News Release

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Camizestrant significantly delayed disease progression in advanced ER-positive breast cancer, adding at least 3.5 months benefit versus *Faslodex*

SERENA-2 Phase II trial results presented at SABCS 2022 show potential of camizestrant as next-generation SERD in endocrine therapy

Detailed results from the SERENA-2 Phase II trial showed AstraZeneca's next-generation oral selective estrogen receptor degrader (ngSERD) camizestrant demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS) at both 75mg and 150mg dose levels versus *Faslodex* (fulvestrant) 500mg in post-menopausal patients with estrogen receptor (ER)-positive locally advanced or metastatic breast cancer, previously treated with endocrine therapy. Results will be presented today in an oral presentation at the 2022 San Antonio Breast Cancer Symposium (SABCS).

In the overall population, camizestrant significantly reduced the risk of disease progression or death by 42% at a 75mg dose (based on a hazard ratio [HR] of 0.58, 90% confidence interval [CI] 0.41-0.81; p=0.0124; median PFS of 7.2 versus 3.7 months) and 33% at a 150mg dose (HR 0.67, 90% CI 0.48-0.92; p=0.0161; median PFS of 7.7 versus 3.7 months) compared to *Faslodex,* the current SERD standard of care.

Among the prespecified subgroup of patients with ESR1 mutations – comprising 36.7% of the trial population – camizestrant showed a 67% reduction in the risk of disease progression or death at a 75mg dose (HR 0.33, 90% CI 0.18-0.58; median PFS of 6.3 versus 2.2 months) and a 45% reduction at a 150mg dose (HR 0.55, 90% CI 0.33-0.89; median PFS of 9.2 versus 2.2 months) compared to *Faslodex*. Efficacy was also seen in patients without a detectable ESR1 mutation, with a 22% and 24% reduction in the risk of disease progression or death (HR 0.78, 90% CI 0.50-1.22 and HR 0.76, 90% CI 0.48-1.20) respectively for the 75mg and 150mg dose levels.

A clinically meaningful PFS benefit was also observed across other prespecified subgroups, including in patients previously treated with prior cyclin-dependent kinase (CDK) 4/6 inhibitors, those with lung and/or liver metastases and those with ER-driven disease.

Mafalda Oliveira, MD, PhD, Vall d'Hebron Hospital and Vall d'Hebron Institute of Oncology in Barcelona, Spain, and lead investigator for the SERENA-2 Phase II trial, said: "These data reflect an important step toward a potential new treatment option for patients with advanced ER-positive disease. Based on the SERENA-2 results, camizestrant was at both doses and significantly improved patient outcomes, nearly doubling median progression-free survival in this setting compared with the current SERD standard of care."

Cristian Massacesi, Chief Medical Officer & Oncology Chief Development Officer, Oncology R&D, AstraZeneca, said: "SERENA-2 showed a meaningful improvement over fulvestrant, demonstrating the potential of camizestrant, our next-generation SERD, to optimise outcomes for patients with advanced ER-driven breast cancer, irrespective of ESR1 mutation status and prior treatment with CDK4/6 inhibitors. Our focus on bringing new medicines to patients across

the breast cancer spectrum is unwavering and we look forward to additional findings from our ongoing Phase III development programme for camizestrant including SERENA-4 and SERENA-6."

Summary of results: SERENA-2

Efficacy measure	**Camizestrant (75mg)**	**Camizestrant (150mg)**	***Faslodex* (500mg)**
Primary endpoint			
Overall population (n)	74	73	73
Median PFS (months)	7.2	7.7	3.7
Adjusted HR (90% CI)	0.58 (0.41-0.81)	0.67 (0.48-0.92)	-
P-value	0.0124*	0.0161*	-
Prespecified sub-populations of interest			
ESR1m detected (n)	22	26	35
Median PFS (months)	6.3	9.2	2.2
Adjusted HR (90% CI)	0.33 (0.18-0.58)	0.55 (0.33-0.89)	-
ESR1m not detected (n)	51	46	37
Median PFS (months)	7.2	5.8	7.2
Adjusted HR (90% CI)	0.78 (0.50-1.22)	0.76 (0.48-1.20)	-
Prior treatment with CDK4/6 inhibitors (n)	38	37	37
Median PFS (months)	5.5	3.8	2.1
Adjusted HR (90% CI)	0.49 (0.31-0.75)	0.68 (0.44-1.04)	-
Presence of lung and/or liver metastasis (n)	43	43	43
Median PFS (months)	7.2	5.6	2.0
Adjusted HR (90% CI)	0.43 (0.28-0.65)	0.55 (0.37-0.82)	-
Evidence of ER-driven disease (n)	50	53	53
Median PFS (months)	7.4	12.0	3.2
Adjusted HR (90% CI)	0.53 (0.35-0.79)	0.58 (0.39-0.86)	-

*Statistically significant; HR, hazard ratio (adjusted for stratification factors [prior use of CDK4/6i and presence of lung and/or liver metastases]); CI, confidence interval; PFS, progression free survival; ESR1m, ESR1 mutation.

