LYNPARZA® (olaparib) Recommended by FDA Advisory Committee for First-Line Maintenance Therapy in Germline BRCA-Mutated Metastatic Pancreatic Cancer That Has Not Progressed on Platinum-Based Chemotherapy

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Oncologic Drugs Advisory Committee Voted That LYNPARZA Demonstrated a Favorable Benefit-Risk Profile for Patients Based on Phase 3 POLO Trial Results

KENILWORTH, N.J.--(BUSINESS WIRE)--AstraZeneca and Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced that the U.S. Food and Drug Administration (FDA) Oncologic Drugs Advisory Committee (ODAC) voted 7-5 to recommend LYNPARZA as a first-line maintenance monotherapy for patients with germline BRCA-mutated (gBRCAm) metastatic adenocarcinoma of the pancreas (pancreatic cancer), whose disease has not progressed on at least 16 weeks of first-line platinum-based chemotherapy.

In August 2019, the FDA accepted the supplemental New Drug Application (sNDA) for LYNPARZA for this indication with Priority Review and set a Prescription Drug User Fee Act (PDUFA) date for the fourth quarter of 2019.

Dr. José Baselga, executive vice president, oncology R&D, AstraZeneca, said, “We are pleased with the ODAC’s recommendation for LYNPARZA and the potential to bring a personalized, biomarker-targeted medicine to patients with germline BRCA-mutated metastatic pancreatic cancer. Patients with advanced pancreatic cancer historically have faced poor outcomes due to the aggressive nature of the disease and limited treatment advances over the last few decades. We look forward to working with the FDA as it completes the review of our application.”

Dr. Roy Baynes, senior vice president and head of global clinical development, chief medical officer, Merck Research Laboratories, said, “We are encouraged by the ODAC’s favorable vote for LYNPARZA as a first-line maintenance therapy in germline BRCA-mutated metastatic pancreatic cancer. This recommendation is a significant step towards reaching our goal to help patients with this deadly disease.”

The sNDA submission was based on the positive results from the Phase 3 POLO trial published in the New England Journal of Medicine and presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting. The results showed a statistically significant and clinically meaningful improvement in progression-free survival (PFS) and reduced the risk of disease progression or death by 47% (HR 0.53 [95% CI, 0.35-0.82], p=0.004). LYNPARZA nearly doubled the time patients with gBRCAm metastatic pancreatic cancer lived without disease progression or death to a median of 7.4 months vs. 3.8 months on placebo.

The most common adverse events (AEs) ≥20% were fatigue/asthenia (60%), nausea (45%), abdominal pain (29%), diarrhea (29%), anemia (28%), decreased appetite (25%) and constipation (23%). The most common ≥ grade 3 AEs were anemia (11%), fatigue/asthenia (5%), decreased appetite (3%), abdominal pain (2%), vomiting (1%) and arthralgia (1%). Around 84% of patients on LYNPARZA remained on the recommended starting dose, while 16% had a dose reduction vs. 97% who remained on the recommended dose with placebo, while 3% had a dose reduction. Additionally, 95% of patients on LYNPARZA continued treatment without an AE-related discontinuation, while 5% had an AE-related discontinuation vs. 98% who continued treatment without an AE-related discontinuation and 2% that had an AE-related discontinuation with placebo.

The ODAC provides the FDA with independent, expert advice and recommendations on marketed and investigational medicines for use in the treatment of cancer. The FDA is not bound by the committee’s guidance but takes its advice into consideration when deciding whether or not to approve the application.

In addition to the U.S., LYNPARZA is currently under regulatory review in the European Union (EU), Canada and other jurisdictions as a first-line maintenance treatment for patients with gBRCAm metastatic pancreatic cancer.
Germline BRCAm pancreatic cancer accounts for 5-7% of all cases globally. The FDA granted LYNPARZA orphan drug designation on October 18, 2018 for gBRCAm metastatic pancreatic cancer. Orphan drug designation is for medicines intended to treat, diagnose or prevent rare diseases or disorders that affect fewer than 200,000 people in the U.S.

LYNPARZA is currently approved in 65 countries, including the U.S., for the maintenance treatment of platinum-sensitive relapsed ovarian cancer, regardless of BRCA status. It is approved in the U.S., EU, Japan and several other countries as first-line maintenance treatment of BRCA-mutated advanced ovarian cancer following response to platinum-based chemotherapy. It is also approved in 44 countries, including the U.S. and Japan, for gBRCAm, HER2-negative metastatic breast cancer previously treated with chemotherapy; in the EU, this includes locally advanced breast cancer.

