LYNPARZA® (olaparib) Phase 3 PAOLA-1 Trial Significantly Increased Progression-Free Survival as First-Line Maintenance Treatment with Bevacizumab for Newly-Diagnosed Advanced Ovarian Cancer

9/28/2019

AstraZeneca and Merck's LYNPARZA Added to Bevacizumab Reduced the Risk of Disease Progression or Death by 41% in the Overall Trial Population of Women 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 detailed positive results from the Phase 3 PAOLA-1 trial showing LYNPARZA added to bevacizumab demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS) in women with newly-diagnosed advanced ovarian cancer who had a complete or partial response to first-line treatment with platinum-based chemotherapy and bevacizumab.

The trial compared LYNPARZA when added to standard-of-care (SoC) bevacizumab versus bevacizumab alone in women in the first-line maintenance setting, irrespective of their genetic biomarker status or outcome from previous surgery. Investigator-assessed results showed LYNPARZA added to bevacizumab reduced the risk of disease progression or death by 41% and improved PFS to a median of 22.1 months versus 16.6 months for those treated with bevacizumab alone (HR 0.59 [95% CI, 0.49-0.72], p<0.0001).

The sensitivity analysis of blinded independent central review (BICR) of PFS was consistent, showing a similar improvement with a median of 26.1 months for LYNPARZA added to bevacizumab versus 18.3 months for bevacizumab alone (HR 0.63 [95% CI, 0.51-0.77], p<0.0001).
The safety and tolerability profile of LYNPARZA and bevacizumab were consistent with those known from previous trials for each medicine.

The results were presented at the Presidential Symposium of the 2019 European Society of Medical Oncology (ESMO) congress in Barcelona, Spain (Abstract #LBA2_PR).

Dr. José Baselga, executive vice president, Oncology R&D, AstraZeneca, said, “This trial was designed to reflect everyday clinical practice and used a global standard-of-care treatment with LYNPARZA. We are working with regulatory authorities to bring LYNPARZA to these patients as quickly as possible.”

Dr. Roy Baynes, senior vice president and head of global clinical development, chief medical officer, Merck Research Laboratories, said, “PAOLA-1 is the second positive Phase 3 trial involving LYNPARZA in the first-line maintenance setting for advanced ovarian cancer. Following the positive SOLO-1 trial, we are encouraged by the PAOLA-1 results which reaffirm AstraZeneca and Merck’s ongoing commitment to explore potential treatment options for more women with ovarian cancer.”

Isabelle Ray Coquard, principal investigator of the PAOLA-1 trial and medical oncologist, Department of Medical Oncology at the Clinical Science Institute of the Léon Bérard Centre and President of the GINECO (Groupe d’Investigateurs National des Etudes des Cancers Ovariens et du sein) group, said, “The goal of first-line, including maintenance treatment for women with newly-diagnosed advanced ovarian cancer, is to delay relapse. Unfortunately, the risk of relapse is high, as two out of three women relapse within three years of initial diagnosis. In PAOLA-1, the results of LYNPARZA added to bevacizumab were significant and have the potential to change clinical practice in how women with advanced ovarian cancer are treated in the first-line maintenance setting.”

The trial also included exploratory sub-group analyses including BRCA-mutated (BRCAm) and broader homologous recombination deficiency (HRD) populations. In the BRCAm-positive sub-group, LYNPARZA added to SoC bevacizumab vs. bevacizumab alone resulted in median PFS of 37.2 months versus 21.7 months (HR 0.31 [95% CI, 0.20-0.47]) and 18.9 months versus 16 months in the non-BRCAm sub-group (HR 0.71 [95% CI, 0.58-0.88]). For the HRD-positive sub-group, median PFS for LYNPARZA added to bevacizumab was 37.2 months versus 17.7 months with bevacizumab alone (HR 0.33 [95% CI, 0.25-0.45]). In the HRD-positive, non-BRCAm sub-group, there was a median PFS of 28.1 months with LYNPARZA added to bevacizumab versus 16.6 months on bevacizumab alone (HR 0.43 [95% CI, 0.28-0.66]). The HRD-negative/unknown sub-group results showed a median PFS of 16.9 months for LYNPARZA added to bevacizumab vs. 16 months for bevacizumab alone (HR 0.92 [95% CI, 0.72-1.17]).

