AstraZeneca and Merck's LYNPARZA® (olaparib) Approved in Japan as First-Line Maintenance Therapy in Patients with BRCA-Mutated Advanced Ovarian Cancer

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LYNPARZA is the Only PARP Inhibitor Approved in Japan

KENILWORTH, N.J.--(BUSINESS WIRE)--AstraZeneca and Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced that Japan's Pharmaceuticals and Medical Devices Agency (PMDA) has approved LYNPARZA as a maintenance treatment after first-line chemotherapy in patients with BRCA-mutated (BRCAm) ovarian cancer.

The approval in Japan was based on data from the randomized, double-blinded Phase 3 SOLO-1 trial which evaluated LYNPARZA as maintenance monotherapy compared with placebo in patients with BRCAm advanced ovarian cancer following first-line platinum-based chemotherapy.

Dave Fredrickson, executive vice-president, oncology, AstraZeneca, said, “This approval in Japan is a critical advance for women with ovarian cancer and a BRCA mutation. The goals of front-line therapy are long-term remission or a cure, yet currently 70% of patients relapse within three years of initial treatment. The progression-free survival benefit of Lynparza observed in SOLO-1 represents a major step forward in our ambition to improve patient outcomes.”

Dr. Roy Baynes, senior vice president and head of global clinical development, chief medical officer, Merck Research Laboratories, said, “Advances in understanding the role of BRCA mutations and PARP inhibition have fundamentally changed how physicians can treat this aggressive type of cancer. With the approval of this new indication, patients in Japan with BRCA-mutated advanced ovarian cancer who respond to chemotherapy will have the opportunity to benefit from LYNPARZA in the first-line maintenance setting.”

Results from the SOLO-1 trial showed that LYNPARZA reduced the risk of disease progression or death by 70% versus placebo following response to platinum-based chemotherapy (HR 0.30 [95% CI 0.23-0.41], p<0.001).

LYNPARZA is the only PARP inhibitor approved in Japan. AstraZeneca and Merck are exploring additional trials in ovarian cancer, including the ongoing Phase 3 PAOLA-1 trial, which is testing LYNPARZA in combination with bevacizumab as a first-line maintenance treatment for women with advanced, stage IIIB-IV high-grade serous or endometrioid, fallopian tube or peritoneal ovarian cancer, regardless of BRCA status.

About SOLO-1

SOLO-1 was a Phase 3, randomized, double-blinded, placebo-controlled, multi-center trial to evaluate the efficacy and safety of LYNPARZA tablets (300 mg twice daily) as maintenance monotherapy compared with placebo in patients with BRCAm advanced ovarian cancer following first-line platinum-based chemotherapy. The trial randomized 391 patients with a deleterious or suspected deleterious germline or somatic BRCA1 or BRCA2 mutation who were in clinical complete or partial response following platinum-based chemotherapy. Patients were randomized (2:1) to receive LYNPARZA or placebo for up to two years or until disease progression. Patients who had a partial response at two years were permitted to stay on therapy at the investigator's discretion. The primary endpoint was progression-free survival (PFS) and key secondary endpoints included time to second disease progression or death, time to first subsequent treatment and overall survival.

The data were presented on Oct. 21, 2018, at the Presidential Symposium of the ESMO 2018 Congress in Munich, Germany and published simultaneously online in the New England Journal of Medicine.

Summary of PFS i,ii

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<th>LYNPARZA (n=260)</th>
<th>Placebo (n=131)</th>
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<tr>
<td>PFS HR</td>
<td>0.30</td>
<td>1.00</td>
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<tr>
<td>95% CI</td>
<td>0.23-0.41</td>
<td>0.80-1.24</td>
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<tr>
<td>p</td>
<td>&lt;0.001</td>
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The SOLO-1 safety profile was in line with that observed in prior clinical trials. The most common adverse events (AEs) ≥20% were nausea (77%), fatigue (64%), vomiting (40%), anemia (39%) and diarrhea (34%). The most common ≥ Grade 3 AEs were anemia (22%) and neutropenia (8%). Seventy-one percent of patients on LYNYRZA remained on the recommended starting dose. Additionally, 88% of patients on LYNYRZA continued treatment without an AE-related discontinuation. Further, 48% of patients on LYNYRZA did not have a dose interruption as a result of an AE.

**About Ovarian Cancer**

Worldwide, ovarian cancer is the eighth most-commonly diagnosed cancer and seventh most-common cause of cancer deaths in women. In Japan, an estimated 10,672 new cases were expected to be diagnosed in 2018, with approximately 5,215 deaths. For newly-diagnosed advanced ovarian cancer, the primary aim of treatment is to delay progression of the disease for as long as possible.

**About BRCA Mutations**

Breast cancer susceptibility gene 1/2 (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 LYNYRZA ® (olaparib)**

LYNYRZA 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 LYNYRZA 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. LYNYRZA is being tested in a range of tumor types with defects and dependencies in the DDR.

LYNYRZA, 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.

**IMPORTANT SAFETY INFORMATION**

**CONTRAINDICATIONS**

There are no contraindications for LYNYRZA.

**WARNINGS AND PRECAUTIONS**

**Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML):** Occurred in <1.5% of patients exposed to LYNYRZA 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 LYNYRZA 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 LYNYRZA 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 LYNYRZA if MDS/AML is confirmed.

**Pneumonitis:** Occurred in <1% of patients exposed to LYNYRZA, 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 LYNYRZA treatment and initiate prompt investigation. Discontinue LYNYRZA if pneumonitis is confirmed and treat patient appropriately.

**Embryo-Fetal Toxicity:** Based on its mechanism of action and findings in animals, LYNYRZA can cause fetal harm. A pregnancy test is recommended for females of reproductive potential prior to initiating treatment.

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**Table:**

<table>
<thead>
<tr>
<th>Number of patients with event (%)</th>
<th>Median (in months)</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>102 (39)</td>
<td>Not reached</td>
<td>0.30 (0.23-0.41)</td>
<td>p&lt;0.001</td>
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<tr>
<td>96 (73)</td>
<td>13.8</td>
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i Investigator-assessed

ii Median (interquartile range) duration of follow-up 40.7 months (34.9–42.9) for LYNYRZA and 41.2 months (32.2–41.6) for placebo

iii Analysis was done at 50.6% maturity
**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/bronchitis (28%), dysgeusia (26%), decreased appetite (20%), dizziness (20%), neutropenia (17%), dyspepsia (17%), dysnea (15%), leukopenia (13%), UTI (13%), thrombocytopenia (11%), and stomatitis (11%).

**ADVERSE REACTIONS—Maintenance Recurrent Ovarian Cancer**

Most common adverse reactions (Grades 1-4) in ≥25% of patients in clinical trials of LYNPARZA in the first-line maintenance setting for SOLO-2 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—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/myalgia (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 the AstraZeneca and Merck Strategic Oncology Collaboration**

In July 2017, AstraZeneca and Merck, 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 immunoncology 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](http://www.merck.com/clinicaltrials).

**About Merck**

For more than a century, Merck, a leading global biopharmaceutical company known as MSD outside 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](http://www.merck.com) and connect with us on [Twitter](http://twitter.com), [Facebook](http://facebook.com), [Instagram](http://instagram.com), [YouTube](http://youtube.com) and [LinkedIn](http://linkedin.com).

**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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