FDA Accepts Regulatory Submission of Supplemental New Drug Application for LYNPARZA® (olaparib) in HRR-Mutated Metastatic Castration-Resistant Prostate Cancer and Grants Priority Review

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**Submission Based on PROfound, the First Phase 3 Trial Evaluating a Targeted Treatment in Biomarker-Selected Prostate Cancer Patients**

KENILWORTH, N.J.--(BUSINESS WIRE)--AstraZeneca and Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced that a supplemental New Drug Application (sNDA) for LYNPARZA has been accepted and granted priority review by the U.S. Food and Drug Administration (FDA) for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) and deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene mutations, who have progressed following prior treatment with a new hormonal agent.

A Prescription Drug User Fee Act (PDUFA) date is set for the second quarter of 2020.

The sNDA acceptance for review by the FDA is based on positive results from the Phase 3 PROfound trial, which were presented during a Presidential Symposium at the 2019 European Society of Medical Oncology congress.

Results of the PROfound trial showed LYNPARZA met its primary endpoint, significantly reducing the risk of radiographic disease progression or death by 66% in patients with *BRCA1* or *ATM*-mutated mCRPC and improved radiographic progression-Free survival (rPFS) to a median of 7.4 months vs. 3.6 months for patients receiving abiraterone or enzalutamide (HR 0.34 [95% CI, 0.25-0.47], p<0.0001).

The trial also met the key secondary endpoint of rPFS in the overall population of men with HRR-mutated (HRRm) mCRPC (those with mutations in *BRCA1/2, ATM, CDK12* or 11 other HRRm genes), where LYNPARZA reduced the risk of radiographic disease progression or death by 51% and improved rPFS to a median of 5.8 months vs. 3.5 months for those receiving abiraterone or enzalutamide (HR 0.49 [95% CI, 0.38-0.63], p<0.0001).

The safety and tolerability profile of LYNPARZA in the PROfound trial did not differ from that observed in prior clinical trials. The most common adverse events (AEs) ≥20% for LYNPARZA compared to abiraterone or enzalutamide were anemia (47% vs. 15%), nausea (41% vs. 19%), fatigue and asthenia (41% vs. 32%), decreased appetite (30% vs. 18%) and diarrhea (21% vs. 7%). Grade 3 or above AEs were anemia (22% vs. 5%), fatigue and asthenia (3% vs. 5%), vomiting (2% vs. 1%), dyspnea (2% vs. 0%), urinary tract infection (2% vs. 4%), nausea (1% vs. 0%), decreased appetite (1% each), diarrhea (1% vs. 0%) and back pain (1% vs. 2%). AEs led to dose interruptions in 22% of patients on LYNPARZA vs. 4% of patients on abiraterone and enzalutamide and discontinuation of treatment in 16% of patients on LYNPARZA vs. 9% on abiraterone and enzalutamide.

PROfound is the first Phase 3 trial evaluating a targeted treatment in biomarker-selected prostate cancer patients. LYNPARZA, which is being jointly developed and commercialized by AstraZeneca and Merck, was most recently approved in the U.S. on Dec. 27, 2019, as a first-line maintenance treatment for germline *BRCA*-mutated (g*BRCA*m) metastatic pancreatic cancer that has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen. It is also approved in the U.S. as a first-line maintenance treatment in *BRCA*-mutated advanced ovarian cancer following response to platinum-based chemotherapy and for the treatment of g*BRCA*m HER2-negative metastatic breast cancer patients previously treated with chemotherapy.

**About PROfound**

PROfound is a prospective, multi-center, randomized, open-label, Phase 3 trial evaluating the efficacy and safety of LYNPARZA vs. new hormonal agents (e.g. abiraterone or enzalutamide) in patients with mCRPC who have progressed on prior treatment with a new hormonal anticancer treatment and have a qualifying tumor mutation in one of 15 genes involved in the homologous recombination repair (HRR) pathway, among them *BRCA1/2, ATM* and *CDK12*.

The trial was designed to analyze patients with HRRm genes in two cohorts: the primary endpoint was in those with...
mutations in *BRCA1/2* or *ATM* genes and then, if LYNPARZA showed clinical benefit, a formal analysis was performed of the overall trial population of patients with HRRm genes (*BRCA1/2, ATM, CDK12* and 11 other HRRm genes; key secondary endpoint).

