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Health Technology Briefing
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Capivasertib with fulvestrant for HR+/HER2- locally advanced or metastatic breast cancer

Company/Developer	AstraZeneca UK Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 29683	NICE TSID: 10575	UKPS ID: 666721

Licensing and Market Availability Plans

Currently in phase III clinical trials

Summary

Capivasertib with fulvestrant is in development for the treatment of patients with locally advanced (inoperable) or metastatic Hormone Receptor-Positive (HR+) and Human Epidermal growth factor Receptor 2-Negative (HER2-) breast cancer. A locally advanced breast cancer is stage 3, where cancer has spread from the breast to areas close to the breast or to the chest wall. Metastatic breast cancer is stage 4, where the cancer has spread to other parts of the body. HR+ breast cancer has either or both the oestrogen and progesterone sex hormone receptors (receptors are proteins within or on body cells). HER2 is a protein that helps breast cancer cells grow quickly. HER2- breast cancers have zero to normal levels of the HER2 protein. The symptoms may include; breast lump, breast swelling, breast or nipple pain, and bloody nipple discharge.

Capivasertib is a medicinal product that is given orally. It is expected to inhibit specific proteins (AKT1/2/3) that are associated with breast cancer and the PIK3CA/AKT/PTEN pathway which is frequently activated in cancers. If licenced, capivasertib with fulvestrant may provide a new treatment option for patients with locally advanced (inoperable) or metastatic HR+/HER2- breast cancer. Breast cancer cells are able to become resistant to endocrine therapy over time, acquiring mutations in genes that enable endocrine resistance, targeted therapies remain an unmet need in the treatment of locally advanced or metastatic HR+/HER2- breast cancer. Capivasertib with fulvestrant could provide such a treatment option.

Proposed Indication

Treatment of locally advanced or metastatic breast cancer.[6]

Technology

Description

Capivasertib (AZD5363) is an oral, potent, selective adenosine triphosphate competitive pan-AKT kinase inhibitor.[1] 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.[2,3] Hence, AKT is a critical protein kinase that drives cancer proliferation, modulates metabolism, and is activated by C-terminal phosphorylation.[4] Capivasertib prevents substrate phosphorylation by AKT and down-regulates the phosphorylation levels of AKT downstream substrates GSK3β and PRAS40 in many cancer cells.[5] As a novel pyrrolopyrimidine-derived compound, Capivasertib inhibits all AKT isoforms (AKT1, AKT2, and AKT3).[5]

Capivasertib with fulvestrant is currently in clinical development for the treatment of locally advanced (inoperable) or metastatic HR+/HER2- breast cancer.[6] In phase III clinical trial (NCT04305496; CAPItello-291), participants received two oral tablets of capivasertib 400 mg twice a day on the first four days of each week in a four-week period, together with two intramuscular injections of fulvestrant 500 mg every 14 days for the first three injections and every 28 days thereafter.[6]

Key Innovation

Targeted therapies remain an unmet need for the treatment of locally advanced breast cancer, aside from HER2-positive tumours.[7] For metastatic HR+/HER2- breast cancer, endocrine therapy remains the recommended treatment option according to available international guidelines.[8-11] However, there are several cases of patients developing resistance to endocrine therapy.[12] As activation of the PI3K/AKT/mTOR pathway is heightened in HR+/HER2- breast cancer, inhibition of this signalling pathway may help overcome resistance to endocrine therapy and provide potential therapeutic strategies for patients with tumours which rely on activation of this signalling pathway.[13,14] As inhibition of the PI3K/AKT/mTOR pathway potentially results in an increase in ER-dependent transcriptional activity, use of an ER antagonist along with PI3K/AKT/mTOR inhibition may be a beneficial treatment strategy for patients with HR+/HER2- breast cancer with aberrant activation of the PI3K/AKT/mTOR signalling pathway.[15,16]

If licenced, Capivasertib with fulvestrant may provide a new treatment option for patients with locally advanced (inoperable) or metastatic HR+/HER2- breast cancer.[17]

Regulatory & Development Status

Capivasertib as a monotherapy or in combination does not currently have Marketing Authorisation in the EU/UK for any indication.

