Health Technology Briefing
January 2024

Inavolisib with palbociclib and fulvestrant for treating HR+/HER2-, PIK3CA mutated locally advanced or metastatic breast cancer

Company/Developer	Roche Products Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 29599	NICE ID: Not available	UKPS ID: 665601

Licensing and Market Availability Plans

Currently in phase III clinical development

Summary

Inavolisib in combination with palbociclib and fulvestrant is in clinical development for the treatment of patients with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-), PIK3CA-mutated locally advanced or metastatic breast cancer. Breast cancer occurs when abnormal cells in the breast begin to grow and divide in an uncontrolled way and eventually form a growth (tumour). The PIK3CA gene holds the instructions for making a protein called p110 alpha (p110α) responsible for cell growth and division, cell movements, and protein production. A mutation in the PIK3CA gene can disrupt this process.. Symptoms can sometimes include fatigue, hair loss, general pain, lump in breast, and nausea, People diagnosed with HR+ metastatic breast cancer often face the risk of disease progression and treatment side effects, creating a need for additional treatment options.

Inavolisib is an orally administered, new medicinal product that blocks the activity of PI3Ka and specifically triggers the breakdown of mutant PI3Ka proteins. Studies show inavolisib has anti-tumour activity and a manageable safety profile in patients with PIK3CA-mutant, HR+/HER2- breast cancer as a single agent or in combination therapy. If approved, inavolisib in combination with palbociclib and fulvestrant will add an alternative treatment option for HR+/HER2-, PIK3CA-mutated locally advanced or metastatic breast cancer patients.

Proposed Indication

Inavolisib in combination with palbociclib and fulvestrant for treatment of patients with PIK3CA-mutant, Hormone Receptor-Positive, Her2-Negative, Locally Advanced or Metastatic Breast Cancer whose disease progressed during treatment or within 12 months of completing adjuvant endocrine therapy and who have not received prior systemic therapy for metastatic disease .[1]

Technology

Description

Inavolisib (GDC-0077) is a potent, orally available, and selective PI3Kα inhibitor (IC50=0.038 nM) that has demonstrated robust efficacy in PIK3CA-mutant breast cancer models.[2] Inavolisib binds to and inhibits PI3K family kinases, including activating mutations in the catalytic alpha isoform PIK3CA (PI3Kα). PIK3CA is frequently mutated in a variety of cancer cell types, and this underlies the dysregulation of the PI3K pathway that plays a key role in cancer cell growth and invasion. Pharmacological inactivation of the PI3K pathway inhibits growth and survival of PI3K-overexpressing tumour cells.[3] Fulvestrant is a competitive oestrogen receptor (ER) antagonist with an affinity comparable to oestradiol. Fulvestrant blocks the trophic actions of oestrogens without any partial agonist (oestrogen-like) activity. The mechanism of action is associated with downregulation of oestrogen receptor protein levels.[4] Palbociclib is a highly selective, reversible inhibitor of cyclin-dependent kinases (CDK) 4 and 6. Cyclin D1 and CDK4/6 are downstream of multiple signalling pathways which lead to cellular proliferation.[5]

Inavolisib in combination with palbociclib and fulvestrant is in a phase III clinical trial (NCT04191499) where participants receive oral inavolisib on Days 1-28 of each 28-day cycle, oral palbociclib on Days 1-21 of each 28-day cycle and intramuscular (IM) fulvestrant approximately every 4 weeks.[1]

Key Innovation

Inavolisib is a PI3Kα-selective inhibitor and degrader of mutated PI3Kα.[6] It was discovered to inhibit PI3K signalling more potently as well as reduce cell viability through unique HER2-dependent mutant p110α degradation, making it more effective at prolonging PI3K pathway suppression than other PI3K inhibitors.[7] Inavolisib has also demonstrated greater inhibition of cell proliferation and increased apoptosis in human PIK3CA mutant breast cancer cell lines to a greater extent when compared to PIK3CA wild-type cells. In vivo efficacy in a PIK3CA-mutant human breast cancer xenograft model was also improved when inavolisib was combined with standard-of-care therapies for hormone-receptor positive (HR+) breast cancer such as anti-oestrogens (fulvestrant) or CDK4/6 inhibitor (palbociclib).[2] Inavolisib has demonstrated encouraging preliminary antitumor activity in patients with PIK3CA-mutated HR+ breast cancer as a single agent, and in combination with antioestrogen therapy.[6] If licensed, inavolisib in combination with palbociclib and fulvestrant will provide additional treatment option for patients with HR+/HER2-, PIK3CA-mutated locally advabced or metastatic breast cancer.

Regulatory & Development Status

Inavolisib does not currently have Marketing Authorisation in the EU/UK for any indication.

