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Lynparza and *Imfinzi* combination recommended for approval in the EU by CHMP for patients with mismatch repair proficient advanced or recurrent endometrial cancer

Imfinzi also recommended for patients with mismatch repair deficient disease

Recommendation based on DUO-E Phase III results, which showed both regimens demonstrated statistically significant and clinically meaningful improvement in progression-free survival vs. chemotherapy alone

AstraZeneca's *Imfinzi* (durvalumab) and *Lynparza* (olaparib) have been recommended for approval in the European Union (EU) as treatment for certain patients with primary advanced or recurrent endometrial cancer. *Imfinzi* plus chemotherapy as 1st-line treatment followed by *Lynparza* and *Imfinzi* has been recommended for patients with mismatch repair proficient (pMMR) disease. *Imfinzi* plus chemotherapy followed by *Imfinzi* alone has been recommended for patients with mismatch repair deficient (dMMR) disease.

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) based its positive opinion on a prespecified exploratory subgroup analysis by mismatch repair (MMR) status from the DUO-E Phase III trial, which was published in the *Journal of Clinical Oncology* in October 2023.

This analysis showed a reduction in the risk of disease progression or death for pMMR patients in the *Lynparza* and *Imfinzi* arm by 43% (median 15.0 months versus 9.7 months, hazard ratio [HR] 0.57; 95% confidence interval [CI] 0.44-0.73) versus the control arm.[1] Results for dMMR patients showed a reduction in the risk of disease progression or death in the *Imfinzi* arm by 58% (median not reached versus 7.0 months, HR 0.42; 95% CI 0.22-0.80) versus the control arm.[1]

In Europe, endometrial cancer is the fourth most common cancer in women, with nearly 125,000 diagnoses and more than 30,000 deaths in 2022.[2,3] Patients diagnosed at an early stage of disease have a five-year survival rate of approximately 80-90%, but that falls to less than 20% for people with advanced disease.[4,5] There is a significant need for new treatment options, especially for the 70-80% of patients with pMMR disease.[5,6] This recommendation underscores the importance of MMR testing at point of diagnosis, which is well established and widely available.[7,8]

Els Van Nieuwenhuysen, Gynaecological Oncologist at the UZ Leuven, Belgium and trial investigator, said: "Patients with advanced or recurrent endometrial cancer currently have a very poor prognosis, especially those with mismatch repair proficient disease. This recommendation underscores the significant benefit shown with durvalumab as well as with the olaparib and durvalumab combination for patients with both mismatch repair deficient and mismatch repair proficient status. This marks an important step toward improving outcomes for these patients in Europe."

Susan Galbraith, Executive Vice President, Oncology R&D, AstraZeneca, said: "Today's recommendation for approval in the EU recognises the potential of the *Lynparza* and *Imfinzi* combination to provide clinical benefit for patients with endometrial cancer, especially for those with mismatch repair proficient disease who have few available treatments today. If approved, patients in Europe will have a new option for combination treatment that brings the additional benefit of PARP inhibition to immunotherapy."

The safety profiles of both experimental regimens were manageable, well-tolerated and broadly consistent with the known profiles of the individual agents.[1,9,10]

Regulatory submissions for *Imfinzi* and *Lynparza* are currently under review in Japan and several other countries based on the DUO-E trial. *Imfinzi* plus chemotherapy was recently approved for dMMR patients with primary advanced or recurrent endometrial cancer in the US.[11]

Notes

Endometrial cancer
Endometrial cancer is a highly heterogeneous disease that originates in the tissue lining of the uterus and is most common in women who have already been through menopause, with the average age at diagnosis being over 60 years old.[12-15]

The majority of patients with endometrial cancer are diagnosed at an early stage of disease, where the cancer is confined to the uterus.[16] They are typically treated with surgery and/or radiation, and the five-year survival rate is high (approximately 80-90%).[17] Patients with advanced disease (Stage III-IV) usually have a much poorer prognosis, with the five-year survival rate falling to less than 20%.[4] Immunotherapy combined with chemotherapy is emerging as a new standard of care for advanced endometrial cancer, particularly for patients with dMMR disease, who make up approximately 20-30% of all patients.[11,17-20] There remains a high unmet need for treatments for the remaining 70-80% of endometrial cancer patients with pMMR disease.[5,6]

DUO-E
The DUO-E trial (GOG 3041/ENGOT-EN10) is a three-arm, randomised, double-blind, placebo-controlled, multicentre Phase III trial of 1st-line *Imfinzi* (durvalumab) plus platinum-based chemotherapy (carboplatin and paclitaxel) followed by either *Imfinzi* monotherapy or *Imfinzi* plus *Lynparza* (olaparib) as maintenance therapy versus platinum-based chemotherapy alone as a treatment for patients with newly diagnosed advanced or recurrent endometrial cancer.

