Lynparza recommended in EU for early breast cancer

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Lynparza recommended for approval in the EU by CHMP as adjuvant treatment for patients with germline BRCA-mutated HER2-negative high-risk early breast cancer

First PARP inhibitor to improve overall survival in early-stage breast cancer

AstraZeneca and MSD's *Lynparza* (olaparib) has been recommended for marketing authorisation in the European Union (EU) as monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline BRCA1/2 mutations (gBRCAm) who have HER2-negative high-risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy.

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency based its positive opinion on results from the OlympiA Phase III trial published in *The New England Journal of Medicine* in June 2021.[1]

In the trial, *Lynparza* demonstrated a statistically significant and clinically meaningful improvement in invasive disease-free survival (iDFS), reducing the risk of invasive breast cancer recurrences, new cancers, or death by 42% versus placebo (based on a hazard ratio [HR] of 0.58; 99.5% confidence interval [CI] 0.41-0.82; p<0.0001).

Lynparza also demonstrated a statistically significant and clinically meaningful improvement in overall survival (OS), reducing the risk of death by 32% versus placebo (based on a HR of 0.68; 98.5% CI 0.47-0.97; p=0.009). The safety and tolerability profile of *Lynparza* in this trial was in line with that observed in prior clinical trials.

Breast cancer is the most diagnosed cancer worldwide with an estimated 2.3 million patients diagnosed in 2020.[2] Approximately 90% of all breast cancer patients are diagnosed with early breast cancer.[4,5] In Europe, BRCA mutations are found in up to 10% of patients.[6]

Professor Andrew Tutt, Global Chair of the OlympiA Phase III trial and Professor of Oncology at The Institute of Cancer Research, London and King's College London, said: "For patients with high-risk, early-stage breast cancer, the risk of recurrence remains unacceptably high and cancer will return for more than one in four of these patients. Today's recommendation is hopeful news for patients in Europe, as we move closer to setting a potential new standard of care that improves overall survival in patients suitable for treatment with olaparib."

Susan Galbraith, Executive Vice President, Oncology R&D, AstraZeneca, said: "If approved, *Lynparza* will become a new targeted treatment option for patients with germline BRCA-mutated HER2-negative early breast cancer in Europe. By treating patients with curative-intent as early as possible in their disease, we hope to avoid life-threatening recurrence and give people more time with their loved ones."

Dr. Eliav Barr, Head of Global Clinical Development and Chief Medical Officer, MSD Research Laboratories, said: "Patients with germline BRCA-mutated HER2-negative early breast cancer will often develop breast cancer at an earlier age than those without BRCA mutations, impacting people in their prime. Today's announcement brings us closer to our goal of offering a much-needed new treatment option to these patients."

In March 2022, *Lynparza* was approved in the US for the treatment of gBRCAm, HER2-negative high-risk early breast cancer. *Lynparza* is also approved in the US, EU, Japan and many other countries for the treatment of patients with gBRCAm, HER2-negative, metastatic breast cancer previously treated with chemotherapy based on results from the OlympiAD Phase III trial. In the EU, this indication also includes patients with locally advanced breast cancer.

Notes

Early breast cancer

Early breast cancer is defined as cancer confined to the breast with or without regional lymph node involvement, and the absence of distant metastatic disease.[7,8] In the US, the 5-year survival rate is 99% for localised breast cancer (only found in the breast area) and 86% for regional breast cancer (cancer that has spread outside the breast to nearby structures or lymph nodes).[6] Despite advancements in the treatment of early breast cancer, up to 30% of patients with high-risk clinical and/or pathologic features recur within the first few years and patients with gBRCAm are more likely to be diagnosed at a younger age than those without these mutations.[6,9]

Breast cancer is one of the most biologically diverse tumour types with various factors fuelling its development and progression.[10] The discovery of biomarkers in the development of breast cancer has greatly impacted scientific understanding of the disease.[11]

OlympiA

OlympiA is a Phase III, double-blind, parallel group, 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.[12]

The primary endpoint of the trial was iDFS defined as time from randomisation to date of first locoregional or distant recurrence or new cancer or death from any cause.[1]

The OlympiA Phase III trial is led by the Breast International Group in partnership with the Frontier Science & Technology Research Foundation, NRG Oncology, the US National Cancer Institute, AstraZeneca and MSD. The trial is sponsored by NRG Oncology in the US and by AstraZeneca outside the US.

BRCA

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.[10] 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*.[13-16]

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 those with mutations in BRCA1 and/or BRCA2, or those where deficiency is induced by other agents (such as new hormonal agents - NHAs).

Inhibition of PARP proteins 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 currently approved in a number of countries across PARP-dependent tumour types with defects and dependencies in the DDR pathway including maintenance treatment of platinum-sensitive relapsed ovarian cancer and as both monotherapy and in combination with bevacizumab for the 1st-line maintenance treatment of BRCA-mutated and homologous recombination repair deficient (HRD)-positive advanced ovarian cancer, respectively; for gBRCAm, HER2-negative metastatic breast cancer (in the EU and Japan this includes locally advanced breast cancer); for gBRCAm, HER2-negative high-risk early breast cancer (US only); for gBRCAm metastatic pancreatic cancer; and HRR gene-mutated metastatic castration-resistant prostate cancer (BRCAm only in the EU and Japan).

Lynparza, which is being jointly developed and commercialised by AstraZeneca and MSD, 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. The companies will develop *Lynparza* and *Koselugo* in combination with their respective PD-L1 and PD-1 medicines independently.

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. The Company has 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* and *Zoladex* and the next-generation oral selective oestrogen receptor degrader (SERD) and potential new medicine camizestrant.

The PARP inhibitor, *Lynparza*, is an approved targeted treatment option for early and metastatic breast cancer patients with an inherited BRCA mutation. AstraZeneca with MSD continue to research *Lynparza* in breast cancer patients with an inherited BRCA mutation.

Building on the initial approvals of *Enhertu*, 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* in combination with other oncology medicines, including *Lynparza* and *Enhertu*, evaluating 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, Rare Diseases, 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

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