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Lynparza improved the time women lived without disease progression to 22 months in the broad population and to 37 months in HRD-positive patients as 1st-line maintenance treatment with bevacizumab for newly-diagnosed advanced ovarian cancer

AstraZeneca and MSD's Lynparza added to bevacizumab reduced the risk of disease progression or death by 41% in the overall trial population

AstraZeneca and MSD Inc., Kenilworth, N.J., US (MSD: known as Merck & Co., Inc. inside the US and Canada) today announced detailed positive results from the Phase III PAOLA-1 trial, showing *Lynparza* (olaparib) demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS) in women with newly-diagnosed advanced ovarian cancer.

The trial compared *Lynparza* when added to standard-of-care (SoC) bevacizumab vs. bevacizumab alone in women in the 1st-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% (equal to a hazard ratio of 0.59) and improved PFS to a median of 22.1 months vs. 16.6 months for those treated with bevacizumab alone. At two years since trial initiation, 46% of women treated with *Lynparza* added to bevacizumab showed no disease progression vs. 28% of women receiving bevacizumab alone.

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. The safety and tolerability profile of *Lynparza* and bevacizumab were consistent with those known from previous trials for each medicine, and with no detriment to quality of life.

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

The trial also included exploratory sub-group analyses including BRCA-mutated (BRCAm) and broader homologous recombination deficiency (HRD) populations, which showed treatment with *Lynparza* added to bevacizumab demonstrated greater benefit vs. bevacizumab alone. In the BRCAm-positive sub-group, *Lynparza* added to bevacizumab reduced the risk of disease progression or death by 69% (equal to a hazard ratio of 0.31). In the broader HRD-positive sub-group, which represents approximately half of women with newly-diagnosed advanced ovarian cancer and includes BRCAm, *Lynparza* added to bevacizumab reduced the risk of disease progression or death by 67% (equal to a hazard ratio of 0.33).

José Baselga, Executive Vice President, Oncology R&D, said: "This trial was designed to reflect everyday clinical practice using a global standard-of-care treatment with *Lynparza.* The results showed at two years nearly half of women with advanced ovarian cancer were progression-free with *Lynparza* added to bevacizumab as a 1st-line maintenance treatment, regardless of their biomarker status or surgical outcome. We are working with regulatory authorities to bring *Lynparza*to these patients as quickly as possible."

Roy Baynes, Senior Vice President and Head of Global Clinical Development, Chief Medical Officer, MSD Research Laboratories, said: "PAOLA-1 is the second positive Phase III trial involving *Lynparza* in the 1st-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 MSD'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, Centre Léon Bérard and President of the GINECO group, said: "The goal of 1st-line, including maintenance, treatment for women with newly-diagnosed advanced ovarian cancer is to delay relapse. Unfortunately, the risk of relapsing 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 1st-line maintenance setting."

Summary of PFS in overall population

	Median in months		**Hazard Ratio (95% CI)**
	Lynparza + bevacizumab	bevacizumab alone	
PFS (investigator assessed) (n=806)	22.1	16.6	0.59 (0.49-0.72) p<0.0001
PFS (BICR)	26.1	18.3	0.63 (0.51-0.77) p<0.0001

Summary of PFS in exploratory subgroup analyses

	Median in months		**Hazard Ratio (95% CI)**
	Lynparza + bevacizumab	bevacizumab alone	
PFS by BRCAm status			
BRCAm (n=237)	37.2[i]	21.7	0.31 (0.20-0.47)
Non-BRCAm (n=569)	18.9	16.0	0.71 (0.58-0.88)
PFS by HRD status			
HRD-positive (n=387)	37.2[i]	17.7	0.33 (0.25-0.45)
HRD-positive, non-BRCAm (n=152)	28.1[i]	16.6	0.43 (0.28-0.66)
HRD-negative/unknown (n=419)	16.9	16.0	0.92 (0.72-1.17)

[i] The median PFS estimate is immature at this time (below 50% maturity) and will evolve with additional follow up

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 while 20% of patients discontinued treatment.

Lynparza, which is being jointly developed and commercialised by AstraZeneca and MSD, is approved for the treatment of advanced ovarian cancer and metastatic breast cancer and has been used to treat over 25,000 patients worldwide. It is the only PARP inhibitor with positive Phase III trials in four different cancer types (ovarian, breast, pancreatic and prostate).

About PAOLA-1

PAOLA-1 is a double-blind Phase III trial testing the efficacy and safety of *Lynparza* added to SoC 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.

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).

About 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]

About homologous recombination deficiency
Homologous recombination deficiencies (HRDs) encompass a wide range of genetic abnormalities, including BRCA mutations, that can be detected using tests. As the BRCA gene drives DNA repair via homologous recombination, mutation of this gene leads to HR deficiency thereby interfering with normal cell DNA repair mechanisms. BRCA mutations are just one of many HRDs which are found in up to half of all newly diagnosed advanced ovarian cancer patients and confer sensitivity to PARP inhibitors including *Lynparza*.

About *Lynparza*
Lynparza 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 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 US, the EU, Japan 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 43 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. 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 and metastatic breast cancer and has been used to treat over 25,000 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.

About GINECO
GINECO (Groupe d'Investigateurs National des Etudes 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 a 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 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.

About 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.

About AstraZeneca
AstraZeneca 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 (CVRM), 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 us on Twitter @AstraZeneca.

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