The DUO-E trial randomised 699 patients with newly diagnosed advanced or recurrent epithelial endometrial carcinoma to receive either *Imfinzi* (1120mg) or placebo, given every three weeks in addition to standard-of-care

carcinoma to receive either *Imfinzi* (1120mg) or placebo, given every three weeks in addition to standard-of-care platinum-based chemotherapy. After 4-6 cycles of chemotherapy, patients (whose disease had not progressed) then received either *Imfinzi* (1500mg) or placebo every four weeks as maintenance, plus 300mg *Lynparza* (300mg BID [2x150mg tablets, twice a day]) or placebo until disease progression.

The dual primary endpoint was progression-free survival (PFS) of each treatment arm versus standard of care. Key secondary endpoints included overall survival (OS), safety and tolerability. The trial continues to assess OS for both *Imfinzi* monotherapy and *Imfinzi* plus *Lynparza* as maintenance therapy in the overall trial population. Mismatch repair (MMR) status, recurrence status and geographic location were stratification factors. The trial was sponsored independently by AstraZeneca and conducted in 253 study locations across 22 countries including the US, Europe, South America and Asia.

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

Imfinzi
Imfinzi (durvalumab) is a human monoclonal antibody that binds to the PD-L1 protein and blocks the interaction of PD-L1 with the PD-1 and CD80 proteins, countering the tumour's immune-evading tactics and releasing the inhibition of immune responses.

Imfinzi is the only approved immunotherapy and the global standard of care in the curative-intent setting of unresectable, Stage III non-small cell lung cancer (NSCLC) in patients whose disease has not progressed after chemoradiation therapy. *Imfinzi* is also approved for the treatment of extensive-stage small cell lung cancer (SCLC) and in combination with a short course of *Imjudo* (tremelimumab) and chemotherapy for the treatment of metastatic NSCLC.

In addition to its indications in lung cancers, *Imfinzi* is approved in combination with chemotherapy (gemcitabine plus cisplatin) in locally advanced or metastatic biliary tract cancer and in combination with *Imjudo* in unresectable hepatocellular carcinoma (HCC). *Imfinzi* is also approved as a monotherapy in unresectable HCC in Japan and the EU.

Since the first approval in May 2017, more than 220,000 patients have been treated with *Imfinzi*. As part of a broad development programme, *Imfinzi* is being tested as a single treatment and in combinations with other anti-cancer treatments for patients with SCLC, NSCLC, bladder cancer, breast cancer, several gastrointestinal cancers and other solid tumours.

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-related (HRR) genes, 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 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* may also help enhance immunogenicity and increase the impact of anti-tumour immune responses.

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 germline BRCA mutation (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; in combination with abiraterone for the treatment of metastatic castration-resistant prostate cancer (mCRPC) when chemotherapy is not clinically indicated (EU only) and for BRCAm mCRPC (US and Japan); and as monotherapy for HRR gene-mutated mCRPC in patients who have progressed on prior NHA treatment (BRCAm only in the EU and Japan). In China, *Lynparza* is approved for the treatment of BRCA-mutated mCRPC as well as 1st-line maintenance treatment with bevacizumab for HRD-positive advanced ovarian cancer.

Lynparza is being jointly developed and commercialised by AstraZeneca and MSD, both as a monotherapy and in combination with other potential medicines. Independently, the companies are developing and will commercialise *Lynparza* in combination with their respective PD-L1 and PD-1 medicines, *Imfinzi* (durvalumab) and *Keytruda* (pembrolizumab). *Lynparza* has been used to treat approximately 140,000 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.

AstraZeneca in immuno-oncology (IO)
AstraZeneca is a pioneer in introducing the concept of immunotherapy into dedicated clinical areas of high unmet medical need. The Company has a comprehensive and diverse IO portfolio and pipeline anchored in immunotherapies designed to overcome evasion of the anti-tumour immune response and stimulate the body's immune system to attack tumours.

AstraZeneca aims to reimagine cancer care and help transform outcomes for patients with *Imfinzi* as monotherapy and in combination with *Imjudo* as well as other novel immunotherapies and modalities. The Company is also exploring next-generation immunotherapies like bispecific antibodies and therapeutics that harness different aspects of immunity to target cancer.

AstraZeneca is boldly pursuing an innovative clinical strategy to bring IO-based therapies that deliver long-term survival to new settings across a wide range of cancer types. With an extensive clinical programme, the Company also champions the use of IO treatment in earlier disease stages, where there is the greatest potential for cure.

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's innovative medicines are sold in more than 125 countries and used by millions of patients worldwide. Please visit astrazeneca.com and follow the Company on social media @AstraZeneca.

Contacts

For details on how to contact the Investor Relations Team, please click here. For Media contacts, click here.

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Adrian Kemp
Company Secretary
AstraZeneca PLC

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