Inavolisib as combination is currently in phase III clinical trials:

- As a maintenance therapy for PIK3CA-mutated HER2-positive locally advanced or metastatic breast cancer.[8]

- In patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2) -negative, PIK3CA-mutated, locally advanced (LA) or metastatic breast cancer (mBC), who progressed during or after cyclin dependent kinase 4/6i (CDK4/6i)-based therapy.[9]

Patient Group

Disease Area and Clinical Need

Breast cancer most commonly starts in the cells that line the milk ducts of the breast. It is the most common cancer in the UK. It mainly affects women, but men can get it too.[10] Some breast cancers are sensitive to the body's naturally occurring female hormones — oestrogen and progesterone.[11] If the cancer cell has one or both of the hormone receptors above, the term hormone-receptive positive (also called hormone-positive or HR+) may be used.[12] HER2 is a protein that helps breast cancer cells grow quickly.[13] If breast cancer cells do not have abnormal levels of HER2 proteins, the breast cancer is considered HER2-negative.[14] A mutation in the PIK3CA gene can cause cells to divide and replicate uncontrollably. It contributes to the growth of many cancers, including metastatic breast cancer (mBC).[15] Metastasis (M) describes whether the cancer has spread to a different part of the body.[16] A study suggests that patients with HR+/Her2− mBC and PIK3CA mutation present a resistance to chemotherapy and a worse outcome, and that this population represents an unmet medical need.[17] Symptoms of breast cancer include a lump or thickened area of breast tissue, changes in the size of one or both breasts, discharge from the nipples, lumps or swelling underneath the armpits, changes in the look or feel of the skin of the breast, and changes in the overall appearance of the nipple (e.g. becoming sunken into the breast).[18] The causes of breast cancer are not fully understood, however there are risk factors known to affect the likelihood of developing breast cancer which include age, family history, previous breast cancer or lump, dense breast tissue and other lifestyle factors like being overweight, and drinking alcohol.[19]

It is estimated that between 2016 and 2018 there were around 55,900 new cases of breast cancer in the UK each year, with rates in women increasing by 5% over the past decade and rates in men remaining stable. Approximately 11,500 people die from breast cancer in the UK each year (2017-2019); it is the second most common form of cancer death in women in the UK.[20] In England 2017, there were 46,109 registrations of newly diagnosed cases of malignant neoplasm of breast (ICD-10 code C50), 9,569 deaths due to malignant neoplasm of the breast; and the directly age-standardised rates per 100,000 population were 166.7 among females and 1.3 among males.[21] In 2022-23, there were 259,866 finished consultant episodes (FCEs) for malignant neoplasm of breast (ICD-10 code C50), and 256,441 admissions resulting in 233,521 day cases and 61,787 bed days.[22]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) recommends alpelisib plus fulvestrant as an option for treating HR+, HER2-negative, PIK3CA-mutated, locally advanced or metastatic breast cancer in adults, only if their cancer has progressed after a CDK4/6 inhibitor plus an aromatase inhibitor.[23]

Currently, there this no NICE recommended first line treatment for HR+, HER2-negative, PIK3CA-mutated, locally advanced or metastatic breast cancer.

Clinical Trial Information

Trial	NCT04191499; 2019-002455-42. A Phase III, Randomised, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Inavolisib Plus Palbociclib and Fulvestrant Versus Placebo Plus Palbociclib and Fulvestrant in Patients with PIK3CA-Mutant, Hormone Receptor-Positive, Her2-Negative, Locally Advanced or Metastatic Breast Cancer. **Phase III:** Recruiting **Location(s):**11 EU countries, USA, Canada, Australia, UK, and others **Primary completion date:** September 2023
Trial Design	Randomised, parallel assignment, double blinded
Population	N=325 (estimated); patients with PIK3CA-Mutant, HR+, HER2, locally advanced or metastatic breast cancer. aged 18 years and older.
Intervention(s)	Inavolisib with palbociclib and fulvestrant
Comparator(s)	Matched placebo + palbociclib + fulvestrant
Outcome(s)	Primary outcomes: - Progression-Free Survival (PFS) [Time Frame: From randomisation to the first occurrence of disease progression or death from any cause, whichever occurs first (up to 6 years)] See trial record for full list of outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of inavolisib is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Taselisib for previously treated ER-positive, HER2-negative, PIK3CA-positive breast cancer in postmenopausal women. [GID-TA10326]. Expected publication date to be confirmed.
- NICE technology appraisal. Alpelisib with fulvestrant for treating hormone receptor-positive, HER2-negative, PIK3CA-mutated advanced breast cancer (TA816). August 2022.
- NICE guideline. Suspected cancer: recognition and referral (NG12). December 2021.
- NICE guideline. Early and locally advanced breast cancer: diagnosis and management (NG101). July 2018.
- 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.
- NICE quality standard. Suspected cancer (QS124). December 2017.
- NICE quality standard. Breast cancer (QS12). June 2016

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

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- Gradishar, W. J., Anderson, B. O., Abraham, J., Aft, R., Agnese, D., Allison, K. H., et al. Breast Cancer, Version 3.2020, NCCN Clinical Practice Guidelines in Oncology. April 2020.[25]
- ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. 2021.[26]

Additional Information

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