News Release

Regulatory News Service

8 December 2022 13:30 GMT

Capivasertib plus *Faslodex* reduced the risk of disease progression or death by 40% versus *Faslodex* in advanced HR-positive breast cancer

CAPItello-291 Phase III trial results presented at SABCS 2022 show potential of capivasertib as first-in-class AKT inhibitor

Detailed results from the CAPItello-291 Phase III trial showed AstraZeneca's capivasertib in combination with *Faslodex* (fulvestrant) demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS) versus placebo plus *Faslodex* in patients with hormone receptor (HR)-positive, HER2-low or negative, locally advanced or metastatic breast cancer, following recurrence or progression on, or after, endocrine therapy (with or without a CDK4/6 inhibitor).[1] Results will be presented today in an oral presentation at the 2022 San Antonio Breast Cancer Symposium (SABCS).

Results showed capivasertib in combination with *Faslodex* demonstrated a 40% reduction in the risk of disease progression or death versus placebo plus *Faslodex* in the overall trial population (based on a hazard ratio [HR] of 0.60, 95% confidence interval [CI] 0.51-0.71; p=<0.001; median 7.2 versus 3.6 months).[1] In the AKT pathway biomarker-altered population, capivasertib plus *Faslodex* reduced the risk of disease progression or death by 50% versus placebo plus *Faslodex* (HR of 0.50, 95% CI 0.38-0.65; p=<0.001; median 7.3 versus 3.1 months).[1] Alterations within the AKT pathway (PI3K/AKT/PTEN) occur frequently in breast cancer, affecting up to 50% of patients with advanced HR-positive breast cancer.[2-4]

Nicholas Turner, MD, PhD, Professor of Molecular Oncology at The Institute of Cancer Research, London, and The Royal Marsden NHS Foundation Trust, London, UK, and principal investigator in the CAPItello-291 Phase III trial, said: "These data demonstrate the practice-changing potential of capivasertib as a new treatment option for patients with advanced HR-positive breast cancer. Critically, this potentially first-in-class treatment has shown it delays disease progression for those who have progressed on, or become resistant to, endocrine therapies and CDK4/6 inhibitors."

Susan Galbraith, Executive Vice President, Oncology R&D, AstraZeneca, said: "Capivasertib brings important progress to an area with persistent treatment gaps as the first therapy of its kind shown to be effective in a Phase III trial in patients with advanced HR-positive, HER2-low or negative breast cancer. We believe these results which showed benefit in all-comers and biomarker positive populations can reshape HR-positive breast cancer treatment, and that capivasertib can become an important new option for patients."

Summary of results: CAPItello-291[1]

	Capivasertib plus *Faslodex* n=355	**Placebo plus *Faslodex* n=353**
Median PFS in overall population (months)	7.2	3.6

HR (95% CI)	0.60 (0.51-0.71)	
p-value	p=<0.001	
Median PFS in the biomarker-altered population (months)	7.3	3.1
HR (95% CI)	0.50 (0.38-0.65)	
p-value	p=<0.001	
ORR in overall population	22.9%	12.2%
ORR in biomarker-altered population	28.8%	9.7%

HR, hazard ratio; CI, confidence interval; PFS, progression-free survival; ORR, objective response rate

Confirmed objective response rate (ORR) was 22.9% for the capivasertib plus *Faslodex* arm versus 12.2% for the placebo plus *Faslodex* arm in the overall trial population, and 28.8% versus 9.7%, respectively, in the biomarker-altered population.[1] Although the overall survival (OS) data were immature at the time of the analysis, early data are encouraging.[1] The trial will continue to assess OS as a key secondary endpoint.

The safety profile of capivasertib plus *Faslodex* was similar to that observed in previous trials evaluating this combination.[1] In the overall trial population, the most frequent any grade adverse events (AEs) with capivasertib plus *Faslodex* occurring in 20% or more of patients were diarrhoea (72.4%), nausea (34.6%), rash (group term including rash, rash macular, maculo-papular rash, rash papular and rash pruritic; 38%) fatigue (20.8%) and vomiting (20.6%).[1] The most frequent Grade 3 or higher AEs occurring in 5% or more of patients were diarrhoea (9.3%) and rash (12.1%).[1]

Notes

HR-positive breast cancer

Breast cancer is the most common cancer and is one of the leading causes of cancer-related deaths worldwide.[5] More than two million patients were diagnosed with breast cancer in 2020, with nearly 685,000 deaths globally.[5]

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.[6]

The growth of HR-positive breast cancer cells is often driven by estrogen receptors (ER),[7] 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.[8,9] However, resistance to CDK4/6 inhibitors and current endocrine therapies develops in many patients with advanced disease.[9] Once this occurs, treatment options are limited[9] – with chemotherapy being the current standard of care[10] – and survival rates are low with 30% of patients anticipated to live beyond five years after diagnosis.[6]

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.

CAPItello-291
CAPItello-291 is a Phase III, double-blind, randomised trial that is part of a larger clinical programme focused on capivasertib, an investigational AKT (serine/threonine kinase) inhibitor. CAPItello-291 is evaluating the efficacy of capivasertib in combination with *Faslodex* versus placebo plus *Faslodex* for the treatment of locally advanced (inoperable) or metastatic HR-positive, HER2-low or negative breast cancer.

The global trial enrolled 708 adult patients with histologically confirmed HR-positive, HER2-low or negative breast cancer whose disease has recurred or progressed during or after aromatase inhibitor therapy, with or without a CDK4/6 inhibitor, and up to one line of chemotherapy for advanced disease. The trial has dual primary endpoints of PFS in the overall patient population and in a population of patients whose tumours have qualifying alterations in the AKT pathway (PIK3CA, AKT1 or PTEN genes). In the trial, approximately 40% of tumours had these alterations.

Capivasertib
Capivasertib is an investigational oral treatment currently in Phase III trials for the treatment of multiple subtypes of breast cancer, prostate cancer and a Phase II trial for haematologic malignancies. A potent, selective adenosine triphosphate (ATP)-competitive inhibitor of all three AKT isoforms (AKT1/2/3), capivasertib is being evaluated as a monotherapy and in combination with existing therapies in tumours harbouring alterations in the AKT pathway (PI3K/AKT/PTEN), and in tumours reliant on signalling via this pathway for survival. Capivasertib 400 mg is administered twice daily according to an intermittent dosing schedule of four days on and three days off. This was chosen in early phase trials based on tolerability and the degree of target inhibition.

The capivasertib clinical research programme is investigating the safety and efficacy of capivasertib when used alone and in combination with established treatment regimens.

Capivasertib was discovered by AstraZeneca subsequent to a collaboration with Astex Therapeutics (and its collaboration with the Institute of Cancer Research and Cancer Research Technology Limited).

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 next-generation SERD 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
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