Health Technology Briefing
July 2023

Capivasertib with paclitaxel for previously untreated locally advanced or metastatic triple-negative breast cancer

Company/Developer	AstraZeneca UK Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 27283	NICE TSID: 10555	UKPS ID: 670211

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Capivasertib with paclitaxel is currently in clinical development for previously untreated locally advanced (inoperable) or metastatic triple-negative breast cancer (TNBC). TNBC is a rare form of breast cancer where the tumour cells do not have receptors for oestrogen, progesterone, or the human epidermal growth factor receptor 2 (HER2) protein. Symptoms of TNBC include: a new lump or thickening in the breast or armpit, a change in size, shape or feel of the breast and skin changes in the breast. Established risk factors of breast cancer include age, early onset of menstruation, late menopause, older age at first completed pregnancy, and a family history. There is a need for novel therapies as treatment options for TNBC are limited to sequential chemotherapy which is often associated with short-lived benefits and higher susceptibility to resistance.

Capivasertib is administered orally in patients. It inhibits specific proteins (AKT1/2/3) that are associated with breast cancer and the PIK3CA/AKT/PTEN pathway which is frequently activated in cancers. If licensed, capivasertib in combination with paclitaxel will offer an additional treatment option for patients with TNBC.

Proposed Indication

Adults with previously untreated locally advanced (inoperable) or metastatic triple-negative breast cancer (TNBC).[1]

Technology

Description

Capivasertib (AZD5363) is an oral, potent, selective adenosine triphosphate competitive pan-AKT kinase inhibitor.[2] AKT kinases, which include AKT1, AKT2, and AKT3, are key intermediates of signalling pathways that regulate cellular processes controlling cell size/growth, proliferation, survival, glucose metabolism, genome stability, and neo-vascularisation.[3,4] Hence, AKT is a critical protein kinase that drives cancer proliferation, modulates metabolism, and is activated by C-terminal phosphorylation.[5] Capivasertib prevents substrate phosphorylation by AKT and down-regulates the phosphorylation levels of AKT downstream substrates GSK3β and PRAS40 in many cancer cells.[6] As a novel pyrrolopyrimidine-derived compound, Capivasertib inhibits all AKT isoforms (AKT1, AKT2, and AKT3).[6]

In the phase III clinical trial (CAPItello-290, NCT03997123), patients were randomised to 400mg capivasertib orally twice daily (days 2–5, 9–12 and 16–19) or placebo with paclitaxel 80 mg/m^2 intravenous (days 1, 8 and 15) every 28 days.[7]

Key Innovation

There is a need for novel therapies as treatment options for TNBC are limited to sequential chemotherapy, which is often associated with short-lived benefits and susceptibility to resistance.[8] The PI3K/AKT signalling pathway is frequently activated in TNBC through activating mutations in PIK3CA or AKT1 and/or inactivating alterations in PTEN.[7] The prevalence of TNBC patients with tumours harbouring PIK3CA/AKT1/PTEN alterations is reported to be in the range of 23% to 41%.[9,10] Previous studies have shown that the presence of AKT inhibitor with first-line paclitaxel yields significantly longer progression-free survival and overall survival among patients with advanced TNBC.[7] If licensed, capivasertib in combination with paclitaxel will offer an additional treatment option for patients with locally advanced (inoperable) or metastatic TNBC.

Regulatory & Development Status

Capivasertib does not currently have marketing authorisation in the EU/UK for any indication.

Capivasertib is in phase II and III clinical development for the following indications:[11]

- HR+/HER- locally advanced unresectable or metastatic breast cancer
- Relapsed or refractory B-cell non-Hodgkin lymphoma
- Prostate cancer
- Endometrial cancer
- Meningioma

