Lynparza reduced recurrence risk in breast cancer

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Lynparza reduced the risk of cancer recurrence by 42% in the adjuvant treatment of patients with germline BRCA-mutated high-risk early breast cancer in OlympiA Phase III trial

First medicine targeting BRCA mutations to show clinical benefit in adjuvant setting

Results from the OlympiA Phase III trial showed AstraZeneca and MSD's *Lynparza* (olaparib) demonstrated a statistically significant and clinically meaningful improvement in invasive disease-free survival (iDFS) versus placebo in the adjuvant treatment of patients with germline BRCA-mutated (gBRCAm) high-risk human epidermal growth factor receptor 2 (HER2)-negative early breast cancer.

The results will be presented during the plenary session of the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting on 6 June 2021 (abstract LBA#1) and were published today in *The New England Journal of Medicine.*

An estimated 2.3 million people were diagnosed with breast cancer worldwide in 2020 and BRCA mutations are found in approximately 5% of breast cancer patients.[1,2]

Sue Friedman, Executive Director, Facing Our Risk of Cancer Empowered (FORCE) and member of the OlympiA trial steering committee, said: "While there have been great strides in the early treatment of breast cancer, the fear of cancer returning is still at the forefront of patients' minds. New targeted treatment approaches are needed in the adjuvant setting that can help keep cancer and that fear at bay."

Andrew Tutt, chair of the OlympiA trial steering committee and professor of Oncology at The Institute of Cancer Research, London and Kings College London, said: "We are thrilled that our global academic and industry partnership in OlympiA has been able to help identify a possible new treatment option for patients with early-stage breast cancer and who have inherited mutations in their BRCA1 or BRCA2 genes. Patients with early-stage breast cancer who have inherited BRCA mutations are typically diagnosed at a younger age compared to those without such a mutation. Olaparib has the potential to be used as a follow-on to all the standard initial breast cancer treatments to reduce the rate of life-threatening recurrence and cancer spread for many patients identified through genetic testing to have mutations in these genes."

Dave Fredrickson, Executive Vice President, Oncology Business Unit, said: "This is the first time that any medicine targeting a BRCA mutation has demonstrated the potential to change the course of early-stage breast cancer and offer hope for a cure. By providing a treatment which significantly reduces the risk of breast cancer returning in these high-risk patients, we hope *Lynparza* will set a new benchmark demonstrating sustained clinical benefit. 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: "Results of the OlympiA trial represent a potential step forward for patients with high-risk early breast cancer. These new data support the importance of testing at diagnosis for BRCA1/2 mutations, which are actionable biomarkers that can help identify patients with early breast cancer who may be eligible for adjuvant treatment with *Lynparza.* Testing for BRCA mutations in addition to hormone receptor status and the expression of the HER2 protein will allow clinicians to better inform potential treatment plans for their patients."

In the overall trial population of patients who had completed local treatment and standard neoadjuvant or adjuvant chemotherapy, results showed *Lynparza* reduced the risk of invasive breast cancer recurrences, second cancers or death by 42% (based on a hazard ratio [HR] of 0.58; 99.5% confidence interval [CI] 0.41-0.82; p<0.0001). At three years, 85.9% of patients treated with *Lynparza* remained alive and free of invasive breast cancer and second cancers versus 77.1% on placebo.

Lynparza also demonstrated a statistically significant and clinically meaningful improvement in the key secondary endpoint of distant disease-free survival (DDFS) in the overall trial population. *Lynparza* reduced the risk of distant disease recurrence or death by 43% (based on an HR of 0.57; 99.5% CI 0.39-0.83; p<0.0001). At the time of this initial data cut-off, fewer deaths had occurred in patients receiving *Lynparza*, but the difference in overall survival (OS) did not reach statistical significance. The trial will continue to assess OS as a secondary endpoint.

In February 2021, the Independent Data Monitoring Committee recommended for the OlympiA trial to move to early primary analysis and reporting. Based on the planned interim analysis, the IDMC concluded that the trial crossed the superiority boundary for its primary endpoint of iDFS and demonstrated a sustainable and clinically relevant treatment effect for *Lynparza* versus placebo.