Its safety profile was consistent with that observed in previous trials with no new safety signals identified. The most frequent treatment-emergent adverse events (TEAEs) were photopsia (12.2%, 24.7%, 35.0% and 0%) and bradycardia (5.4%, 26.0%, 40.0% and 0%), for 75mg, 150mg or 300mg camizestrant or fulvestrant, respectively, all of which were Grade 1 or 2. TEAEs at Grade 3 or higher occurred in 1.4%, 2.7%, 5.0% and 1.4% of patients in the 75mg, 150mg and 300mg camizestrant or fulvestrant arms, respectively, with only two patients in the 75mg camizestrant arm and no patients in the 150mg, 300mg camizestrant or fulvestrant arms discontinuing therapy due to TEAEs.

AstraZeneca has a broad clinical development programme for camizestrant in advanced breast cancer. The SERENA-6 Phase III trial is assessing camizestrant in combination with CDK4/6 inhibitors for the 1st-line treatment of patients with HR-positive metastatic breast cancer who have developed detectable ESR1 mutations during treatment with aromatase inhibitors, and the SERENA-4 Phase III trial is evaluating camizestrant plus palbociclib (CDK4/6 inhibitor) for the 1st-line treatment of patients with HR-positive, locally advanced or

metastatic breast cancer. The indication sought for SERENA-6 has been granted Fast Track Designation by the US Food and Drug Administration.

Notes

Hormone Receptor (HR)-positive breast cancer

Breast cancer is the most common cancer and is one of the leading causes of cancer-related deaths worldwide.[1] More than two million patients were diagnosed with breast cancer in 2020, with nearly 685,000 deaths globally.[1]

HR-positive breast cancer (expressing estrogen or progesterone receptors, or both) is the most common subtype of breast cancer with approximately 70% of breast cancer tumours considered HR-positive and HER2-low or negative.[2]

The growth of HR-positive breast cancer cells is often driven by estrogen receptors (ER),[3] and endocrine therapies that target ER-driven disease are widely used as 1st-line treatment in the advanced setting, and often paired with cyclin-dependent kinase (CDK) 4/6 inhibitors.[4,5] However, resistance to CDK4/6 inhibitors and current endocrine therapies develops in many patients with advanced disease.[5] Once this occurs, the treatment options are limited[5] – with chemotherapy being the current standard of care[6] – and survival rates are low with 30% of patients anticipated to live beyond five years after diagnosis.[2]

Optimising endocrine therapy and overcoming resistance for patients with ER-driven disease at all stages of treatment as well as identifying new therapies for those who no longer have ER-driven disease are active areas of focus for breast cancer research.

SERENA-2

SERENA-2 is a randomised, open-label, parallel group, multicentre Phase II trial evaluating camizestrant at several dose levels compared to *Faslodex* in advanced ER-positive, HER2-negative breast cancer. The primary endpoints are PFS defined by response evaluation criteria in solid tumours (RECIST) version 1.1 for 75mg camizestrant versus *Faslodex* and for 150mg camizestrant versus *Faslodex*. 240 patients were randomised to receive camizestrant or *Faslodex* until disease progression. Secondary endpoints include safety, objective response rate and clinical benefit rate at 24 weeks.

Camizestrant

Camizestrant is a potent, next-generation oral SERD and pure ERα antagonist, that has demonstrated anti-cancer activity across a range of preclinical models, including those with ER-activating mutations.

AstraZeneca has a broad clinical development programme 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 HR-positive breast cancer.

In addition to SERENA-2 and the ongoing SERENA-4 and SERENA-6 trials, the SERENA-1 Phase I trial demonstrated that camizestrant has a promising anti-tumour profile when administered alone or in combination with palbociclib, a CDK4/6 inhibitor. Combinations with other agents are ongoing in SERENA-1.

AstraZeneca in breast cancer
Driven by a growing understanding of breast cancer biology, AstraZeneca is starting to challenge, and redefine, 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 and HER2-low 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* (fulvestrant) and *Zoladex* (goserelin) and aims to reshape the HR-positive space with ngSERD and potential new medicine camizestrant as well as a potential first-in-class AKT kinase inhibitor, capivasertib. AstraZeneca is also collaborating with Daiichi Sankyo to explore the potential of TROP2-directed ADC, datopotamab deruxtecan, in this setting.

PARP inhibitor *Lynparza* (olaparib) is a targeted treatment option that has been studied in early and metastatic breast cancer 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.

To bring much-needed treatment options to patients with triple-negative breast cancer, an aggressive form of breast cancer, AstraZeneca is evaluating the potential of datopotamab deruxtecan alone and in combination with immunotherapy *Imfinzi* (durvalumab), capivasertib in combination with chemotherapy, and *Imfinzi* in combination with other oncology medicines, including *Lynparza* and *Enhertu*.

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 operates in over 100 countries and its innovative medicines are used by millions of patients worldwide. Please visit astrazeneca.com and follow the Company on Twitter @AstraZeneca.

Contacts

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

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