

Health Technology Briefing November 2023

Tucatinib with trastuzumab and pertuzumab for maintenance treatment of unresectable locally advanced or metastatic HER2-positive breast cancer

Company/Developer

Seagen UK Ltd

New Active Substance

Significant Licence Extension (SLE)

NIHRIO ID: 34113

NICE ID: Not Available

UKPS ID: 664417

Licensing and Market Availability Plans

Currently in phase III trials

Summary

Tucatinib in combination with trastuzumab and pertuzumab is in clinical development for the maintenance treatment of unresectable locally advanced, or metastatic HER2-positive (HER2-POSITIVE) breast cancer. Breast cancer is cancer that starts in the breast tissue. HER2-positive breast cancer means that the cancer cells express more of the HER2 protein on their surface. HER2 encourages cell growth and therefore HER2-positive cancers can grow more quickly. Unresectable cancer is cancer that cannot be removed by surgery. Locally advanced means cancer has grown outside the body part it started in but has not yet spread to other parts of the body, whereas metastatic cancer is cancer that has spread to other parts of the body. A high mortality rate is reported in HER2-positive breast cancer, due to limited therapeutic options. Despite advances in medicinal products to treat metastatic breast cancer, HER2-positive metastatic breast cancer is still challenging for patients particularly given the emergence of drug resistance to some treatment options.

Tucatinib inhibits a protein called tyrosine kinase inhibitor (TKI) that targets the HER2 protein in HER2-positive breast cancer. TKIs work by blocking the activity of enzymes called tyrosine kinases involved in the growth and division of cells, thereby slowing cancer cells from growing and spreading. It is administered orally in combination with trastuzumab and petruzumab (both administered intravenously). If licensed, tucatinib in combination with trastuzumab and pertuzumab will offer a new combination therapy for targeting HER2 proteins in HER2-positive locally advanced or metastatic breast cancer.

Proposed Indication

Maintenance treatment of patients with unresectable locally advanced, or metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer whose disease has not progressed on induction chemotherapy with trastuzumab, pertuzumab, and taxane.¹

Technology

Description

Tucatinib (TUKYSA, ONT-380, ARRY-380) is a medicinal product that targets the HER2 protein in HER2-positive breast cancer. HER2 is a protein receptor that controls cell growth, survival differentiation, and migration.² Tucatinib is a reversible, potent, and selective tyrosine kinase inhibitor (TKI) of HER2.^{3,4} TKIs work by blocking the activity of enzymes called tyrosine kinases involved in the growth and division of cells, thereby slowing cancer cells from growing and multiplying.⁵ Tucatinib has a higher specificity for HER2.³

Tucatinib in combination with trastuzumab and pertuzumab is in clinical development for the maintenance treatment of unresectable locally advanced, or metastatic HER2-positive breast cancer. In the phase III trial HER2CLIMB-05 (NCT05132582), tucatinib 300mg is administered orally twice daily, in combination with trastuzumab which is administered intravenously (IV) or subcutaneously (SC) at a fixed dose of 600mg every 21 days and pertuzumab which is administered IV at 420 mg every 21 days.¹ Alternatively, tucatinib 300mg twice daily is administered in combination with a fixed dose combination of 600mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase given SC, once every 21 days, in lieu of trastuzumab and pertuzumab individually.¹

Key Innovation

HER2-positive breast cancer is a type of cancer characterised by the over-amplification or over-expression of HER2 whereby the tumour depends on HER2 to thrive.³ It is a more aggressive type of breast cancer, as diagnosis and prognosis are difficult for HER2-positive breast cancers.⁶ High mortality rate is reported in HER2-positive breast cancer, due to availability of limited therapeutic options.⁶ Despite advances in systemic medications to treat metastatic breast cancer, HER2-positive metastatic breast cancer is still challenging for patients and treating clinicians.⁶ The emergence of drug resistance in anti-HER2 therapies has also been observed.⁶ Small molecule TKIs such as tucatinib represent another option for patients with early stage or advanced HER2-positive breast cancer and have shown good outcomes in phase 3 trials for patients with HER2-positive breast cancer.^{2,7-9}

The pivotal HER2CLIMB trial demonstrated superiority of the tucatinib plus capecitabine-trastuzumab combination in extending progression-free survival and overall survival in HER2-positive metastatic breast cancer previously treated with anti-HER2 therapies.^{3,8,10} If licensed, tucatinib in combination with trastuzumab and pertuzumab will offer a new combination therapy for targeting HER2 proteins in HER2-positive unresectable locally advanced or metastatic breast cancer.

Regulatory & Development Status

Tucatinib in combination with trastuzumab and pertuzumab does not currently have marketing authorisation for any indication in the UK.

Tucatinib in combination with trastuzumab and capecitabine currently has marketing authorisation in the UK for the treatment of adult patients with HER2-positive locally advanced or metastatic breast cancer who have received at least 2 prior anti-HER2 treatment regimens.⁴

Tucatinib in combination with pertuzumab, and trastuzumab is not in clinical development for any other indication.