Summary of OlympiA results

	Lynparza(n=921)	**Placebo**(n=915)
iDFS (primary endpoint)		
HR (99.5% CI)	0.58 (0.41, 0.82)	
p-value	p<0.0001	
iDFS rates		
One year	93.3%	88.4%
Two years	89.2%	81.5%
Three years	85.9%	77.1%
DDFS (secondary endpoint)		
HR (99.5% CI)	0.57 (0.39, 0.83)	
p-value	p<0.0001	
DDFS rates		
One year	94.3%	90.2%
Two years	90.0%	83.9%
Three years	87.5%	80.4%
OS at interim (secondary endpoint)[ii]		
HR (99% CI)	0.68 (0.44, 1.05)	
p-value	p=0.024	

OS rates		
One year	98.1%	96.9%
Two years	94.8%	92.3%
Three years	92.0%	88.3%

i The data cut-off date for the interim analysis was 27 March 2020.

ii Statistical significance not reached based on the interim analysis plan for alpha conservation for future survival analyses.

The safety and tolerability profile of *Lynparza* in this trial was in line with that observed in prior clinical trials. The most common adverse events (AEs) were nausea (57%), fatigue (40%), anaemia (23%) and vomiting (23%). Grade 3 or higher AEs were anaemia (9%), neutropenia (5%), leukopenia (3%), fatigue (2%), and nausea (1%). Approximately 10% of patients treated with *Lynparza* discontinued treatment early due to AEs.

OlympiA is a global collaborative Phase III trial coordinated by the Breast International Group (BIG) worldwide, in partnership with NRG Oncology, the US National Cancer Institute (NCI), Frontier Science & Technology Research Foundation (FSTRF), AstraZeneca and MSD.[3] The trial is sponsored by NRG Oncology in the US and by AstraZeneca outside the US.

Lynparza is approved in the US, Japan, and a number of other countries for gBRCAm, HER2-negative, metastatic breast cancer previously treated with chemotherapy; in the EU, this includes locally advanced breast cancer.

Early breast cancer

Breast cancer is the most common cancer among women worldwide and an estimated 70% of all breast cancer is diagnosed at an early stage.[4,5] Breast cancer is one of the most biologically diverse tumour types with various factors underlying its development and progression.[6] The discovery of biomarkers in the development of breast cancer has greatly impacted scientific understanding of the disease and treatment of patients who develop the disease.[7]

OlympiA

OlympiA is a Phase III, double-blind, placebo-controlled, multicentre trial testing the efficacy and safety of *Lynparza* tablets versus placebo as adjuvant treatment in patients with gBRCAm, high-risk, HER2-negative early breast cancer, who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy. The primary endpoint of the trial is iDFS defined as time from randomisation to date of first loco-regional or distant recurrence, new cancer or death from any cause. Key secondary endpoints include OS and DDFS, which is defined as time from randomisation until documented evidence of first distant recurrence of breast cancer or death without distant recurrence.[3]

BIG

The Breast International Group (BIG) is an international not-for-profit organisation for academic breast cancer research groups from around the world, based in Brussels, Belgium.

Founded by leading European opinion leaders in 1999, the organisation aims to address fragmentation in breast cancer research and now represents a network of over 50 like-minded research groups affiliated with specialised hospitals, research centres and leading experts across approximately 70 countries on six continents.

BIG's research is supported in part by its philanthropy unit, known as BIG against breast cancer, which is used to interact with the general public and donors, and to raise funds for BIG's purely academic breast cancer trials and research programmes.

FSTRF

Frontier Science & Technology Research Foundation (FSTRF) is a non-profit, research organisation which supports research networks, pharmaceutical companies and investigators to conduct scientifically meaningful high-quality clinical trials. The OlympiA trial involved research staff in the US and in the Affiliate office in Scotland.

FSTRF works with scientists and technicians in more than 800 laboratories, universities and medical centres around the world to provide a comprehensive range of research services throughout the clinical trial process including design, analysis and reporting.

Through its work, FSTRF aims to advance the application of statistical science and practice and data management techniques in science, healthcare and education.

NRG Oncology

NRG Oncology is a network group funded by the US National Cancer Institute (NCI), a part of the National Institutes of Health. NRG Oncology brings together the National Surgical Adjuvant Breast and Bowel Project (NSABP), the Radiation Therapy Oncology Group (RTOG), and the Gynecologic Oncology Group (GOG), with the mission to improve the lives of cancer patients by conducting practice-changing multi-institutional clinical and translational research. NRG Oncology sponsored OlympiA in the US and collaborated with the other adult cancer clinical trials research groups funded by the NCI, Alliance, ECOG/ACRIN and the Southwest Oncology Group. The NCI and AstraZeneca are collaborating under a Cooperative Research and Development Agreement between the parties.

