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Lynparza approved in the US for HRR gene-mutated metastatic castration-resistant prostate cancer

Only PARP inhibitor to improve overall survival vs. enzalutamide or abiraterone in a biomarker-based subset of prostate cancer patients with BRCA1/2 or ATM mutations

Approximately 20-30% of men with metastatic castration-resistant prostate cancer have an HRR gene mutation

AstraZeneca and MSD Inc., Kenilworth, N.J., US (MSD: known as Merck & Co., Inc. inside the US and Canada) today announced that *Lynparza* (olaparib) has been approved in the US for patients with homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC).

The approval by the US Food and Drug Administration (FDA) was based on results from the Phase III PROfound trial, which were published in *The New England Journal of Medicine.*

Prostate cancer is the second-most common cancer in men and despite an increase in the number of available therapies for men with mCRPC, five-year survival remains low. HRR gene mutations occur in approximately 20-30% of patients with mCRPC.

Maha Hussain, one of the principal investigators of the PROfound trial and deputy director of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University, said: "Prostate cancer has lagged behind other solid tumours in the era of precision medicine. I am thrilled by the approval of *Lynparza* which now brings a molecularly targeted treatment to men with HRR gene-mutated metastatic castration-resistant prostate cancer in the US. The PROfound trial was an international effort and I want to thank the patients, their families, the investigators and their teams involved in making it possible."

Dave Fredrickson, Executive Vice President, Oncology Business Unit, said: "Today marks the first approval for *Lynparza* in prostate cancer. In the PROfound trial, *Lynparza* more than doubled the median radiographic progression-free survival and is the only PARP inhibitor to improve overall survival, versus enzalutamide or abiraterone for men with BRCA or ATM mutations. These results further establish that genomic testing for HRR mutations should be a critical step for the diagnosis and determination of treatment options for men with advanced prostate cancer."

Roy Baynes, Senior Vice President and Head of Global Clinical Development, Chief Medical Officer, MSD Research Laboratories, said, "*Lynparza* is the only PARP inhibitor approved with Phase III data for men with HRR gene-mutated metastatic castration-resistant prostate cancer. This approval highlights the importance of genomic testing to help identify treatment options for men in this patient population. We are proud to work in collaboration with AstraZeneca toward our overall goal of improving outcomes for patients."

The primary endpoint of the trial was radiographic progression-free survival (rPFS) in men with BRCA1/2 or ATM gene mutations, a subpopulation of HRR gene mutations. Results showed *Lynparza* reduced the risk of disease progression or death by 66% (equal to a hazard ratio of 0.34; p-value <0.0001) and improved rPFS to a median of 7.4 months versus 3.6 months with enzalutamide or abiraterone.

Lynparza also showed an rPFS benefit in the overall HRR gene-mutated trial population, a key secondary endpoint, and reduced the risk of disease progression or death by 51% (equal to a hazard ratio of 0.49; p-value <0.0001) and improved rPFS to a median of 5.8 months versus 3.5 months with enzalutamide or abiraterone.

Additional results from the PROfound trial announced on 24 April 2020 demonstrated a statistically significant and clinically meaningful improvement in the key secondary endpoint of overall survival (OS) with *Lynparza* versus enzalutamide or abiraterone in men with mCRPC and BRCA1/2 or ATM gene mutations. Results showed *Lynparza* reduced the risk of death by 31% (equal to a hazard ratio of 0.69; p-value=0.0175) and improved OS to a median of 19.0 months versus 14.6 months with enzalutamide or abiraterone.

The full indication is for the treatment of adult patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC who have progressed following prior treatment with enzalutamide or abiraterone. Patients are to be selected for treatment based on an FDA-approved companion diagnostic test for *Lynparza*.

Lynparza is currently under regulatory review in the EU and other jurisdictions as a treatment for men with HRR gene-mutated mCRPC.

AstraZeneca and MSD are testing *Lynparza* in additional trials in metastatic prostate cancer including the ongoing Phase III PROpel trial as a 1st-line treatment in combination with abiraterone acetate for patients with mCRPC versus abiraterone acetate alone.

Financial considerations
Following this approval for *Lynparza* in the US, AstraZeneca will receive a regulatory milestone payment from MSD of $35m, anticipated to be booked as Collaboration Revenue by the Company during the second quarter of 2020.

Metastatic castration-resistant prostate cancer
Prostate cancer is the second-most common cancer in men, with an estimated 1.3 million new cases diagnosed worldwide in 2018 and is associated with a significant mortality rate.[1] Development of prostate cancer is often driven by male sex hormones called androgens, including testosterone.[2] mCRPC occurs when prostate cancer grows and spreads to other parts of the body despite the use of androgen-deprivation therapy to block the action of male sex hormones.[2] Approximately 10-20% of men with advanced prostate cancer will develop CRPC within five years, and at least 84% of these will have metastases at the time of CRPC diagnosis.[3] Of men with no metastases at CRPC diagnosis, 33% are likely to develop metastases within two years.[3] Despite an increase in the number of available therapies for men with mCRPC, five-year survival remains low.[3]

HRR gene mutations
HRR gene mutations occur in approximately 20-30% of patients with mCRPC.[4,] HRR genes allow for accurate repair of damaged DNA in normal cells.[5,6] HRR deficiency (HRD) interferes with normal cell DNA repair mechanisms and can result in normal cell death.[6] This is different in cancer cells, where a mutation in HRR pathways leads to abnormal cell growth and therefore cancer.[6] The inability to properly repair DNA damage leads to genomic instability and contributes to cancer aetiology.[6] HRD is a well-documented target for PARP inhibitors, such as *Lynparza*. PARP inhibitors block a rescue DNA damage repair mechanism by trapping PARP bound to DNA single-strand breaks which leads to replication fork stalling causing their collapse and the generation of DNA double-strand breaks, which in turn lead to cancer cell death.[6]

PROfound

PROfound is a prospective, multicentre, randomised, open-label, Phase III trial testing the efficacy and safety of *Lynparza* versus enzalutamide or abiraterone in patients with mCRPC who have progressed on prior treatment with enzalutamide or abiraterone and have a qualifying tumour mutation in BRCA1/2, ATM or one of 12 other genes involved in the HRR pathway.

The trial was designed to analyse patients with HRRm genes in two cohorts: the primary endpoint was in those with mutations in BRCA1/2 or ATM genes and then, if *Lynparza* showed clinical benefit, a formal analysis was performed of the overall trial population of patients with HRRm genes (BRCA1/2, ATM, CDK12 and 11 other HRRm genes; key secondary endpoint).

In the US, patients are selected for treatment with *Lynparza* based on the following FDA-approved companion diagnostics*:*

- FoundationOne CDX: to identify patients with HRR-gene alterations in prostate tumour tissue. FoundationOne is a registered trademark of Foundation Medicine, Inc.
- BRACAnalysis CDX: a germline test to identify patients with BRCA1 and BRCA2 gene mutations. Myriad Genetics, Inc. owns and commercialises BRACAnalysis CDX.

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 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, 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. *Lynparza* is approved in the US and several other countries for the treatment of germline BRCA-mutated metastatic pancreatic cancer. Regulatory reviews are underway in several jurisdictions 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 30,000 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*, a kinase 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 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 six new medicines 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.

AstraZeneca
AstraZeneca (LSE/STO/NYSE: AZN) 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 & 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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