Patient Group

Disease Area and Clinical Need

Breast cancer occurs when abnormal cells in the breast grow and divide in an uncontrolled way and eventually form a tumour.[12] TNBC is a rare form of breast cancer where the tumour cells do not have

receptors for the hormones oestrogen and progesterone, or the human epidermal growth factor receptor 2 (HER2) protein. Some women with TNBC also have a breast cancer type 1 (BRCA1) gene fault. BRCA1 is one of the gene faults that can increase the risk of breast cancer within families. Symptoms of TNBC include: a new lump or thickening in the breast or armpit, a change in size, shape or feel of the breast and skin changes in the breast.[13] Established risk factors of breast cancer include age, early onset of menstruation, late menopause, older age at first completed pregnancy, and a family history.[14] Locally advanced cancer is when the cancer has grown outside of its original site but has not spread to other parts of the body and is incurable. Metastatic cancer occurs when the cancer has spread to other areas of the body and may or may not be advanced.[15]

Breast cancer is the most common cancer in the UK.[16] The age standardised incidence rate of breast cancer in England is 375 and 55,545 per 100,000 amongst males and females respectively.[17] For patients diagnosed between 2013 and 2017, followed up to 2018, the 1-year and 5-year survival rates for all stages of breast cancer were 95.8% and 85% (age-standardised) respectively. For stage 4 breast cancer, 1-year survival rate of 66% and 5-year survival rate of 26.2% was reported.[18] In England (2021-22), there were 244,374 finished consultant episodes (FCEs) and 240,790 admissions for malignant neoplasm of breast (ICD-10 code C50), which resulted in 218,006 day cases and 60,220 FCE bed days.[19] Based on estimates that around 15% of breast cancer cases are the TNBC subtype.[16] It can be approximated that there were 36,656 FCEs and 36,119 admissions specifically for TNBC, which results in 32,701 day cases and 9,033 FCE bed days.

Recommended Treatment Options

Chemotherapy is the main treatment for advanced TNBC, and the National Institute for Health and Care Excellence (NICE) currently recommends the following therapy:[20]

- Atezolizumab with nab-paclitaxel for treating triple-negative, unresectable, locally advanced or metastatic breast cancer in adults whose tumours express programmed death-ligand 1 (PD-L1) at a level of 1% or more and who have not had previous chemotherapy for metastatic disease.

Clinical Trial Information

Trial	**CAPItello-290,** NCT03997123; A Phase III Double-blind Randomised Study Assessing the Efficacy and Safety of Capivasertib/+Paclitaxel vs Placebo+Paclitaxel as First-line Treatment for Patients With Locally Advanced (Inoperable) or Metastatic TNBC **Phase III**- Active, not recruiting **Location(s)**: 9 EU countries, UK, USA, Canada, and other countries **Primary completion date**: October 2023
Trial Design	Randomised, parallel assignment, double-blind
Population	N=922; all adults aged 18+; histologically confirmed TNBC from most recently collected tumour tissue sample
Intervention(s)	• Capivasertib 400mg orally twice daily given on an intermittent weekly dosing schedule. Dosed on Days 2 to 5 of Weeks 1, 2 and 3 followed by 1 week off-treatment within each 28-day treatment cycle
Comparator(s)	Matched placebo and paclitaxel

Outcome(s)	Primary outcome: • Overall Survival (OS) [Time frame: The time from date of randomisation to the date of death due to any cause up to approximately 42 months] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of capivasertib is currently unknown.

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Pembrolizumab for neoadjuvant and adjuvant treatment of triple-negative early or locally advanced breast cancer (TA851). December 2022.
- NICE technology appraisal. Pembrolizumab plus chemotherapy for untreated, triple-negative, locally recurrent unresectable or metastatic breast cancer (TA801). June 2022.
- NICE technology appraisal. Atezolizumab with nab-paclitaxel for untreated PD-L1-positive, locally advanced or metastatic, triple-negative breast cancer (TA639). July 2020.
- NICE guideline. Early and locally advanced breast cancer: diagnosis and management (NG101). June 2023.
- NICE clinical guideline. Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer (CG164). November 2019.
- NICE clinical guideline. Advanced breast cancer: diagnosis and treatment (CG81). August 2017

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

Other Guidance

- European School of Oncology (ESO)-European Society for Medical Oncology (ESMO) Advanced Breast Cancer (ABC) Clinical Practice. 5th ESO-ESMO International Consensus Guidelines for ABC (ABC 5). 2020.[21]
- Insights: Breast Cancer, Version 4.2023 National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. 2023.[22]

Additional Information

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