BRCA1 and BRCA2

BRCA1 and BRCA2 are human genes that produce proteins responsible for repairing damaged DNA and play an important role 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 and confer sensitivity to PARP inhibitors including *Lynparza*.[8-11]

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 (HRR), 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 a number of countries, including those in the EU, for the maintenance treatment of platinum-sensitive relapsed ovarian cancer. 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 the US, EU and Japan as a 1st-line maintenance treatment with bevacizumab for patients with HRD-positive advanced ovarian cancer (BRCAm and/or genomic instability). *Lynparza* is approved in the US, Japan, and a number of other countries for germline BRCA-mutated, HER2-negative, metastatic breast cancer, previously treated with chemotherapy; in the EU, this includes locally advanced breast cancer. It is also approved in the US, the EU, Japan and several other countries for the treatment of germline BRCAm metastatic pancreatic cancer. *Lynparza* is approved in the US for HRR gene-mutated metastatic castration-resistant prostate cancer (BRCAm and other HRR gene mutations) and in the EU and Japan for BRCAm metastatic castration-resistant prostate cancer. Regulatory reviews are underway in several countries for ovarian, breast, pancreatic and prostate cancers.

Lynparza, which is being jointly developed and commercialised by AstraZeneca and MSD, has been used to treat over 40,000 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 *Koselugo* (selumetinib), a mitogen-activated protein kinase (MEK) inhibitor, for multiple cancer types. Working together, the companies will develop *Lynparza* and *Koselugo* in combination with other potential new medicines and as monotherapies. Independently, the companies will develop *Lynparza* and *Koselugo* in combination with their respective PD-L1 and PD-1 medicines.

AstraZeneca in breast cancer

Driven by a growing understanding of breast cancer biology, AstraZeneca is starting to challenge, and redefine, the current clinical paradigm for how breast cancer is classified and treated to deliver even more effective treatments to patients in need - with the bold ambition to one day eliminate breast cancer as a cause of death.

AstraZeneca has a comprehensive portfolio of approved and promising compounds in development that leverage different mechanisms of action to address the biologically diverse breast cancer tumour environment. AstraZeneca aims to continue to transform outcomes for HR-positive breast cancer with foundational medicines *Faslodex* (fulvestrant) and *Zoladex* (goserelin) and the next-generation SERD and potential new medicine camizestrant. PARP inhibitor, *Lynparza* (olaparib) is a targeted treatment option for metastatic breast cancer patients with an inherited BRCA mutation. AstraZeneca with MSD continue to research *Lynparza* in metastatic breast cancer patients with an inherited BRCA mutation and are exploring new opportunities to treat these patients earlier in their disease state.

Building on the first approval of *Enhertu* (trastuzumab deruxtecan), a HER2-directed antibody-drug conjugate (ADC), in previously treated HER2-positive metastatic breast cancer, AstraZeneca and Daiichi Sankyo are exploring its potential in earlier lines of treatment and in new breast cancer settings. To bring much needed treatment options to patients with triple-negative breast cancer, an aggressive form of breast cancer, AstraZeneca is testing immunotherapy *Imfinzi* (durvalumab) in combination with other oncology medicines, including *Lynparza* and *Enhertu*, assessing the potential of AKT kinase inhibitor, capivasertib, in combination with chemotherapy, and collaborating with Daiichi Sankyo to explore the potential of TROP2-directed ADC, datopotamab deruxtecan.

AstraZeneca in oncology

AstraZeneca is leading a revolution in oncology with the ambition to provide cures for cancer in every form, following the science to understand cancer and all its complexities to discover, develop and deliver life-changing medicines to patients.

The Company's focus is on some of the most challenging cancers. It is through persistent innovation that AstraZeneca has built one of the most diverse portfolios and pipelines in the industry, with the potential to catalyse changes in the practice of medicine and transform the patient experience.

AstraZeneca has the vision to redefine cancer care and, one day, eliminate cancer as a cause of death.

AstraZeneca

AstraZeneca (LSE/STO/Nasdaq: AZN) is a global, science-led biopharmaceutical company that focuses on the discovery, development and commercialisation of prescription medicines in Oncology and BioPharmaceuticals, including Cardiovascular, Renal & Metabolism, and Respiratory & Immunology. Based in Cambridge, UK, 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.

Contacts

For details on how to contact the Investor Relations Team, please click here. For Media contacts, click here.

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Adrian Kemp

Company Secretary
AstraZeneca PLC