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Update on FDA Advisory Committee vote on camizestrant in combination with a CDK4/6 inhibitor for advanced HR-positive breast cancer

The US Food and Drug Administration's (FDA) Oncologic Drugs Advisory Committee (ODAC) did not reach a majority vote in favor of the benefit risk profile of AstraZeneca's camizestrant in combination with a cyclin-dependent kinase (CDK) 4/6 inhibitor (palbociclib, ribociclib or abemaciclib) for the 1st-line treatment of patients with hormone receptor (HR)-positive, HER2-negative advanced breast cancer whose tumours have an emergent *ESR1* mutation, based on the SERENA-6 Phase III trial. The Committee voted 3 to 6.

In July 2025, the FDA accepted the New Drug Application (NDA) for camizestrant in combination with a CDK4/6 inhibitor based on positive results from the pivotal SERENA-6 Phase III trial presented at the 2025 American Society of Clinical Oncology (ASCO) Annual Meeting and simultaneously published in *The New England Journal of Medicine*.[1] The FDA granted Breakthrough Therapy Designation (BTD) for the camizestrant combination in this setting in May 2025.

The FDA is not bound by the Committee's guidance but takes its advice into consideration. AstraZeneca will continue to work with the FDA as it completes its review of the application.

Kevin Kalinsky, MD, MS, FASCO, Division Director of Medical Oncology, Winship Cancer Institute of Emory University and investigator for the trial, said: "Patients with this specific form of breast cancer are in urgent need of new treatments that delay disease progression. Today's recommendation by the ODAC is disappointing, as new options and innovative treatment strategies which address emerging resistance ahead of disease progression and deterioration in quality of life are needed in the 1st-line setting."

Susan Galbraith, Executive Vice President, Oncology Haematology R&D, AstraZeneca, said: "New innovations and novel treatment strategies that provide benefit to patients are required to drive advances in this 1st-line setting, and so we are disappointed with the mixed outcome of today's ODAC meeting. We strongly believe in the results of the SERENA-6 trial, and are encouraged that the Committee saw camizestrant as a safe and effective potential new medicine. We remain confident in the clinical benefit the combination can bring to patients by changing therapeutic strategy at the earliest opportunity, and are committed to challenging the status quo in the pursuit of innovation that optimises outcomes for patients."

Results from a planned interim analysis of the SERENA-6 Phase III trial showed a highly statistically significant and clinically meaningful 56% reduction in the risk of disease progression or death with the camizestrant combination 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).[1] Median PFS was 16.0 months for patients who switched to the camizestrant combination versus 9.2 months for the comparator arm, and nearly one third (29.7%) of patients in the camizestrant arm showed sustained disease control at 24 months of treatment, versus 5.4% patients in the AI arm.[1]

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, CI: 0.57-1.30). The trial will continue to assess OS as a key secondary endpoint. Additional analyses of patient reported outcome (PRO) measures published in *Annals of Oncology* showed that the camizestrant combination demonstrated consistent benefit in delaying time to deterioration (TTD) in quality of life and reduced the risk of deterioration in patient-reported cancer symptoms and functioning, where the camizestrant combination reduced the risk of deterioration in global health status and quality of life by 46% compared with the AI combination (HR 0.54; 95% CI, 0.34-0.84; nominal p<0.001).[2]

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.

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.

Regulatory applications for camizestrant in this setting are also under review in the EU, 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.[3] More than two million patients were diagnosed with breast cancer in 2022, with more than 665,000 deaths globally.[3] In the US, breast cancer is the most common cancer in women, with more than 300,000 new cases of the disease diagnosed annually, and more than 42,000 deaths.[4] 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.[5]

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.[5] Estrogen receptor (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] In the US, approximately 37,000 patients with HR-positive metastatic breast cancer are treated with these therapies in the 1st-line setting.[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.[5,9]

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 Diseases, and BioPharmaceuticals, including Cardiovascular, Renal &

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Contacts
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