Patient Group

Disease Area and Clinical Need

Breast cancer is a cancer that starts in the breast tissue.¹¹ This begins when abnormal cells in the breast begin to grow and divide in an uncontrolled way and eventually form a growth (tumour).¹² It is the most common cancer in the UK and it mainly affects women, but men can get it too.¹² HER2-positive breast cancer is a specific form of breast cancer where the cancer cells have large amounts of HER2, a protein involved in cell growth, found in small amounts on some normal cells, including breast cells, stomach and bladder cells.¹³ These cancer cells are called HER2-positive and can be treated with drugs that target the HER2 protein.¹³ Locally advanced (also known as stage III) HER2-positive breast cancer occurs when the cancer cells have advanced from the area where it started in the breast to surrounding breast tissue.¹⁴ Metastatic (called stage IV) HER2-positive breast cancer occurs when the cancer cells have spread to another part of the body, most commonly the bones, lungs, brain, or liver.¹⁵ Symptoms of breast cancer include a new lump or thickening in the breast or armpit, changes in size or feel of the breast, skin on the breast, position of the nipple, and fluid leaking from the nipple in a woman who is not pregnant or breastfeeding.¹⁶ Breast cancer risk is higher in older women, women who consume alcohol, obese or overweight people, women taking the contraceptive pill or on hormone replacement therapy (HRT), women with dense breast tissue, etc.¹⁷

Breast cancer (invasive) is the most common cancer in the UK, accounting for 15% of all new cancer cases (2016-18).¹⁸ Invasive breast cancer means that the cancer cells have grown through the lining of the ducts into the surrounding breast tissue.¹⁹ The age standardised incidence rate of breast cancer (invasive) in England is 169.2 per 100,000 females.²⁰ In England (2022-23) there were 259,866 finished consultant episodes (FCEs) and 256,441 admissions for breast cancer (ICD-10 code C50), which resulted in 233,521 day cases and 61,787 FCE bed days.²¹ In England (2017), there were 46,109 patients diagnosed with malignant neoplasm of the breast (breast cancer) and 9,569 deaths registered where malignant neoplasm of the breast was the underlying cause.²² For patients diagnosed between 2013 and 2017, followed up to 2018, the 1-year and 5-year survival rates were 95.8% and 85% respectively.²³

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) recommended treatment options for unresectable HER2-positive locally advanced or metastatic breast cancer include:

- pertuzumab with trastuzumab and docetaxel²⁴
- trastuzumab deruxtecan (after at least 1 anti-HER2 therapy)^{25,26}
- tucatinib with trastuzumab and capecitabine (after at least 2 anti-HER2 therapies)²⁷
- trastuzumab emtansine (after at least one line of therapy).²⁸

Clinical Trial Information

Trial

HER2CLIMB-05; [NCT05132582](#), [EudACT 2021-002491-39](#); A Randomized, Double-blind, Phase 3 Study of Tucatinib or Placebo in Combination With Trastuzumab and Pertuzumab as Maintenance Therapy for Metastatic HER2-POSITIVE Breast Cancer (HER2CLIMB-05)
Phase III - Recruiting
Location(s): 12 EU countries, UK, USA, Canada and other countries

	Primary completion date: October 2024
Trial Design	Randomised, parallel assignment, quadruple masking
Population	N = 650; adults with centrally confirmed HER2-positive breast cancer who have received 4-8 cycles of pertuzumab with trastuzumab and taxane as first-line treatment; aged 18 years and older.
Intervention(s)	<ul style="list-style-type: none"> • Tucatinib 300mg is administered orally twice daily, in combination with • Trastuzumab, administered intravenously (IV) or subcutaneously (SC) at a fixed dose of 600mg every 21 days, and • Pertuzumab which is administered IV at 420 mg every 21 days. <p>Alternatively,</p> <ul style="list-style-type: none"> • Tucatinib 300mg twice daily is administered in combination with • A fixed dose combination of 600mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase SC, given once every 21 days
Comparator(s)	Matched placebo
Outcome(s)	Progression free survival (PFS) by investigator assessment per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1
Results (efficacy)	--
Results (safety)	--

Estimated Cost

The cost of tucatinib in combination with trastuzumab and pertuzumab is not yet known. The NHS indicative cost for phesgo, a combination of pertuzumab 60mg and trastuzumab 60mg per ml, in a 10ml solution is £3,617.²⁹ In addition, the NHS indicative price for tucatinib 150mg per tablet in a pack of 84 tablets is £5,636.84.³⁰

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Tucatinib with trastuzumab emtansine for treating HER2-positive unresectable or advanced breast cancer after a taxane, trastuzumab or both together (GID-TA11110). Expected publication date: TBC.
- NICE technology appraisal in development. Palbociclib with trastuzumab and endocrine therapy for maintenance treatment of hormone-receptor positive, HER2-positive metastatic breast cancer (GID-TA11273). Expected publication date: TBC .
- NICE technology appraisal. Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 1 or more anti-HER2 treatments (TA862). February 2023.
- Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies (TA704). May 2021.
- NICE technology appraisal. Pertuzumab with trastuzumab and docetaxel for treating HER2-positive breast cancer (TA509). March 2018.
- NICE technology appraisal. Trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane (TA458). November 2017.

- NICE clinical guideline. Early and locally advanced breast cancer: diagnosis and management (NG101). July 2018, updated June 2023.
- NICE clinical guideline. Advanced breast cancer: diagnosis and treatment (CG81). February 2009, updated August 2017.
- NICE clinical evidence summary. Early and metastatic HER2-positive breast cancer: subcutaneous trastuzumab (ESNM13). March 2013.

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

Other Guidance

- National Comprehensive Cancer Network (NCCN). NCCN Guidelines® Insights: Breast Cancer, Version 4.2023. June 2023.³¹
- European Society of Medical Oncology (ESMO). ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. December 2021.³²

Additional Information

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