About POLO
POLO is a Phase 3 randomized, double-blinded, placebo-controlled, multi-center trial of LYNPARZA tablets (300 mg twice daily) as maintenance monotherapy vs. placebo. The trial randomized 154 patients with gBRCAm metastatic pancreatic cancer whose disease had not progressed on first-line platinum-based chemotherapy. Patients were randomized (3:2) to receive LYNPARZA or placebo until disease progression. The primary endpoint was PFS and key secondary endpoints included OS, time to second disease progression, overall response rate and health-related quality of life.

Results showed a statistically significant and clinically meaningful improvement in PFS, where LYNPARZA nearly doubled the time patients with gBRCAm metastatic pancreatic cancer lived without disease progression or death to a median of 7.4 months vs. 3.8 months on placebo. LYNPARZA reduced the risk of disease progression or death by 47% (HR 0.53 [95% CI, 0.35-0.82], p=0.004).

The safety and tolerability profile of LYNPARZA in the POLO trial was in line with that observed in prior clinical trials.

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.

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.

ADVERSE REACTIONS—First-Line Maintenance BRCAm Advanced Ovarian Cancer
Most common adverse reactions (Grades 1-4) in ≥10% of patients in clinical trials of LYNPARZA in the first-line maintenance setting for SOLO-1 were: nausea (77%), fatigue (67%), abdominal pain (45%), vomiting (40%), anemia (38%), constipation (37%), constipation (28%), upper respiratory tract infection/influenza/ nasopharyngitis/bronchitis (28%), dysgeusia (26%), decreased appetite (20%), dizziness (20%), neutropenia (17%), dyspepsia (17%), dyspepsia (15%), leukopenia (13%), UTI (13%), thrombocytopenia (11%), and stomatitis (11%).

Most common laboratory abnormalities (Grades 1-4) in ≥25% of patients in clinical trials of 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—Maintenance Recurrent Ovarian Cancer
Most common adverse reactions (Grades 1-4) in ≥20% of patients in clinical trials of LYNPARZA in the maintenance
Advanced gBRCAm ovarian cancer

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

Maintenance Recurrent Ovarian Cancer

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.

Advanced gBRCAm ovarian cancer

ADVERSE REACTIONS—Advanced gBRCAm ovarian cancer

Most common laboratory abnormalities (Grades 1-4) in ≥25% of patients in clinical trials of LYNPARZA in the maintenance setting (SOLO-2/Study 19) were: increase in mean corpuscular volume (89%/82%), decrease in hemoglobin (83%/82%), decrease in leukocytes (69%/58%), decrease in lymphocytes (67%/52%), decrease in absolute neutrophil count (51%/47%), increase in serum creatinine (44%/45%), and decrease in platelets (42%/36%).

ADVERSE REACTIONS—gBRCAm, HER2-negative metastatic breast cancer

Most common adverse reactions (Grades 1-4) in ≥20% of patients in clinical trials of LYNPARZA for advanced gBRCAm ovarian cancer after 3 or more lines of chemotherapy (pooled from 6 studies) were: fatigue/asthenia (66%), nausea (64%), vomiting (43%), anemia (34%), diarrhea (31%), nasopharyngitis/upper respiratory tract infection (URI) (26%), dyspepsia (25%), myalgia (22%), decreased appetite (22%), and arthralgia/musculoskeletal pain (21%).

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 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 adjustment to the starting dose is necessary in patients with mild renal impairment (CLcr=51-80 mL/min) but patients should be monitored closely for toxicity. 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).

INDICATIONS

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

First-Line Maintenance BRCAm Advanced Ovarian Cancer

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

Maintenance Recurrent Ovarian Cancer

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.

Advanced gBRCAm ovarian cancer
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.

**gBRCAm, HER2-negative metastatic breast cancer**

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

Please click here for complete Prescribing Information, including Patient Information (Medication Guide).

**About LYNPARZA® (olaparib)**

LYNPARZA is a first-in-class PARP inhibitor and the first targeted treatment to potentially exploit DNA damage response (DDR) pathway deficiencies, such as BRCA4 mutations, to preferentially kill cancer cells. Inhibition of PARP with LYNPARZA leads to the trapping of PARP bound to DNA single-strand breaks, stalling of replication forks, their collapse and the generation of DNA double-strand breaks and cancer cell death. LYNPARZA is being tested in a range of tumor types with defects and dependencies in the DDR.

