Lynparza granted FDA Priority Review for PAOLA-1

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Lynparza regulatory submission granted Priority Review in the US for 1st-line maintenance treatment with bevacizumab in advanced ovarian cancer

Submission based on Phase III PAOLA-1 trial for patients with advanced ovarian cancer regardless of biomarker status or surgical outcome

AstraZeneca and MSD Inc., Kenilworth, N.J., US (MSD: known as Merck & Co., Inc. inside the US and Canada) today announced that a supplemental New Drug Application for *Lynparza* (olaparib) in combination with bevacizumab has been accepted and granted Priority Review in the US for the maintenance treatment of patients with advanced ovarian cancer who are in complete or partial response to 1st-line platinum-based chemotherapy with bevacizumab.

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

The Priority Review by the US Food and Drug Administration (FDA) was based on results from the pivotal Phase III 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 vs. bevacizumab alone in patients with advanced ovarian cancer in the 1st-line maintenance setting, regardless of their 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% based on a hazard ratio of 0.59 ($p<0.0001$) and improved progression-free survival (PFS) to a median of 22.1 months vs. 16.6 months for patients treated with bevacizumab alone.

At two years after trial initiation, 46% of patients treated with *Lynparza* added to bevacizumab showed no disease progression vs. 28% of patients treated with bevacizumab alone. The safety and tolerability profiles of *Lynparza* and bevacizumab were consistent with previous trials for each medicine and showed no detriment to quality of life.

Lynparza is the only PARP inhibitor with two positive randomised Phase III trials in the 1st-line maintenance setting for advanced ovarian cancer. It is the only PARP inhibitor approved in the US as a 1st-line maintenance treatment for patients with BRCA-mutated advanced ovarian cancer, based on the SOLO-1 trial. If approved, this would be the fourth indication for ovarian cancer patients in the US for *Lynparza*.

Ovarian cancer

Ovarian cancer is the eighth most common cause of death from cancer in women worldwide. In 2018, there were nearly 300,000 new cases diagnosed and around 185,000 deaths.[1] Most women are diagnosed with advanced (Stage III or IV) ovarian cancer and have a five-year survival rate of approximately 30%.[2] For newly diagnosed advanced ovarian cancer, the primary aim of treatment is to delay progression of the disease for as long as possible and maintain the patient's quality of life with the intent of achieving complete remission or cure.[3,4,5,6]

PAOLA-1

PAOLA-1 is a double-blind Phase III trial testing the efficacy and safety of *Lynparza* added to standard-of-care bevacizumab vs. bevacizumab alone, as a 1st-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 1st-line treatment with platinum-based chemotherapy and bevacizumab.

Results showed *Lynparza* added to bevacizumab demonstrated a statistically significant and clinically meaningful improvement in PFS, reducing the risk of disease progression or death by 41% and improving 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 vs. 18.3 months for bevacizumab alone (HR 0.63 [95% CI, 0.51-0.77], $p<0.0001$).

Overall Grade 3 or above adverse events (AEs) were 57% for *Lynparza* added to bevacizumab and 51% for bevacizumab alone. The most common AEs ≥20% were nausea (53%), fatigue (53%), hypertension (46%), anaemia (41%), lymphopenia (24%), vomiting (22%) and arthralgia (22%). Grade 3 or above AEs were hypertension (19%), anaemia (17%), lymphopenia (7%), neutropenia (6%), fatigue (5%), nausea (2%), diarrhoea (2%), leukopenia (2%) vomiting (1%) and abdominal pain (1%). AEs led to dose interruption in 54% of patients on *Lynparza* added to bevacizumab while 20% of patients discontinued treatment.

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 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).

Lynparza

Lynparza (olaparib) is a first-in-class PARP inhibitor and the first targeted treatment to block DNA damage response (DDR) in cells/tumours harbouring a deficiency in homologous recombination repair, such as mutations in BRCA1 and/or BRCA2. 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 PARP-dependent tumour types with defects and dependencies in the DDR pathway.

Lynparza is currently approved in 65 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 US, the EU, Japan, China and several other countries as 1st-line maintenance treatment of BRCA-mutated advanced ovarian cancer following response to platinum-based chemotherapy. It is also approved in 44 countries, including the US and Japan, for germline BRCA-mutated, HER2-negative, metastatic breast cancer, previously treated with chemotherapy; in the EU, this includes locally advanced breast cancer. It is approved in the US as a 1st-line maintenance treatment for germline BRCA-mutated metastatic pancreatic cancer. Regulatory reviews are underway in other jurisdictions for ovarian, breast and pancreatic cancers.

Lynparza, which is being jointly developed and commercialised by AstraZeneca and MSD, is approved for the treatment of advanced ovarian cancer, metastatic breast cancer and metastatic pancreatic cancer and has been used to treat over 30,000 patients worldwide. *Lynparza* has the broadest and most advanced clinical-trial development programme of any PARP inhibitor, and AstraZeneca and MSD are working together to understand how it may affect multiple PARP-dependent tumours as a monotherapy and in combination across multiple cancer types. *Lynparza* is the foundation of AstraZeneca's industry-leading portfolio of potential new medicines targeting DDR mechanisms in cancer cells.

The AstraZeneca and MSD strategic oncology collaboration

In July 2017, AstraZeneca and Merck & Co., Inc., Kenilworth, NJ, US, known as MSD outside the US and Canada, announced a global strategic oncology collaboration to co-develop and co-commercialise *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.

AstraZeneca in oncology

AstraZeneca has a deep-rooted heritage in oncology and offers a quickly growing portfolio of new medicines that has the potential to transform patients' lives and the Company's future. With at least six new medicines to be launched between 2014 and 2020, and a broad pipeline of small molecules and biologics in development, the Company is committed to advance oncology as a key growth driver for AstraZeneca focused on lung, ovarian, breast and blood cancers. In addition to AstraZeneca's main capabilities, the Company is actively pursuing innovative partnerships and investment that accelerate the delivery of our strategy, as illustrated by the investment in Acerta Pharma in haematology.

By harnessing the power of four scientific platforms - Immuno-Oncology, Tumour Drivers and Resistance, DNA Damage Response and Antibody Drug Conjugates - and by championing the development of personalised combinations, AstraZeneca has the vision to redefine cancer treatment and, one day, eliminate cancer as a cause of death.

AstraZeneca

AstraZeneca (LSE/STO/NYSE: AZN) is a global, science-led biopharmaceutical company that focuses on the discovery, development and commercialisation of prescription medicines, primarily for the treatment of diseases in three therapy areas - Oncology, Cardiovascular, Renal and Metabolism, and Respiratory. AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide. Please visit astrazeneca.com and follow the Company on Twitter @AstraZeneca.

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References

1. The World Health Organization. IARC. Globocan 2018. Available at: www.gco.iarc.fr/ [Accessed December 2019].
2. National Cancer Institute. (2019). Cancer Stat Facts: Ovarian Cancer Available at: https://seer.cancer.gov/statfacts/html/ovary.html [Accessed December 2019].
3. Moore K et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. Presented at ESMO October 2018.
4. Raja, F. A., Chopra, N. & Ledermann, J. A. 2012. Optimal first-line treatment in ovarian cancer. *Annals of Oncology. Official Journal of the European Society for Medical Oncology.* 23 Suppl 10, x118-127.
5. NHS Choices. Ovarian Cancer. Available at: https://www.nhs.uk/conditions/ovarian-cancer/treatment/ [Accessed December 2019].
6. Ledermann.et al. 2013. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice for diagnosis, treatment and follow-up. *Annals of Oncology*, 24(suppl 6), pp.vi24-vi32.

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