Press Release

3 June 2021, 5 p.m. EDT (11 p.m. CEST, 10 p.m. BST)

Olaparib *(Lynparza)* in the adjuvant treatment of patients with germline *BRCA1/2* mutations and high-risk early breast cancer reduced the risk of cancer recurrence by 42% in OlympiA Phase III trial

Results from the OlympiA Phase III trial showed olaparib (*Lynparza*) 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. Upon review of the planned interim analysis in February 2021, the IDMC concluded that the trial had crossed the superiority boundary for its primary endpoint and recommended for the OlympiA trial to move early to primary analysis and reporting.

Results of this analysis will be presented during the plenary session of the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting (abstract LBA#1). The results are being made available by ASCO on 3rd June and simultaneously published in *The New England Journal of Medicine* prior to their presentation in the plenary session.

An estimated 2.3 million people were diagnosed with breast cancer worldwide in 2020, and *BRCA1* and *BRCA2* mutations are found in approximately 5% of breast cancer patients.[1,2]

In the overall trial population of patients who had completed local treatment and standard neoadjuvant or adjuvant chemotherapy, results showed olaparib *(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 olaparib (*Lynparza)* remained alive and free of invasive breast cancer and second cancers versus 77.1% on placebo.

Olaparib *(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. Olaparib *(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 olaparib *(Lynparza),* but the difference in overall survival (OS) did not reach statistical significance. The trial will continue to assess OS as a secondary endpoint.

OlympiA Steering Committee Chair Andrew Tutt, Professor of Oncology at The Institute of Cancer Research, London, and King's College London, said: "We are thrilled that our global academic and industry partnership has been able to help identify a possible new treatment for women with early-stage breast cancer who have mutations in their BRCA1 or BRCA2 genes. 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."

"Women with early-stage breast cancer who have inherited BRCA mutations are typically diagnosed at a younger age. Up to now, there has been no treatment that specifically targets these mutations to reduce the risk of recurrence beyond the standard treatments available for early breast cancer. This major international study coordinated by the Breast International Group shows that giving olaparib for a year after completion of chemotherapy to patients with BRCA1 and 2 mutations increases the chances that they will remain free of invasive or metastatic cancer. These results reinforce how collaborative cancer research deepens our understanding of treating familial cancers and shows the value of testing for these mutations in patients with early breast cancer."

Charles Geyer, OlympiA Steering Committee co-Chair, Professor and Deputy Director of the *Houston Methodist* Cancer Center, said: "OlympiA represents a remarkable and successful global collaboration between leading international academic breast cancer research groups, cancer genetics experts, the National Cancer Institute and pharmaceutical industry partners to evaluate the efficacy and safety of olaparib to address the unmet need for improved therapy for individuals with high risk, inherited BRCA mutation-associated early breast cancer."

Judy Garber, OlympiA Steering Committee co-Chair, Professor and Chief, Division of Cancer Risk and Prevention, Dana-Farber Cancer Institute, said: "The results of OlympiA highlight the importance of inherited cancer genetic testing being widely available, as the results have become essential to modern oncology for targeted therapy decisions, now at breast cancer diagnosis as well as at presentation with metastatic disease."

Sue Friedman, Executive Director, Facing Our Risk of Cancer Empowered (FORCE, a leading advocacy organisation for individuals and families facing hereditary cancer), and member of the OlympiA trial steering committee, said: "While we have made 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."

Summary of OlympiA results

	Olaparib *(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 olaparib *(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 (24%) and vomiting (22%). Grade 3 or higher AEs were anaemia (9%), neutropenia (5%), leukopenia (3%), fatigue (2%), and nausea (1%). Approximately 10% of patients treated with olaparib *(Lynparza)* discontinued treatment early due to AEs compared to approximately 4% with placebo treatment.

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. We make a special mention of Professor Bella Kaufman (Sheba Medical Center, Israel), one of the OlympiA Steering Committee co-Chairs, who tragically passed away recently, before the results of this trial to which she contributed so much could be shared publicly.

Olaparib *(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 olaparib *(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 U.S. 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 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 certain cells accumulate genetic changes including loss of the normal copy of *BRCA1* or *BRCA2* and 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]

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
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.

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References

1. World Health Organization. Estimated number of cases in 2020, worldwide, both sexes, all ages. Available at: https://gco.iarc.fr/today/data/factsheets/cancers/20-Breast-fact-sheet.pdf. Accessed May 2021.

2. Mitri Z, *et al*. The HER2 Receptor in Breast Cancer: Pathophysiology, Clinical Use, and New Advances in Therapy. *Chemother Res Pract*. 2012;743193.

3. ClinicalTrials.gov. Olaparib as Adjuvant Treatment in Patients with Germline BRCA Mutated High Risk HER2 Negative Primary Breast Cancer (OlympiA). Available at clinicaltrials.gov/ct2/show/NCT02032823. Accessed May 2021.

4. Breast Cancer School. Will I survive breast cancer? Available at: https://www.breastcancercourse.org/will-i-survive-breast-cancer/. Accessed May 2021.

5. Bertozzi S, *et al*. Biomarkers in Breast Cancer. *Intechopen*. 2018.

6. Yersal O, and Barutca S. Biological Subtypes of Breast Cancer: Prognostic and therapeutic implications. *World J Clin Oncol*. 2014;5(3):412-424.

7. Rivenbark A, *et al*. Molecular and Cellular Heterogeneity in Breast Cancer: Challenges for Personalized Medicine. *Am J Pathol*. 2013;183(4):1113-1124

8. Roy R, *et al*. BRCA1 and BRCA2: Different Roles in a Common Pathway of Genome Protection. *Nat Rev Cancer*. 2021;12(1):68–78.

9. Wu J, *et al*. The Role of BRCA1 in DNA Damage Response. *Protein Cell*. 2010;1(2):117-11.

10. Gorodetska I, *et al*. BRCA Genes: The Role in Genome Stability, Cancer Stemness and Therapy Resistance. *J Cancer*. 2019;10(9):2109-2127.

11. Li H, *et al*. PARP Inhibitor Resistance: The Underlying Mechanisms and Clinical Implications. *Mol Cancer*. 2020;19:107.