Lynparza combo recommended in the EU for mCRPC

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Lynparza in combination with abiraterone recommended for approval in the EU by CHMP as 1st-line treatment for patients with metastatic castration-resistant prostate cancer

First PARP inhibitor to demonstrate clinical benefit in combination with a new hormonal agent in this setting

AstraZeneca and MSD's *Lynparza* (olaparib) in combination with abiraterone and prednisone or prednisolone has been recommended for marketing authorisation in the European Union (EU) for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) for whom chemotherapy is not clinically indicated.

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency based its positive opinion on results from the PROpel Phase III trial which were published in *NEJM Evidence* in June 2022.

In the trial, *Lynparza* in combination with abiraterone and prednisone or prednisolone, reduced the risk of disease progression or death by 34% versus abiraterone alone (based on a hazard ratio [HR] of 0.66; 95% confidence interval [CI] 0.54-0.81; p<0.0001). Median radiographic progression-free survival (rPFS) was 24.8 months for *Lynparza* plus abiraterone versus 16.6 months for abiraterone alone. Results also showed that *Lynparza* in combination with abiraterone extended median rPFS by almost one year, with a median rPFS of 27.6 months versus 16.4 with abiraterone alone, as assessed by blinded independent central review (BICR).

Updated results also showed a favourable trend in improved overall survival with *Lynparza* plus abiraterone versus abiraterone alone, however the difference did not reach statistical significance at the time of this data cut-off (analysis at 40% data maturity).

Prostate cancer is the most common cancer in men in Europe, with an estimated 473,000 patients diagnosed and 108,000 deaths in 2020.[1-2] Overall survival for patients with mCRPC is approximately three years in clinical trial settings, and even shorter in real-world settings.[3] Approximately half of patients with mCRPC may receive only one line of active treatment, with diminishing benefit of subsequent therapies.[4-9]

Noel Clarke, Urological Surgeon and Professor of Urological Oncology at Manchester's Christie/Salford Royal Hospitals and Manchester University, the PROpel trial joint senior investigator, said: "Patients with metastatic castration-resistant prostate cancer in the European Union have limited treatment options. This form of advanced prostate cancer has a poor prognosis and treatment decisions after initial diagnosis are critical. If approved in the European Union for prostate cancer of this type, olaparib in combination with abiraterone will provide a much-needed new treatment option for the many men with this condition."

Susan Galbraith, Executive Vice President, Oncology R&D, AstraZeneca, said: "With the incidence and mortality of prostate cancer set to double in the coming decades, it is more important than ever that we bring new treatment options to suitable patients at the earliest possible moment in their care. If approved, *Lynparza* in combination with abiraterone and prednisone or prednisolone will represent the first combination of a PARP inhibitor and new hormonal agent available to patients in the European Union."

Eliav Barr, Senior Vice President, Head of Global Clinical Development and Chief Medical Officer, MSD Research Laboratories, said: "While prostate cancer has seen many advances in care in recent decades, for those with mCRPC, new treatment options are urgently needed. We are fully committed to bringing *Lynparza* in combination with abiraterone and prednisone or prednisolone to suitable patients in the European Union as quickly as possible."

Lynparza in combination with abiraterone and prednisone or prednisolone is undergoing Priority Review in the US for the treatment of mCRPC in adult patients based on results from the PROpel Phase III trial, with a decision expected in Q4 2022.

Lynparza is approved in the US based on results from the PROfound Phase III trial as monotherapy for patients with homologous recombination repair (HRR) gene-mutated mCRPC (BRCA-mutated and other HRR gene mutations) who have progressed following prior treatment with enzalutamide or abiraterone; and in the EU, Japan, and China for patients with BRCA-mutated mCRPC who have progressed following prior therapy that included a new hormonal agent.

Notes

Metastatic castration-resistant prostate cancer
Metastatic prostate cancer is associated with a significant mortality rate.[10] Development of prostate cancer is often driven by male sex hormones called androgens, including testosterone.[11]

In patients with mCRPC, their 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.[5] Approximately 10-20% of men with advanced prostate cancer will develop castration-resistant prostate cancer (CRPC) within five years, and at least 84% of these men will have metastases at the time of CRPC diagnosis.[5] Of patients with no metastases at CRPC diagnosis, 33% are likely to develop metastases within two years.[5]

Despite the advances in mCRPC treatment in the past decade with taxane and new hormonal agent (NHA) treatment, there is high unmet need in this population.[5,7,8,12]

PROpel
PROpel is a randomised, double-blind, multi-centre Phase III trial testing the efficacy, safety, and tolerability of *Lynparza* versus placebo when given in addition to abiraterone in men with mCRPC who had not received prior chemotherapy or NHAs in the mCRPC setting.

Men in both treatment groups also receive either prednisone or prednisolone twice daily. The primary endpoint is rPFS and secondary endpoints include overall survival, time to secondary progression or death, and time to first subsequent therapy.

In the PROpel Phase III trial, *Lynparza* is combined with abiraterone, an NHA which targets the androgen receptor (AR) pathway.

AR signalling engages a transcriptional programme that is critical for tumour cell growth and survival in prostate cancer.[13,14] Preclinical models have identified interactions between PARP signalling and the AR pathway which support the observation of a combined anti-tumour effect of *Lynparza* and NHAs, like abiraterone, in both HRR deficient and HRR proficient prostate cancer.[15-17]

The PARP1 protein has been reported to be required for the transcriptional activity of androgen receptors; therefore, inhibiting PARP with *Lynparza* may impair the expression of androgen receptor target genes and enhance the activity of NHAs.[13,16,18] Additionally, it is thought that abiraterone may alter/inhibit the transcription of some HRR genes which may induce HRR deficiency and increase sensitivity to PARP inhibition.[15,17,19,20]

For more information about the trial please visit ClinicalTrials.gov.

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

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 currently approved in a number of countries across multiple tumour types 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 (BRCAm) 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 (in Japan this includes all BRCAm HER2-negative high-risk early breast cancer); for gBRCAm metastatic pancreatic cancer; and HRR gene-mutated metastatic castration-resistant prostate cancer (BRCAm only in the EU and Japan). In China, *Lynparza* is approved for the treatment of BRCA-mutated metastatic castration-resistant prostate cancer as well as a 1st-line maintenance therapy in BRCA-mutated advanced ovarian cancer.

Lynparza, which is being jointly developed and commercialised by AstraZeneca and MSD, has been used to treat over 75,000 patients worldwide. *Lynparza* has a broad clinical trial development programme, 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* (selumetinib), a mitogen-activated protein kinase (MEK) inhibitor, for multiple cancer types.

Working together, the companies will develop *Lynparza* and *Koselugo* and other potential new medicines as monotherapies and as combinations. The companies will also develop *Lynparza* and *Koselugo* in combination with their respective PD-L1 and PD-1 medicines independently.

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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