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Update on the CAPItello-290 Phase III trial for *Truqap* plus chemotherapy in advanced or metastatic triple-negative breast cancer

The CAPItello-290 Phase III trial for *Truqap* (capivasertib) in combination with paclitaxel in patients with locally advanced (inoperable) or metastatic triple-negative breast cancer (TNBC) did not meet the dual primary endpoints of improvement in overall survival (OS) versus paclitaxel in combination with placebo in either the overall trial population or in a subgroup of patients with tumours harbouring specific biomarker alterations (PIK3CA, AKT1 or PTEN).

Breast cancer is the second most common cancer and one of the leading causes of cancer-related deaths worldwide.[1] While some breast cancers may test positive for estrogen receptors, progesterone receptors or overexpression of human epidermal growth factor receptor 2 (HER2), TNBC is defined as negative for all three.[2] In the 1st-line setting, approximately 59,000 patients with TNBC are treated with a medicine.[3] Collectively, mutations in PIK3CA, AKT1 and alterations in PTEN affect approximately 35% of patients with TNBC.[4]

Peter Schmid, MD, Barts Cancer Institute, London, UK, and principal investigator for the trial said: "Despite modest advances, triple-negative breast cancer remains one of the most challenging forms of disease to treat due to the lack of known actionable biomarker targets, and chemotherapy-based regimens continue to be the mainstay of treatment. While the CAPItello-290 trial results have not shown what we hoped, they provide important information to further understand this aggressive form of breast cancer where patients are in urgent need of new treatments."

Susan Galbraith, Executive Vice President, Oncology R&D, AstraZeneca, said: "We are committed to advancing science for patients in some of the most challenging cancers, including this heterogeneous subtype of breast cancer. While we are disappointed in the CAPItello-290 outcome, these results will further our understanding of the role of the PI3K/AKT pathway in breast cancer as we continue our clinical research across the *Truqap* clinical development programme and across our pipeline."

The safety profile of *Truqap* in combination with paclitaxel in CAPItello-290 was broadly consistent with the known safety profile of each medicine with no new safety concerns identified. Data will be shared in due course.

Truqap is currently being evaluated in Phase III trials for the treatment of breast cancer (CAPItello-292) and prostate cancer (CAPItello-280 and CAPItello-281) in combination with established treatments.

Notes

Triple-negative breast cancer
1st-line treatment for advanced or metastatic TNBC usually consists of chemotherapy alone or in combination with an immunotherapy - options generally associated with response rates between 30 to 50%.[2,5,6] Among patients with tumours that do respond to initial treatment, disease progression is common and rapid, often occurring within two years.[2,6-8] The average overall survival of patients living with advanced or metastatic TNBC is 12 to 18 months, with only about 14% of patients living five years following diagnosis.[9,10]

CAPItello-290
CAPItello-290 is a Phase III, double-blind, randomised trial evaluating the efficacy and safety of *Truqap* in combination with paclitaxel versus placebo in combination with paclitaxel in the 1st-line treatment of patients with locally advanced (inoperable) or metastatic TNBC.

The global trial enrolled 923 adult patients with histologically confirmed locally advanced or metastatic TNBC. The trial has dual primary endpoints of OS in the overall patient population and in a population of patients whose tumours have qualifying alterations in the PI3K/AKT pathway (PIK3CA, AKT1 or PTEN genes).

Truqap
Truqap is a first-in-class, potent, adenosine triphosphate (ATP)-competitive inhibitor of all three AKT isoforms (AKT1/2/3). *Truqap* 400mg 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.

Truqap is approved in the US, Japan and several other countries for the treatment of adult patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer with one or more biomarker alterations (PIK3CA, AKT1 or PTEN) following recurrence or progression on or after an endocrine-based regimen based on the results from the CAPItello-291 trial. *Truqap* is also approved in Australia for the treatment of adult patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer following recurrence or progression on or after an endocrine based regimen based on these trial results.

Truqap is currently being evaluated in Phase III trials for the treatment of breast cancer (CAPItello-292) and prostate cancer (CAPItello-280 and CAPItello-281) in combination with established treatments.

Truqap 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 antibody drug conjugate (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* and *Zoladex* (goserelin) and aims to reshape the HR-positive space with first-in-class AKT inhibitor, *Truqap*, and next-generation SERD and potential new medicine camizestrant. 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 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.

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), 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 social media @AstraZeneca.

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

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Adrian Kemp
Company Secretary
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