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Camizestrant in combination with a CDK4/6 inhibitor recommended for approval in the EU by CHMP for 1st-line advanced ER-positive breast cancer

Recommendation based on SERENA-6 Phase III trial results which showed combination reduced the risk of disease progression or death by 56% in patients with an emergent ESR1 tumour mutation

If approved, camizestrant has the potential to reshape 1st-line treatment for patients in Europe with this type of advanced breast cancer

AstraZeneca's camizestrant in combination with a cyclin-dependent kinase (CDK) 4/6 inhibitor (palbociclib, ribociclib or abemaciclib) has been recommended for approval in the European Union (EU) for the treatment of adult patients with estrogen receptor (ER)-positive, HER2-negative locally advanced or metastatic breast cancer upon detection of *ESR1* mutation and without disease progression during 1st-line endocrine therapy in combination with a CDK4/6 inhibitor.

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) based its positive opinion on the results from the pivotal SERENA-6 Phase III trial, which were presented at the 2025 American Society of Clinical Oncology (ASCO) Annual Meeting and simultaneously published in *The New England Journal of Medicine.*[1]

In a planned interim analysis, the camizestrant combination reduced the risk of disease progression or death by 56% versus standard-of-care treatment with an aromatase inhibitor (AI) (anastrozole or letrozole) in combination with a CDK4/6 inhibitor (based on a hazard ratio [HR] of 0.44; 95% confidence interval [CI] 0.31-0.60; p<0.00001; median progression-free survival (PFS) 16.0 versus 9.2 months). Data for the key secondary endpoints of time to second disease progression (PFS2) and overall survival (OS) were immature at the time of the interim analysis, however a subsequent pre-planned analysis demonstrated a statistically significant and clinically meaningful PFS2 benefit of 25.7 months versus 19.1 months in favour of the camizestrant combination (HR: 0.63; 95% CI: 0.46-0.86; p = 0.00373) and OS continued to mature in favour of the camizestrant combination (HR: 0.87; 95% CI: 0.57-1.30). The trial will continue to assess OS as a key secondary endpoint.

François-Clément Bidard, MD, PhD, Professor of Medical Oncology at Institut Curie & Versailles University (Paris/Saclay), France, and co-principal investigator for the SERENA-6 trial, said: "This recommendation represents an important step forward for patients with advanced breast cancer in Europe and a milestone in the adoption of new treatment strategies. There is a need for new treatments that delay disease progression in the 1st-line setting, after which the cancer becomes harder to treat, and a patient's quality of life may decline. Through prompt intervention with the camizestrant combination to treat emergence of resistance before it causes disease progression and deterioration of quality of life, we are able to extend the benefit of 1st-line treatment and optimise outcomes."

Susan Galbraith, Executive Vice President, Oncology Haematology R&D, AstraZeneca, said: "This decision from the EU's CHMP is a vote of confidence in SERENA-6, the first pivotal trial to demonstrate the clinical value of monitoring circulating tumour DNA to detect emerging endocrine resistance and guide a change of therapeutic strategy in the 1st-line setting. If approved, camizestrant would be the first and only next-generation oral SERD and complete ER antagonist for use in combination with widely approved CDK4/6 inhibitors in this setting, reinforcing the practice-changing potential of this approach to advance patient outcomes and evolve the clinical landscape."

The safety profile of camizestrant in combination with palbociclib, ribociclib or abemaciclib in the SERENA-6 trial was consistent with the known safety profile of each medicine. No new safety concerns were identified and discontinuations were very low and similar in both arms.[1]

SERENA-6 is the first global, double-blind, registrational Phase III trial to use a circulating tumour DNA (ctDNA)-guided approach to detect the emergence of endocrine resistance and inform a switch in therapy before disease progression. The innovative trial design used ctDNA monitoring via a blood test at the time of routine tumour scans every two to three months to identify patients for early signs of

endocrine resistance via the emergence of *ESR1* mutations. Following detection of an *ESR1* mutation without disease progression, the endocrine therapy of patients was switched to camizestrant from ongoing treatment with an AI, while continuing combination with the same CDK4/6 inhibitor.

The camizestrant combination is approved in the United Arab Emirates and Saudi Arabia in hormone receptor (HR)-positive, HER2-negative advanced breast cancer patients whose tumours have an emergent *ESR1* mutation based on the results of the SERENA-6 Phase III trial.

Regulatory applications for camizestrant in this setting are currently under review in the US, Japan and several other countries.

