Press Release
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OlympiA trial: Olaparib *(Lynparza)* as adjuvant treatment reduces risk of death by 32% in patients with germline *BRCA* mutations and high-risk early breast cancer

Updated results from the Phase III OlympiA trial showed that olaparib (*Lynparza*) significantly improved overall survival (OS) in patients with high-risk human epidermal growth factor receptor 2 (HER2)-negative early breast cancer and germline *BRCA* mutations (g*BRCA*m). The detailed results are being presented today by the Global Study Chair Professor Andrew Tutt at a virtual plenary session of the European Society of Medical Oncology (ESMO).

The results of the planned second interim analysis of overall survival (OS), a key secondary endpoint on the OlympiA trial, showed that one year of adjuvant olaparib relative to placebo led to a statistically significant and clinically meaningful improvement in the hazard ratio [HR] for OS of 0.68 (98.5% confidence interval [CI] 0.47-0.97; p=0.009). This corresponds to a 32% reduction in risk for death with olaparib relative to placebo. At 4 years, the OS rate was 89.8% for patients treated with olaparib versus 86.4% for those on placebo.

At this second interim analysis, the previously reported improvements in invasive disease-free survival (IDFS) and distant disease-free survival (DDFS) were maintained with similar benefits. The safety and tolerability profile of olaparib in this trial remains in line with what has been observed in prior clinical trials.

The results of the first interim analysis in the OlympiA trial were presented in June 2021 at the American Society of Clinical Oncology (ASCO) Annual Meeting and simultaneously published in *The New England Journal of Medicine*[1].

OlympiA Steering Committee Chair and co-principal investigator Professor Andrew Tutt, Professor of Oncology at The Institute of Cancer Research, London, and King's College London, says: *"OlympiA's latest results are great news for many patients with an inherited form of breast cancer. Most breast cancers are identified in the early stages and many patients will do very well, but for some the risk of cancer returning remains unacceptably high, even after chemotherapy."*

"OlympiA shows that for women with inherited BRCA mutations, olaparib can not only reduce the risk of their cancer coming back, but can also improve their overall survival. It's an exciting demonstration of the benefits of targeting the specific biology of disease for women with this type of early-stage breast cancer, and raises the prospect that more patients will now be cured of their disease."

Charles Geyer, OlympiA co-principal investigator, Chief Scientific Officer of the NSABP Foundation *(National Surgical Adjuvant Breast and Bowel Project)*, says: *"The updated analyses also strengthens the evidence for meaningful clinical benefit for high-risk patients irrespective of the hormone receptor status of their cancer and whether their inherited pathologic variant was in their BRCA1 or BRCA2 genes."*

[1] Tutt ANJ, Garber JE, Kaufman C et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. N Engl J Med. 2021 Jun 24;384(25):2394-2405. doi: 10.1056/NEJMoa2105215. Epub 2021 Jun 3.

Judy Garber, OlympiA co-principal investigator, Chief of the Division of Cancer Genetics and Prevention at Dana-Farber Cancer Institute, Boston, USA, adds: *"These exciting data confirm the earlier clinical benefits and now demonstrate improved survival across all subsets importantly without additional toxicity. The rationale for identification of the genetic subset of breast cancer patients at least among those who would have been eligible for OlympiA is further strengthened."*

"I am delighted to see that this worldwide collaboration of academic and commercial partners, and so many different doctors, hospitals and countries has generated strong evidence of a new treatment that reduces the risk of dying from this inherited form of breast cancer… but my biggest thank you, however, is to the 1,836 patients who were willing to enrol in this important study", says BIG Chair David Cameron, who is also OlympiA co-principal investigator, and Professor of Oncology at Edinburgh University, UK.

Susan Galbraith, Executive Vice President, Oncology R&D, AstraZeneca, says: *"These exciting results further support how Lynparza could significantly change the way people with germline BRCA-mutated early breast cancer are treated. The OlympiA trial is the first time we've seen a PARP inhibitor deliver survival benefit in early breast cancer, highlighting the importance of persistent innovation in tackling cancer early."*

Changing the lives of patients

An estimated 2.3 million people were diagnosed with breast cancer worldwide in 2020[2], and *BRCA1* and *BRCA2* mutations are found in approximately 5% of breast cancer patients.[3]

Based on the main results of OlympiA, various international guidelines, such as the ASCO guidance for the management of hereditary breast cancer[4] and the 2021 St Gallen International Consensus Guidelines for Treatment of Early Breast Cancer[5], have updated their recommendations for the adjuvant treatment of patients with hereditary, high-risk early breast cancer.

A few days ago the drug olaparib was approved by the Food and Drug Administration for the adjuvant treatment of patients with *BRCA*-mutated HER2-negative high-risk early breast cancer who have already been treated with chemotherapy either before or after surgery. This approval will change the way US-patients with this type of cancer will be treated in the future.

Olaparib was already approved in the US, EU, Japan and several other countries for the treatment of patients with g*BRCA*m, HER2-negative, metastatic breast cancer previously treated with chemotherapy based on results from the OlympiAD Phase III trial. In the EU and Japan, this indication also includes patients with locally advanced breast cancer.

Tanja Spanic, President of Europa Donna Slovenia and a member of the OlympiA Steering Committee, stresses the importance of involving the patient community from the start when conducting trials like Olympia: *"Patients are the core of any trial, so their practical insights are essential to the design of the study, not just after it has started. For example, we can advise on the frequency of hospital visits and ask how much can be done by phone calls and telemedicine, we can advise on the lay language used in information for patients, and we can help look after the quality of life of those taking part in a study - not just the effects of the treatment itself but also in relation to the protocol."*

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[2] 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.

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

[4] ASCO. Management of Hereditary Breast Cancer. August 2021. https://www.asco.org/practice-patients/guidelines/breast-cancer#/143725

[5] Burstein HJ, Curigliano G, Thürlimann B et al. Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021. *Ann Oncol.* 2021 Oct;32(10):1216-1235.

The OlympiA trial: a global collaborative effort
The OlympiA trial enrolled a total of 1,836 patients from over 600 hospitals and cancer centres in 23 countries worldwide.

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

The main objective of OlympiA is to test the efficacy and safety of olaparib *(Lynparza)* tablets versus placebo as post-surgery treatment to prevent cancer recurrence in patients with g*BRCA*m, high-risk, HER2-negative early breast cancer who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy.

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.[6] Breast cancer is one of the most biologically diverse tumour types with various factors underlying its development and progression.[7] 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.[8]

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 olaparib.[9],[10],[11],[12]

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 g*BRCA*m, 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.[13]

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

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

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

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

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

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

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

[13] 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.

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.

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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