Lynparza approved in China for prostate cancer

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Lynparza approved in China for the treatment of BRCA-mutated metastatic castration-resistant prostate cancer

Only PARP inhibitor to improve overall survival versus new hormonal treatments in advanced prostate cancer

First PARP inhibitor approved in China in advanced prostate cancer

AstraZeneca and MSD's *Lynparza* (olaparib) has been granted conditional approval in China to treat adult patients with germline or somatic BRCA-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following treatment that included a new hormonal agent (abiraterone, enzalutamide).

In China, prostate cancer is the sixth most prevalent cancer in men, with approximately 115,000 new patients diagnosed each year and about 7% have germline BRCA mutations.[1,2] Prostate cancer patients with these mutations are more likely to have poorer outcomes than those without the mutations.[3] Around 70% of prostate cancer patients in China have advanced disease at the time of diagnosis, and for those with mCRPC, the median survival is less than two years.[4,5]

The approval by China's National Medical Products Administration was based on a subgroup analysis of the PROfound Phase III trial, which showed that *Lynparza* demonstrated a substantial improvement in radiographic progression-free survival (rPFS) and overall survival (OS) versus abiraterone or enzalutamide in men with BRCA1/2 mutations. Continued approval is contingent upon verification and description of clinical benefit in a planned bridging trial with Chinese patients.

Dave Fredrickson, Executive Vice President, Oncology Business Unit, said: "This approval begins a new era of precision medicine for patients in China with advanced prostate cancer who have historically had a poor prognosis and few treatment options. *Lynparza* more than tripled radiographic progression-free survival in the PROfound trial and is the only PARP inhibitor to show an overall survival benefit compared to treatment with new hormonal agents for men with BRCA-mutated metastatic castration-resistant prostate cancer."

Roy Baynes, Senior Vice President and Head of Global Clinical Development, Chief Medical Officer, MSD Research Laboratories, said: "The approval underscores the critical importance of BRCA testing in men with prostate cancer. We are proud to provide a new personalised treatment option for men with this devastating disease in China, and we will continue to collaborate with the Chinese government and healthcare organisations to bring *Lynparza* to patients who need it."

The subgroup analysis from the PROfound Phase III trial showed *Lynparza* reduced the risk of disease progression or death by 78% (based on a hazard ratio [HR] of 0.22, 95% confidence interval [CI] 0.15-0.32; nominal p<0.0001) and improved rPFS to a median of 9.8 months versus 3.0 with abiraterone or enzalutamide in men with mCRPC with BRCA1/2 mutations. In addition, *Lynparza* reduced the risk of death by 37% (HR of 0.63, 95% CI 0.42-0.95) with median OS of 20.1 months versus 14.4 with abiraterone or enzalutamide.

The primary results and OS results from the PROfound Phase III trial were published in *The New England Journal of Medicine*.

Lynparza is approved in the US to treat men with homologous recombination repair gene-mutated (HRRm) mCRPC and in the EU, Japan and several other countries for BRCA-mutated mCRPC patients based on the PROfound Phase III trial. In addition, regulatory reviews are ongoing in other countries around the world.

AstraZeneca and MSD are testing *Lynparza* in additional trials in metastatic prostate cancer, including the ongoing PROpel Phase III trial of *Lynparza* as a 1st-line treatment for patients with mCRPC in combination with abiraterone versus abiraterone alone. Results are anticipated in the second half of 2021.

Metastatic castration-resistant prostate cancer

Prostate cancer is associated with a significant mortality rate.[6] Prostate cancer is often driven by male sex hormones called androgens, including testosterone.[7] In patients with mCRPC, 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.[7] Approximately 10-20% of men with advanced prostate cancer will develop CRPC within five years, and at least 84% of these men will have metastases at the time of CRPC diagnosis.[8] Of men with no metastases at CRPC diagnosis, 33% are likely to develop metastases within two years.[8] Despite advances in treatment for men with mCRPC, five-year survival is low and extending survival remains a key treatment goal.[8]

PROfound

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

The trial was designed to analyse patients with HRR gene mutations in two cohorts: the primary endpoint was rPFS 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 HRR gene mutations (BRCA1/2, ATM and 12 other HRR gene mutations). AstraZeneca and MSD announced in August 2019 that the trial met its primary endpoint of rPFS.

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*.[9-12]

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 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 several 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 (BRCAm) advanced ovarian cancer following response to platinum-based chemotherapy. It is also approved in the US, the EU, and Japan as 1st-line maintenance treatment with bevacizumab for patients with HRD-positive advanced ovarian cancer (BRCAm and/or genomic instability). In addition, *Lynparza* is approved in the US, Japan, and several other countries for germline BRCAm, 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 to treat germline BRCAm metastatic pancreatic cancer. In addition, *Lynparza* is approved in the US for HRR gene-mutated mCRPC (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. 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 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
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Contacts

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