Notes

HR-positive breast cancer
Breast cancer is the second most common cancer and one of the leading causes of cancer-related deaths worldwide.[2] More than two million patients were diagnosed with breast cancer in 2022, with more than 665,000 deaths globally.[2] While survival rates are high for those diagnosed with early breast cancer, only about 30% of patients diagnosed with or who progress to metastatic disease are expected to live five years following diagnosis.[3]

HR-positive breast cancer, characterised by the expression of estrogen or progesterone receptors, or both, is the most common subtype of breast cancer with 70% of tumours considered HR-positive and HER2-negative.[3] More than 97% of HR-positive breast cancer tumours are ER-positive.[4,5] ERs often drive the growth of HR-positive breast cancer cells.[6]

Globally, approximately 200,000 patients with HR-positive breast cancer are treated with a medicine in the 1st-line setting; most frequently with endocrine therapies that target ER-driven disease, which are often paired with CDK4/6 inhibitors.[7-9] However, resistance to these therapies develops in many patients.[9] Once this occurs, treatment options are limited and survival rates are low with approximately 36% of patients anticipated to live beyond five years after diagnosis.[3,9]

Mutations in the *ESR1* gene are a key driver of endocrine resistance and are associated with poor outcomes, emerging during treatment of the disease and becoming more prevalent as the disease progresses.[10,11] Approximately 30% of patients with endocrine sensitive HR-positive disease develop *ESR1* mutations during 1st-line treatment before disease progression.[7]

The optimisation of endocrine therapy and overcoming resistance to enable patients to continue benefiting from these treatments, as well as identifying new therapies for those who are less likely to benefit, are active areas of focus for breast cancer research.

SERENA-6
SERENA-6 is a Phase III, double-blind, randomised trial evaluating the efficacy and safety of camizestrant in combination with a CDK4/6 inhibitor (palbociclib, ribociclib or abemaciclib) versus treatment with an AI (anastrozole or letrozole) in combination with a CDK4/6 inhibitor (palbociclib, ribociclib or abemaciclib) in patients with HR-positive, HER2-negative advanced breast cancer (patients with either locally advanced disease, or metastatic disease) whose tumours have an emergent *ESR1* mutation.

The global trial enrolled 315 adult patients with histologically confirmed HR-positive, HER2-negative advanced breast cancer, undergoing treatment with an AI in combination with a CDK4/6 inhibitor as 1st-line treatment. The primary endpoint of the SERENA-6 trial is PFS as assessed by investigator, with secondary endpoints including OS, and PFS2 by investigator assessment.

Camizestrant
Camizestrant is an investigational, potent, next-generation oral selective estrogen receptor degrader (SERD) and complete ER antagonist that is currently in Phase III trials for the treatment of HR-positive breast cancer.

AstraZeneca's broad, robust and innovative clinical development programme, including the SERENA-6, SERENA-4, CAMBRIA-1 and CAMBRIA-2 trials, is evaluating the safety and efficacy of camizestrant

when used as a monotherapy or in combination with CDK4/6 inhibitors to address a number of areas of unmet need in HR-positive, HER2-negative breast cancer.

Camizestrant has demonstrated anti-cancer activity across a range of preclinical models, including those with ER-activating mutations. In the SERENA-2 Phase II trial, camizestrant demonstrated a statistically significant and clinically meaningful improvement in PFS versus *Faslodex* (fulvestrant) in the overall trial population, including in patients with *ESR1* tumour mutations irrespective of prior treatment with CDK4/6 inhibitors in patients with ER-positive locally advanced or metastatic breast cancer, previously treated with endocrine therapy. The SERENA-1 Phase I trial demonstrated that camizestrant is well tolerated and has a promising anti-tumour profile when administered alone or in combination with palbociclib, ribociclib and abemaciclib; three widely used CDK4/6 inhibitors.

AstraZeneca in breast cancer
Driven by a growing understanding of breast cancer biology, AstraZeneca is challenging, and redefining, the current clinical paradigm for how breast cancer is classified and treated to deliver even more effective treatments to patients in need - with 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.

With *Enhertu* (trastuzumab deruxtecan), a HER2-directed antibody drug conjugate (ADC), AstraZeneca and Daiichi Sankyo are aiming to improve outcomes in previously treated HER2-positive, HER2-low and HER2-ultralow metastatic breast cancer, and are exploring its potential in earlier lines of treatment and in new breast cancer settings.

In HR-positive breast cancer, AstraZeneca continues to improve outcomes with foundational medicines *Faslodex* and *Zoladex* (goserelin) and aims to reshape the HR-positive space with first-in-class AKT inhibitor, *Truqap*, the TROP-2-directed ADC, *Datroway* (datopotamab deruxtecan) and next-generation oral SERD and potential new medicine camizestrant.

PARP inhibitor *Lynparza* (olaparib) is a targeted treatment option that has been studied in early and metastatic breast cancer patients with an inherited *BRCA* mutation. AstraZeneca with MSD (Merck & Co., Inc. in the US and Canada) continue to research *Lynparza* in these settings. AstraZeneca is also exploring the potential of saruparib, a potent and selective inhibitor of PARP1, in combination with camizestrant in *BRCA*-mutated, HR-positive, HER2-negative advanced breast cancer.

To bring much-needed treatment options to patients with triple-negative breast cancer, an aggressive form of breast cancer, AstraZeneca is collaborating with Daiichi Sankyo to evaluate the potential of *Datroway* alone and in combination with immunotherapy *Imfinzi* (durvalumab).

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/NYSE: AZN) is a global, science-led biopharmaceutical company that focuses on the discovery, development, and commercialisation of prescription medicines in Oncology, Rare Disease, 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.

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