LYNPARZA, which is being jointly developed and commercialized by AstraZeneca and Merck, has a broad and advanced clinical trial development program, and AstraZeneca and Merck are working together to understand how it may affect multiple PARP-dependent tumors as a monotherapy and in combination across multiple cancer types.

**About Pancreatic Cancer**

Pancreatic cancer is a deadly cancer with a high unmet medical need. It is the 12th most commonly occurring cancer and the seventh leading cause of cancer death globally. The disease has the lowest survival rate of the most common cancers and is the only major cancer with a single-digit five-year survival rate (2-9%) in nearly every country. There were approximately 460,000 new cases in 2018 and this number is expected to rise to over 800,000 by the year 2040. As there are often no symptoms, or symptoms may be non-specific in the early stages, it is most commonly diagnosed at an incurable stage. Around 80% of pancreatic cancer patients are diagnosed when the disease is metastatic, and for these the average survival is less than a year. Despite advances in therapy, few improvements have been made in diagnosis and treatment over the decades. Current treatment is surgery (for which approximately only 10-20% of patients are eligible), chemotherapy and radiotherapy, highlighting a critical unmet medical need for more effective treatment options. Gemline BRCA-mutated pancreatic cancer accounts for 5-7% of all cases globally.

**About BRCA Mutations**

BRCA1 and BRCA2 are human genes that produce proteins responsible for repairing damaged DNA and play an important role in maintaining the genetic stability of cells. When either of these genes is mutated, or altered, such that its protein product either is not made or does not function correctly, DNA damage may not be repaired properly, and cells become unstable. As a result, cells are more likely to develop additional genetic alterations that can lead to cancer.

**About the AstraZeneca and Merck Strategic Oncology Collaboration**

In July 2017, AstraZeneca and Merck & Co., Inc., Kenilworth, NJ, US, known as MSD outside the United States and Canada, announced a global strategic oncology collaboration to co-develop and co-commercialize LYNPARZA, the world’s first PARP inhibitor, and potential new medicine selumetinib, a MEK inhibitor, for multiple cancer types. Working together, the companies will develop LYNPARZA and selumetinib in combination with other potential new medicines and as monotherapies. Independently, the companies will develop LYNPARZA and selumetinib in combination with their respective PD-L1 and PD-1 medicines.

**Merck’s Focus on Cancer**

Our goal is to translate breakthrough science into innovative oncology medicines to help people with cancer worldwide. At Merck, the potential to bring new hope to people with cancer drives our purpose and supporting accessibility to our cancer medicines is our commitment. As part of our focus on cancer, Merck is committed to exploring the potential of immuno-oncology with one of the largest development programs in the industry across more than 30 tumor types. We also continue to strengthen our portfolio through strategic acquisitions and are prioritizing the development of several promising oncology candidates with the potential to improve the treatment of advanced cancers. For more information about our oncology clinical trials, visit www.merck.com/clinicaltrials.

**About Merck**

For more than a century, Merck, a leading global biopharmaceutical company known as MSD outside of the United States and Canada, has been inventing for life, bringing forward medicines and vaccines for many of the world’s most challenging diseases. Through our prescription medicines, vaccines, biologic therapies and animal health products, we work with customers and operate in more than 140 countries to deliver innovative health solutions. We also demonstrate our commitment to increasing access to health care through far-reaching policies, programs and partnerships. Today, Merck continues to be at the forefront of research to advance the prevention and treatment of diseases that threaten people and communities around the world - including cancer, cardio-metabolic diseases, emerging animal diseases, Alzheimer’s disease and infectious diseases including HIV and Ebola. For more information, visit www.merck.com and connect with us on Twitter, Facebook, Instagram, YouTube and LinkedIn.

**Forward-Looking Statement of Merck & Co., Inc., Kenilworth, N.J., USA**
This news release of Merck & Co., Inc., Kenilworth, N.J., USA (the “company”) includes “forward-looking statements” within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of the company’s management and are subject to significant risks and uncertainties. There can be no guarantees with respect to pipeline products that the products will receive the necessary regulatory approvals or that they will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.

Risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and health care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; the company’s ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of the company’s patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

The company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in the company’s 2018 Annual Report on Form 10-K and the company’s other filings with the Securities and Exchange Commission (SEC) available at the SEC’s Internet site (www.sec.gov).

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