**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 *BRCA*m 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%), diarrhea (37%), constipation (28%), upper respiratory tract infection/influenza/nasopharyngitis (28%), dysgeusia (26%), decreased appetite (20%), dizziness (20%), neutropenia (17%), dyspepsia (17%), dysnea (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 **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 setting for SOLO-2** were: nausea (76%), fatigue (including asthenia) (66%), anemia (44%), vomiting (37%), nasopharyngitis/upper respiratory tract infection/influenza (36%), diarrhea (33%), arthralgia/myalgia (30%), dysgeusia (27%), headache (26%), decreased appetite (22%), and stomatitis (20%).

**Study 19:** nausea (71%), fatigue (including asthenia) (63%), vomiting (35%), diarrhea (28%), anemia (23%), respiratory tract infection (22%), constipation (22%), headache (21%), decreased appetite (21%), and dyspepsia (20%).

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—Advanced *gBRCA*m Ovarian Cancer**

Most common adverse reactions (Grades 1-4) in ≥20% of patients in clinical trials of LYNPARZA for **advanced *gBRCA*m 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%).

Most common laboratory abnormalities (Grades 1-4) in ≥25% of patients in clinical trials of LYNPARZA for **advanced *gBRCA*m ovarian cancer** (pooled from 6 studies) were: decrease in hemoglobin (90%), mean corpuscular volume...
elevation (57%), decrease in lymphocytes (56%), increase in serum creatinine (30%), decrease in platelets (30%), and decrease in absolute neutrophil count (25%).

ADVERSE REACTIONS—gBRCAm, HER2-negative Metastatic Breast Cancer

Most common adverse reactions (Grades 1-4) in ≥20% of patients in OlympiAD were: nausea (58%), anemia (40%), fatigue (including asthenia) (37%), vomiting (30%), neutropenia (27%), respiratory tract infection (27%), leukopenia (25%), diarrhea (21%), and headache (20%).

Most common laboratory abnormalities (Grades 1-4) in ≥25% of patients in OlympiAD were: decrease in hemoglobin (82%), decrease in lymphocytes (73%), decrease in leukocytes (71%), increase in mean corpuscular volume (71%), decrease in absolute neutrophil count (46%), and decrease in platelets (33%).

ADVERSE REACTIONS—First-Line Maintenance gBRCAm Metastatic Pancreatic Adenocarcinoma

Most common adverse reactions (Grades 1-4) in ≥10% of patients in clinical trials of LYNPARZA in the first-line maintenance setting for POLO were: fatigue (60%), nausea (45%), abdominal pain (34%), diarrhea (29%), anemia (27%), decreased appetite (25%), constipation (23%), vomiting (20%), back pain (19%), arthralgia (15%), rash (15%), thrombocytopenia (14%), dyspnea (13%), neutropenia (12%), nasopharyngitis (12%), dysgeusia (11%), and stomatitis (10%).

Most common laboratory abnormalities (Grades 1-4) in ≥25% of patients in clinical trials of LYNPARZA in the first-line maintenance setting for POLO were: increase in serum creatinine (99%), decrease in hemoglobin (86%), increase in mean corpuscular volume (71%), decrease in lymphocytes (61%), decrease in platelets (56%), decrease in leukocytes (50%), and decrease in absolute neutrophil count (25%).

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 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).

INDICATIONS

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

First-Line Maintenance gBRCAm 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 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.

First-Line Maintenance gBRCAm Metastatic Pancreatic Cancer

For the maintenance treatment of adult patients with deleterious or suspected deleterious gBRCAm metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen. 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 Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Prostate cancer is the second-most common cancer in men and is associated with a significant mortality rate. In the U.S. this year, it is estimated that more than 191,000 people will be diagnosed with prostate cancer and more than 33,000 people will die of this disease. More than one in four patients with mCRPC harbor an HRR mutation.

Development of prostate cancer is often driven by male sex hormones called androgens, including testosterone. mCRPC occurs when prostate cancer grows and spreads to other parts of the body despite the use of androgen-deprivation therapy to block the action of male sex hormones. Approximately 10-20% of men with advanced prostate cancer will develop CRPC within five years, and at least 84% of these will have metastases at the time of CRPC diagnosis. Of men with no metastases at CRPC diagnosis, 33% are likely to develop metastases within two years. Despite an increase in the number of available therapies, five-year survival for men with mCRPC remains low.

About Homologous Recombination Repair (HRR) Mutations

Homologous recombination repair (HRR) plays a significant role in maintaining the genetic stability of cells and suppressing tumor growth by repairing damaged DNA. Mutations, or defects, in homologous recombination (HR) pathway genes – which include ataxia telangiectasia mutated (ATM) and BRCA1/2 genes - increase the risk for breast, ovarian, pancreatic, prostate and other cancers.

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 BRCA 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 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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