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This announcement contains inside information

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Camizestrant demonstrated highly statistically significant and clinically meaningful improvement in progression-free survival in 1st-line advanced HR-positive breast cancer with an emergent *ESR1* tumour mutation in SERENA-6 Phase III trial

First and only next-generation oral SERD and complete ER antagonist to demonstrate 1st-line benefit in combination with widely approved CDK4/6 inhibitors

Positive high-level results from a planned interim analysis of the SERENA-6 Phase III trial showed that AstraZeneca's camizestrant in combination with a cyclin-dependent kinase (CDK) 4/6 inhibitor (palbociclib, ribociclib or abemaciclib) demonstrated a highly statistically significant and clinically meaningful improvement in the primary endpoint of progression-free survival (PFS). The trial evaluated switching to the camizestrant combination versus continuing standard-of-care treatment with an aromatase inhibitor (AI) (anastrozole or letrozole) in combination with a CDK4/6 inhibitor in the 1st-line treatment of patients with hormone receptor (HR)-positive, HER2-negative advanced breast cancer whose tumours have an emergent *ESR1* mutation.

The key secondary endpoints of time to second disease progression (PFS2) and overall survival (OS) were immature at the time of this interim analysis. However, the camizestrant combination demonstrated a trend toward improvement in PFS2. The trial will continue as planned to further assess key secondary endpoints.

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 novel trial design used ctDNA monitoring at the time of routine tumour scan visits to identify patients for early signs of endocrine resistance and 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.

François-Clément Bidard, MD, PhD, Professor of Medical Oncology at Institut Curie & UVSQ/Université Paris-Saclay, France, and co-principal investigator for the trial, said: "Patients have an urgent need for new treatments that delay disease progression on 1st-line endocrine-based therapies. The results from SERENA-6 show that switching from an aromatase inhibitor to camizestrant in combination with any of the three CDK4/6 inhibitors after emergence of an *ESR1* mutation delays progression of disease and extends the benefit of 1st-line treatment, representing an important step forward for patients, and a potential shift in clinical practice."

Susan Galbraith, Executive Vice President, Oncology Haematology R&D, AstraZeneca, said: "These impressive results demonstrate the versatility of camizestrant in combination with all the widely approved CDK4/6 inhibitors to provide a well-tolerated new potential treatment option in the first-line setting for the one in three patients with HR-positive, HER2-negative advanced breast cancer whose tumours develop *ESR1* mutations during treatment with an aromatase inhibitor in combination with a CDK4/6 inhibitor. This critical read-out moves us one step closer to realising the potential of camizestrant to become a new standard-of-care as we look to shift the treatment paradigm and establish this new endocrine therapy backbone in HR-positive breast cancer."

The safety profile of camizestrant in combination with palbociclib, ribociclib or abemaciclib in SERENA-6 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.

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 estrogen receptor (ER)-driven disease, which are often paired with CDK4/6 inhibitors.[1-3] However, resistance to CDK4/6 inhibitors and current endocrine therapies develops in many patients with advanced disease.[3]

Mutations in the *ESR1* gene are a key driver of endocrine resistance and are widely tested for in clinical practice.[4,5] These mutations develop during treatment of the disease, becoming more prevalent as the disease progresses and are associated with poor outcomes.[4,5] Approximately 30% of patients with endocrine sensitive HR-positive disease develop *ESR1* mutations during 1st-line treatment without disease progression.[1]

Data will be presented at a forthcoming medical meeting and shared with global regulatory authorities.

Notes

HR-positive breast cancer
Breast cancer is the second most common cancer and one of the leading causes of cancer-related deaths worldwide.[6] More than two million patients were diagnosed with breast cancer in 2022, with more than 665,000 deaths globally.[6] 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.[7]

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.[7] ERs often drive the growth of HR-positive breast cancer cells.[8]

Once resistance to the treatment of HR-positive breast cancer with CDK4/6 inhibitors and current endocrine therapies occurs, treatment options are limited and survival rates are low with 35% of patients anticipated to live beyond five years after diagnosis.[3,7,9] The optimisation of endocrine therapy and overcoming resistance to enable patients to

years after diagnosis.[2,3] 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 other agents to address a number of areas of unmet need in this specific type of 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 PFS benefit versus *Faslodex* (fulvestrant) irrespective of *ESR1* mutation status or 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. Combinations with other agents are ongoing in SERENA-1.

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 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* (capivasertib), 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 and to explore its potential in earlier disease. AstraZeneca is also exploring the efficacy and safety 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/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
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