FDA Accepts Regulatory Submission of Supplemental New Drug Application for LYNPARZA® (olaparib) as First-Line Maintenance with Bevacizumab in Advanced Ovarian Cancer and Grants Priority Review

Release Date:
Monday, January 13, 2020 6:55 am EST

Terms:
Oncology Oncology Newsroom Research and Development News Corporate News Latest News #Merck #MRK

Dateline City:
KENILWORTH, N.J.

Submission Based on PAOLA-1 Trial Which Studied LYNPARZA with Bevacizumab in Women Regardless of Their Biomarker Status Who Responded to Platinum-Based Chemotherapy

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 in combination with bevacizumab has been accepted and granted priority review by the U.S. Food and Drug Administration (FDA) for the maintenance treatment of women with advanced ovarian cancer whose disease showed a complete or partial response to first-line treatment with platinum-based chemotherapy and bevacizumab.

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

The regulatory submission is based on the results from the pivotal Phase 3 PAOLA-1 trial, which were published in The New England Journal of Medicine. The trial compared LYNPARZA when added to standard-of-care (SoC) bevacizumab versus bevacizumab alone in women with advanced ovarian cancer in the first-line maintenance setting, regardless of their genetic biomarker status or outcome from previous surgery.

The investigator-assessed results showed LYNPARZA added to bevacizumab reduced the risk of disease progression or death by 41% and improved progression-free survival to a median of 22.1 months versus 16.6 months for patients treated with bevacizumab alone (HR 0.59 [95% CI, 0.49-0.72], p<0.0001).

The safety and tolerability profile of LYNPARZA and bevacizumab were consistent with those known from previous trials for each medicine.

The most common adverse events (AEs) ≥20% for LYNPARZA plus bevacizumab compared to bevacizumab alone were fatigue (53% vs. 32%), nausea (53% vs. 22%), hypertension (46% vs. 60%), anemia (41% vs. 10%), lymphopenia (24% vs. 9%), vomiting (22% vs. 11%) and arthralgia (22% vs. 24%). Overall Grade 3 or above (AEs) were 57% for LYNPARZA added to bevacizumab and 51% for bevacizumab alone. Grade 3 or above AEs were hypertension (19% vs. 30%), anemia (17% vs. <1%), lymphopenia (7% vs. 1%), fatigue (5% vs. 1%), neutropenia (6% vs 3%), nausea (2% vs. 1%), diarrhea (2% each), leukopenia (2% vs. 1%), vomiting (1% vs. 2%) and abdominal pain (1% vs. 2%). AEs led to dose interruption in 54% of patients on LYNPARZA plus bevacizumab vs. 24% on bevacizumab alone, while 41% of patients on LYNPARZA plus bevacizumab had a dose reduction vs. 7% on bevacizumab alone. Discontinuation of treatment occurred in 20% of patients on LYNPARZA plus bevacizumab discontinued treatment vs. 6% on bevacizumab alone.

LYNPARZA is the only PARP inhibitor with two positive randomized Phase 3 trials in the 1st-line maintenance setting for advanced ovarian cancer. If approved, this would be the fourth indication for ovarian cancer patients in the U.S. for LYNPARZA. It was most recently approved in the U.S. on December 27, 2019 as a 1st-line maintenance treatment for germline BRCA1-mutated (gBRC1m) 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 BRCAm advanced ovarian cancer following response to platinum-based chemotherapy and for the treatment of gBRCAm HER2-negative metastatic breast cancer patients previously treated with chemotherapy.

About PAOLA-1

PAOLA-1 is a double-blind Phase 3 trial evaluating the efficacy and safety of LYNPARZA added to standard-of-care bevacizumab vs. bevacizumab alone, as a first-line maintenance treatment for advanced FIGO Stage III-IV high grade serous or endometroid ovarian, fallopian tube, or peritoneal cancer patients who had a complete or partial response to first-line
treatment with platinum-based chemotherapy and bevacizumab.

PAOLA-1 is an ENGOT (European Network of Gynaecological Oncological Trial groups) trial, sponsored by ARCAGY Research (Association de Recherche sur les CAncers dont GYNécologiques) on behalf of GINECO (Groupe d’Investigateurs National des Études des Cancers Ovariens et du sein). ARCAGY-GINECO is an academic group specialising in clinical and translational research in patients’ cancers and a member of the GCIG (Gynecologic Cancer InterGroup).

**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%), diarrhea (37%), constipation (28%), upper respiratory tract infection/influenza/nasopharyngitis (28%), dysgeusia (26%), decreased appetite (20%), dizziness (20%), neutropenia (17%), dyspepsia (17%), dyspnea (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 setting for SOLO-2 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%).

**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 gBRCAm ovarian 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%).
Most common laboratory abnormalities (Grades 1-4) in ≥25% of patients in clinical trials of LYNPARZA for advanced gBRCAm 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%).

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 gBRCA-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 gBRCA-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 chemotheraphy 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 Ovarian Cancer**

Ovarian cancer is the fifth most common cause of death from cancer in women in the United States. This year, it is estimated that more than 22,500 women will be diagnosed with ovarian cancer and nearly 14,000 women will die of this disease.

Women with ovarian cancer are often diagnosed with advanced disease, which has a five-year survival rate of about 30%. For newly-diagnosed advanced ovarian cancer, the primary aim of treatment is to delay progression of the disease for as long as possible.

**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).

Language: English

Contact:
Media:
Pamela Eisele
(267) 305-3558

Steve Wanczyk
(267) 305-5563

Investor:
Peter Dannenbaum
(908) 740-1037

Courtney Ronaldo
(908) 740-6132

Ticker Slug: Ticker: MRK
Exchange: NYSE
@Merck

Source URL: https://www.mrknewsroom.com/news-release/oncology/fda-accepts-regulatory-submission-supplemental-new-drug-application-lynparza-o