Fulvestrant currently has Marketing Authorisation in the EU/UK for a number of indications:[18]

- As a monotherapy for the treatment of estrogen receptor positive, locally advanced or metastatic breast cancer in postmenopausal women not previously treated with endocrine therapy, or with

disease relapse on or after adjuvant antioestrogen therapy, or disease progression on antioestrogen therapy.
- In combination with palbociclib for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in women who have received prior endocrine therapy (see section 5.1).
- In pre- or perimenopausal women, the combination treatment with palbociclib should be combined with a luteinising hormone releasing hormone (LHRH) agonist.

Patient Group

Disease Area and Clinical Need

Breast cancer is a cancer that starts in the breast tissue.[19] Breast cancer can be grouped according to types, stages and grades.[20] A locally advanced breast cancer is a stage 3 breast cancer where the cancer has spread from the breast to lymph nodes close to the breast or to the skin of the breast or to the chest wall, while a metastatic breast cancer is a stage 4 breast cancer where the cancer has spread to other parts of the body.[21] HR+ breast cancer is a type of breast cancer that has either the oestrogen (a sex hormone) receptor or the progesterone (a sex hormone) receptor or both (receptors are proteins within or on body cells).[22,23] HER2 is a protein that helps breast cancer cells to grow quickly, and breast cancers with higher than normal levels of HER2 proteins (having a score of 3+ on a scale of 0-3, with 2+ being a borderline) are called HER2-positive (HER2+).[23-25] A HER2-negative (HER2-) breast cancer has zero to normal levels of HER2 proteins (having a score of 0 or 1+ on a scale of 0-3, with 2+ being a borderline), due to absence of HER2 gene amplification.[24-26] HER2- breast cancers tend to be less aggressive than HER2+ breast cancers, but they are also less likely to respond to treatments that target the HER2 protein.[23,24] The HR+/HER2− breast cancer represents about 70% to 74% of all breast cancers, with about 80% and 65% of breast cancers testing positive for oestrogen and progesterone receptors respectively.[8,23] The symptoms of HER2- breast cancer may include; breast lump, breast swelling breast or nipple pain, bloody nipple discharge.[27]

Breast cancer is the most common type of cancer in the UK, accounting for 15% of all new cancer cases (2016-2018), with about 1 in 7 women diagnosed with breast cancer during their lifetime, and in rare cases, men can also be diagnosed with breast cancer.[28,29] The age standardised incidence rate of breast cancer in England is 1.3 and 169.2 per 100,000 amongst males and females respectively.[30] In England (2021-22) there were 244,374 finished consultant episodes (FCEs) and 240,790 admissions for breast cancer (ICD-10 code C50), which resulted in 218,006 day cases and 60,220 FCE bed days.[31] In England (2017), there were 46,109 patients diagnosed with breast cancer (ICD-10 code C50) and 9,569 deaths registered where breast cancer was the underlying cause.[32] For patients diagnosed between 2013 and 2017, and followed up to 2018, the 1-year and 5-year age-standardised survival rates for stage III (locally advanced) breast cancer were 95.5% and 72.0% respectively, and for stage IV (metastatic) breast cancer were 66.0% and 26.2% respectively.[33]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently recommends the following therapies for the treatment of locally advanced (inoperable) or metastatic HR+/HER2- breast cancer.[34]

