66) which was 23% (95% CI 13-35). Patients experienced a confirmed complete response rate of 7.8% for LYNPARZA compared to 1.5% for the chemotherapy arm
- Adverse reactions in the OlympiAD trial in ≥20% of patients who received LYNPARZA were nausea (58%), anemia (40%), fatigue (including asthenia) (37%), vomiting (30%), respiratory tract infections (27%), neutropenia (27%), leukopenia (25%), diarrhea (21%), and headache (20%). The percentage of patients who discontinued treatment in the LYNPARZA arm was 5% compared to the chemotherapy arm which was 8%. In patients receiving LYNPARZA, laboratory abnormalities of any grade reported (≥25%) were decrease in hemoglobin (82%), decrease in lymphocytes (73%), increase in mean corpuscular volume (71%), decrease in leukocytes (71%), decrease in absolute neutrophil count (46%) and decrease in platelets (33%)

LYNPARZA CLINICAL TRIAL PROGRAM IN OVARIAN CANCER[1]

Phase III SOLO-2 Trial: LYNPARZA tablets demonstrated a significant improvement in progression-free survival (PFS) in g*BRCA*, platinum-sensitive, relapsed epithelial ovarian cancer patients compared with placebo in the maintenance setting

- LYNPARZA reduced the risk of disease progression or death by 70% (HR 0.30 [95% CI, 0.22-0.41], P<0.0001), with an investigator-assessed median PFS of 19.1 vs 5.5 months, compared with placebo
- In the LYNPARZA arm, the most common adverse events reported in 20% or more of patients across the SOLO-2 trial were nausea (76%), fatigue (including asthenia) (66%), anemia (44%), vomiting (37%), nasopharyngitis/upper respiratory tract infection (URI)/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 in the maintenance setting (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%)

Phase II Study 19 Trial: LYNPARZA capsules (400 mg twice daily) demonstrated a statistically significant improvement in PFS in platinum-sensitive relapsed ovarian cancer patients treated in the maintenance setting. LYNPARZA capsules are not indicated for maintenance therapy

- Regardless of *BRCA* status, LYNPARZA reduced the risk of disease progression or death by 65% (HR 0.35 [95% CI, 0.25-0.49], P<0.0001), and had a median PFS of 8.4 vs 4.8 months compared with placebo
- Patients in Study 19, treated with LYNPARZA as a maintenance therapy, had a median overall survival of 29.8 months vs 27.8 months with placebo (HR 0.73 [95% CI, 0.55-0.95]) without adjusting for multiplicity
- In the LYNPARZA arm, the most common adverse events reported in 20% or more of patients across the Study 19 trial were nausea (71%), fatigue (including asthenia) (63%), vomiting (35%), diarrhea (28%), anemia (23%), respiratory tract infection (22%), constipation (22%), headache (21%), and decreased appetite (21%). Most common laboratory abnormalities (Grades 1-4) in ≥25% of patients in the maintenance setting (Study 19) were: increase in mean corpuscular volume (82%), decrease in hemoglobin (82%), decrease in leukocytes (58%), decrease in lymphocytes (52%), decrease in absolute neutrophil count (47%), increase in serum creatinine (45%), and decrease in platelets (36%)

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ABOUT ASTRAZENECA

AstraZeneca is a global, science-led biopharmaceutical company that focuses on the discovery, development and commercialization of prescription medicines, primarily for the treatment of diseases in three main therapy areas - Oncology, Cardiovascular & Metabolic Diseases and Respiratory. The Company also is selectively active in the areas of Autoimmunity, Neuroscience and Infection. AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide. For more information, please visit www.astrazeneca-us.com and follow us on Twitter @AstraZenecaUS.