Summary of PFS in overall population:
<table>
<thead>
<tr>
<th></th>
<th>Median in months</th>
<th>Hazard Ratio (95% CI)</th>
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<tbody>
<tr>
<td></td>
<td>LYNPARZA +</td>
<td>bevacizumab alone</td>
</tr>
<tr>
<td>PFS (investigator assessed)</td>
<td>22.1</td>
<td>16.6</td>
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<tr>
<td>(n=806)</td>
<td></td>
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<tr>
<td>PFS (BICR)</td>
<td>26.1</td>
<td>18.3</td>
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Summary of PFS in exploratory subgroup analyses:

<table>
<thead>
<tr>
<th></th>
<th>Median in months</th>
<th>Hazard Ratio (95% CI)</th>
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<tr>
<td></td>
<td>LYNPARZA +</td>
<td>bevacizumab alone</td>
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<tr>
<td>PFS by BRCAm status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCAm (n=237)</td>
<td>37.2i.</td>
<td>21.7</td>
</tr>
<tr>
<td>Non-BRCAm (n=569)</td>
<td>18.9</td>
<td>16.0</td>
</tr>
<tr>
<td>PFS by HRD status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRD-positive (n=387)</td>
<td>37.2i.</td>
<td>17.7</td>
</tr>
<tr>
<td>HRD-positive, non-BRCAm (n=152)</td>
<td>28.1i.</td>
<td>16.6</td>
</tr>
<tr>
<td>HRD-negative/unknown (n=419)</td>
<td>16.9</td>
<td>16.0</td>
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i The median PFS estimate is immature at this time (below 50% maturity) and will evolve with additional follow up

The most common adverse events (AEs) ≥20% for LYNPARZA plus bevacizumab compared to bevacizumab alone were nausea (53% vs. 22%), fatigue (53% vs. 32%), hypertension (46% vs. 60%), anemia (41% vs. 10%), lymphopenia (24% vs. 10%), 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. 0.4%), lymphopenia (7% vs. 1%), fatigue (5% vs. 2%), neutropenia (6% vs 3%), nausea (2% vs. 1%), diarrhea (2% each), leukopenia (2% vs. 1%), vomiting (2% each) 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 20% of patients on LYNPARZA plus bevacizumab discontinued treatment vs. 6% on bevacizumab alone.

LYNPARZA, which is being jointly developed and commercialized by Merck and AstraZeneca, is currently approved in 64 countries, including those in the EU, for the maintenance treatment of platinum-sensitive relapsed ovarian cancer regardless of BRCA status. It is approved in the U.S. as first-line maintenance treatment in BRCAm advanced ovarian cancer following response to platinum-based chemotherapy. It is also approved in 38 countries, including the U.S., countries in the EU, and Japan, for germline BRCAm HER2-negative metastatic breast cancer previously treated with chemotherapy; in the EU this includes locally advanced breast cancer. LYNPARZA has been used to treat over 25,000 patients worldwide.

LYNPARZA is the only PARP inhibitor with positive Phase 3 trials in four different cancer types.

About PAOLA-1

PAOLA-1 is a double-blind Phase 3 trial evaluating the efficacy and safety of LYNPARZA added to SoC bevacizumab vs. bevacizumab alone, as a first-line maintenance treatment for newly-diagnosed 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. The intent-to-treat* population refers to all patients randomized in the trial.

PAOLA-1 is an ENGOT (European Network of Gynaecological Oncological Trial groups) trial, sponsored by ARCAGY Research (Association de Recherche sur les Cancers dont GYNéologiques) on behalf of GINECO (Groupe d’Investigateurs National des Etudes 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/bronchitis (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%).

**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 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 Ovarian Cancer

Ovarian cancer the eighth most common cause of death from cancer in women worldwide, with a five-year survival rate of approximately 19%. In 2018, there were nearly 300,000 new cases diagnosed and around 185,000 deaths.

About Homologous Recombination Deficiency (HRD)

Homologous recombination deficiencies (HRDs), including BRCA, cause genomic instability which can be detected using assays such as the Myriad My Choice HRD test. BRCA mutations are just one of many homologous recombination repair deficiencies which are found in up to half of newly diagnosed advanced ovarian cancer patients.

About GINECO

GINECO (Groupe d’Investigateurs Nationaux pour l’Étude des Cancers Ovariens et du sein) is the French Cooperative Group in Oncology labelled by INCA (Institut National du Cancer or French NCI) developing and conducting gynaecological and metastatic breast cancer clinical trials at the national and international level. Founded in 1993, the GINECO group is member of international consortia such as ENGOT and GCIG.

About ENGOT

ENGOT (European Network for Gynaecological Oncological Trial groups) is a research network of the European Society of Gynaecological Oncology (ESGO). Founded in 2007, ENGOT includes 21 cooperative groups from 25 European countries.
About GCIG

The GCIG (Gynecological Cancer InterGroup) aims to promote and facilitate high quality clinical trials in order to improve outcomes for women with gynaecological cancer. Founded in 1998, GCIG includes 23 cooperative groups from 28 countries worldwide.

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).

Media Contacts:
Pamela Eisele
(267) 305-3558

Steve Wanczyk
(267) 305-5563

Investor Contacts:
Peter Dannenbaum
(908) 740-1037

Courtney Ronaldo