- Abemaciclib withFulvestrant
- Palbociclib-Fulvestrant
- Ribociclib-Fulvestrant

- Everolimus with exemestane

Clinical Trial Information	
Trial	NCT04305496, EudraCT 2019-003629-78; A Phase III Double-blind Randomised Study Assessing the Efficacy and Safety of Capivasertib + Fulvestrant Versus Placebo + Fulvestrant as Treatment for Locally Advanced (Inoperable) or Metastatic Hormone Receptor Positive, Human Epidermal Growth Factor Receptor 2 Negative (HR+/HER2-) Breast Cancer Following Recurrence or Progression On or After Treatment With an Aromatase Inhibitor **Phase III** – Active, not recruiting **Location(s)**: Seven EU countries, UK, US, Canada, Australia and other countries **Primary completion date**: 15th August 2022
Trial Design	Randomised, parallel assignment, double-blinded, quadruple-masked
Population	N = 708 (actual); Adults aged 18+, with histologically confirmed HR+/HER2- breast cancer determined from the most recent tumour sample.[35]
Intervention(s)	Fulvestrant and Capivasertib: Two intramuscular administrations of Fulvestrant (500 mg each) on Day 1 of weeks 1 & 3 of cycle 1, and then on Day 1 of week 1 of each 28-day cycle thereafter. Oral administration of two tablets of Capivasertib (200 mg each) twice a day on an intermittent weekly dosing schedule, dosed on Days 1 & 4 in each week of a 28-day treatment cycle.
Comparator(s)	Fulvestrant and Placebo: Two intramuscular administrations of Fulvestrant (500 mg each) on Day 1 of weeks 1 & 3 of cycle 1, and then on Day 1 of week 1 of each cycle thereafter. Oral administration of two tablets of placebo (200 mg each) twice a day on an intermittent weekly dosing schedule, dosed on Days 1 & 4 in each week of a 28-day treatment cycle.
Outcome(s)	The primary outcome was Progression-Free Survival in the overall population and in the PIK3CA/AKT1/PTEN-altered subgroup [Time Frame: The time from date of randomisation to the date of progression or death due to any cause, whichever occurs earlier, up to approximately 51 months]. See trial record for full list of other outcomes.

Results (efficacy)	In the AKT pathway–altered population, the median progression-free survival was 7.3 months in the capivasertib–fulvestrant group, as compared with 3.1 months in the placebo–fulvestrant group (hazard ratio, 0.50; 95% CI, 0.38 to 0.65; P<0.001).[35]
Results (safety)	The most frequent adverse events of grade 3 or higher in patients receiving capivasertib–fulvestrant were rash (in 12.1% of patients, vs. in 0.3% of those receiving placebo–fulvestrant) and diarrhea (in 9.3% vs. 0.3%). Adverse events leading to discontinuation were reported in 13.0% of the patients receiving capivasertib and in 2.3% of those receiving placebo.[35]

Estimated Cost

Fulvestrant is already marketed in the UK; two 250mg/5ml pre-filled disposable injections cost £522.41.[36]

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance. Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy (TA836). October 2022.
- NICE technology appraisal guidance. Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy (TA725). September 2021.
- NICE technology appraisal guidance. Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy (TA687). March 2021
- NICE technology appraisal guidance. Abemaciclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer (TA563). February 2019.
- NICE technology appraisal guidance. Palbociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer (TA495). December 2017.
- NICE technology appraisal guidance. Ribociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer (TA496). December 2017.
- NICE technology appraisal guidance. Everolimus with exemestane for treating advanced breast cancer after endocrine therapy (TA421). December 2016.

NHS England (Policy/Commissioning) Guidance

- NHS England's West Midlands Expert Advisory Group for Breast Cancer. Clinical Guidelines for the Management of Breast Cancer. December 2016.

Other Guidance

- Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, André F, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). 2018.[9]

- Gradishar WJ, Anderson BO, Blair SL, Burstein HJ, Cyr A, Elias AD, et al. Breast Cancer Version 3.2014. 2014.[11]
- Partridge AH, Rumble RB, Carey LA, Come SE, Davidson NE, Di Leo A, et al. Chemotherapy and targeted therapy for women with human epidermal growth factor receptor 2-negative (or unknown) advanced breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. 2014.[10]

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