References: 1. LYNPARZA (olaparib) Tablets Prescribing Information. AstraZeneca Pharmaceuticals LP, Wilmington, DE. 2. Cleveland Clinic. Diseases and Conditions: Breast Cancer. Available Online Last Updated September 5, 2013. Accessed January 2018. 3. Mayo Clinic. Breast Cancer Diagnosis. Available Online. Last Updated August 16, 2016. Accessed January 2018. 4. American Cancer Society. What Is Advanced Cancer? Atlanta: American Cancer Society; 2014 Available online. Accessed January 2018. 5. CancerMPact.Khapps.com: ONC-Prevalence of Metastatic Breast Cancer in Women 2014-2020. Accessed January 2018. 6. SEER Fact Sheet. Cancer Stat Facts: Female Breast Cancer. Available Online. Accessed January 2018. 7. AstraZeneca Press Release. LYNPARZA® (olaparib) receives additional FDA approval in the US for ovarian cancer. Available Online. Accessed January 2018. 8. Prescribing Information for LYNPARZA Capsules. AstraZeneca Oncology, Wilmington, DE. 9.AstraZeneca Press Release. LYNPARZA™ approved by the US Food and Drug Administration for the treatment of advanced ovarian cancer in patients with germline BRCA-mutations. Available Online. Accessed January 2018. 10. Centers for Disease Control and Prevention. Ovarian Cancer Statistics. Available Online. Accessed January 2018. 11. American Cancer Society. Signs and Symptoms of Ovarian Cancer. Available Online. Accessed January 2018. 12. SEER Fact Sheet. Cancer Stat Facts: Ovarian Cancer. Available Online. Accessed January 2018. 13. Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCAmutant cells as a therapeutic strategy. *Nature*. 2005;434:917-921. 14.Bryant HE, Schultz N, Thomas HD, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature*. 2005;434:913-917. 15. Dai H, Hickey RJ, Liu J, et al. Error-promoting DNA synthesis in ovarian cancer cells. *Gynecol Oncol*. 2013;131:198-206. 16. US Food and Drug Administration. FDA approves Lynparza to treat advanced ovarian cancer. Accessed January 2018. 17. O'Connor M. Targeting the DNA damage response in cancer. *Mol Cell.* 2015; 60:547-560. Accessed January 2018. 18. Tutt ANJ, Lord CJ, McCabe N. Exploiting the DNA repair defect in BRCA mutant cells in the design of new therapeutic strategies for cancer. *Cold Spring Harb Symp Quant Biol*. 2005; 70:139-148.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

There are no contraindications for LYNPARZA.

WARNINGS AND PRECAUTIONS

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML): Occurred in <1.5% of patients exposed to LYNPARZA monotherapy, and the majority of events had a fatal outcome. The duration of therapy in patients who developed secondary MDS/AML varied from <6 months to >2 years. All of these patients had previous chemotherapy with platinum agents and/or other DNA-damaging agents, including radiotherapy, and some also had a history of more than one primary malignancy or of bone marrow dysplasia.

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 count 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: Occurred in <1% of patients exposed to LYNPARZA, and some cases were fatal. If patients present with new or worsening respiratory symptoms such as dyspnea, cough, and fever, or a radiological abnormality occurs, interrupt LYNPARZA treatment and initiate prompt investigation. Discontinue LYNPARZA if pneumonitis is confirmed and treat patient appropriately.

Embryo-Fetal Toxicity: Based on its mechanism of action and findings in animals, LYNPARZA can cause fetal harm. A pregnancy test is recommended for 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.
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> *Males* = 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 and to not donate sperm during this time.

DRUG INTERACTIONS

Anticancer Agents: Clinical studies of LYNPARZA in combination with other myelosuppressive anticancer agents, including DNA-damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity.
CYP3A Inhibitors: Avoid concomitant use of strong or moderate CYP3A inhibitors. If a strong or moderate CYP3A inhibitor must be co-administered, reduce the dose of LYNPARZA. Advise patients to avoid grapefruit, grapefruit juice, Seville oranges, and Seville orange juice during LYNPARZA treatment.
CYP3A Inducers: Avoid concomitant use of strong or moderate CYP3A inducers when using LYNPARZA. If a moderate inducer cannot be avoided, there is a potential for decreased efficacy of 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 hepatic impairment (Child-Pugh classification A). There are no data in patients with moderate or severe hepatic impairment.
Renal Impairment: No adjustment to the starting dose is necessary in patients with mild renal impairment (CLcr=51-80 mL/min). In patients with moderate renal impairment (CLcr=31-50 mL/min), reduce the dose to 200 mg twice daily. There are no data in patients with severe renal impairment or end-stage renal disease (CLcr ≤30 mL/min).

DOSING AND ADMINISTRATION

To avoid substitution errors and overdose, **do not substitute LYNPARZA tablets with LYNPARZA capsules** on a milligram-to-milligram basis due to differences in the dosing and bioavailability of each formulation. Recommended tablet dose is 300 mg, taken orally twice daily, with or without food. Continue treatment until disease progression or unacceptable toxicity. For adverse reactions, consider dose interruption or dose reduction.

INDICATIONS

LYNPARZA is a poly (ADP-ribose) polymerase (PARP) inhibitor 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.

For the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (*gBRCAm*) advanced ovarian cancer who have been treated with 3 or more prior lines of chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA.

In patients with deleterious or suspected deleterious *gBRCAm*, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer who have previously been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine treatment. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA.

Please see complete Prescribing Information for LYNPARZA tablets and complete Prescribing Information for LYNPARZA capsules, including Patient Information (Medication Guides).