NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
July 2022

Tucatinib with trastuzumab emtansine for treating unresectable, locally advanced or metastatic HER2 positive breast cancer

Company/Developer	Seagen Inc

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 28980	NICE TSID: 11781	UKPS ID: 661953

Licensing and Market Availability Plans

Currently in phase II and III clinical trials.

Summary

Tucatinib in combination with trastuzumab emtansine is currently in clinical development for the treatment of unresectable, locally-advanced or metastatic human epidermal growth factor receptor 2 positive (HER2+) breast cancer, after prior treatment. Breast cancer is when abnormal cells in the breast begin to grow and uncontrollably divide and eventually form a growth (tumour). Metastatic breast cancer is cancer that has spread beyond the breast to other organs, and unresectable cancer cannot be treated with surgery. HER2 is a protein on cells that helps cell growth, development, and survival. Cancers associated with overexpression of HER2 are more aggressive. Treatment options for patients who experience disease progression after standard treatment are limited.

Tucatinib is an inhibitor of HER2 and can prevent growth or induce death in HER2 driven tumour cells. Trastuzumab emtansine is a HER2 targeted antibody-drug conjugate that attaches to HER2 receptor which activates the drug and kill the cancer cell. Tucatinib in combination with trastuzumab emtansine is a novel combination, which has shown in early phase clinical trials acceptable toxicity and preliminary antitumor activity among pre-treated patients HER2-positive metastatic breast cancer. Tucatinib will be administered orally in combination with intravenous trastuzumab emtansine. If licensed, tucatinib in combination with trastuzumab emtansine will offer an additional treatment option for patients with unresectable locally-advanced or metastatic HER2+ breast cancer, who have progressed after prior treatment.

Proposed Indication

Treatment of unresectable, locally advanced or metastatic human epidermal growth factor receptor 2 positive (HER2+) breast cancer, after treatment with a taxane and trastuzumab.[1]

Technology

Description

Tucatinib (ONT-380, Tukysa) is a reversible, potent and selective tyrosine kinase inhibitor of HER2.[1,2] In vitro, tucatinib inhibits phosphorylation of HER2 and HER3, resulting in inhibition of downstream cell signalling and cell proliferation, and induces death in HER2 driven tumour cells. In vivo, tucatinib inhibits the growth of HER2 driven tumours and the combination of tucatinib and trastuzumab showed enhanced anti-tumour activity in vitro and in vivo compared to either medicinal product alone.[2]

Trastuzumab emtansine (T-DM1, Kadcyla, ado-trastuzumab emtansine) is a HER2 targeted antibody-drug conjugate which contains the humanised anti-HER2 IgG1, trastuzumab, covalently linked to the microtubule inhibitor DM1 (a maytansine derivative) via the stable thioether linker MCC (4-[N-maleimidomethyl] cyclohexane-1-carboxylate).[1,3] Emtansine refers to the MCC-DM1 complex. An average of 3.5 DM1 molecules are conjugated to each molecule of trastuzumab. Conjugation of DM1 to trastuzumab confers selectivity of the cytotoxic agent for HER2 overexpressing tumour cells, thereby increasing intracellular delivery of DM1 directly to malignant cells. Upon binding to HER2, trastuzumab emtansine undergoes receptor-mediated internalisation and subsequent lysosomal degradation, resulting in release of DM1-containing cytotoxic catabolites (primarily lysine-MCC-DM1).[3]

Tucatinib in combination with trastuzumab emtansine is in clinical development for the treatment of unresectable, locally advanced or metastatic HER2-positive breast cancer, after treatment with a taxane and trastuzumab. In the phase III clinical trial (NCT03975647), 300mg of tucatinib will be given twice per day orally, in combination with 3.6 mg/kg of trastuzumab emtansine given into the vein intravenously (IV) every 21 days.[1]

Key Innovation

Treatment options for patients who experience disease progression after treatment with trastuzumab and pertuzumab, are limited.[4] Trastuzumab emtansine is considered to be standard of care in this setting.[5] Treatment options with better efficacy and improved tolerability for late-stage breast cancer are needed.[4] Tucatinib is highly selective for HER2 without significant inhibition of EGFR. Inhibition of EGFR has been associated with significant toxicities, including skin rash and diarrhoea. Tucatinib has shown activity as a single agent and in combination with both chemotherapy and other HER2 directed agents such as trastuzumab.[6] In a phase Ib trial (NCT01983501), tucatinib in combination with trastuzumab emtansine showed acceptable toxicity and showed preliminary antitumour activity among pre-treated patients with HER2+ metastatic breast cancer with and without brain metastases.[4] Tucatinib in combination with trastuzumab emtansine is a novel combination.[2] If licensed, tucatinib in combination with trastuzumab emtansine will provide an additional treatment options for patients with unresectable, locally-advanced or HER2+ breast cancer, after treatment with a taxane and trastuzumab.

Regulatory & Development Status

Tucatinib is currently licensed in the UK for the following indication:[2]

- In combination with trastuzumab and capecitabine for the treatment of adult patients with HER2+ locally advanced or metastatic breast cancer who have received at least 2 prior anti-HER2 treatment regimens

Trastuzumab emtansine is currently licensed in the UK for the following indications:[3]

- As a single agent, for the adjuvant treatment of adult patients with HER2+ early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2 targeted therapy
- As a single agent, for the treatment of adult patients with HER2+, unresectable locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either:
  - Received prior therapy for locally advanced or metastatic disease
  - Developed disease recurrence during or within six months of completing adjuvant therapy

Tucatinib in combination with trastuzumab emtansine is currently in phase II and III trials for the treatment of HER2+ breast cancer.[7]

Tucatinib has the following regulatory designations:

- A orphan drug in the US in 2017 for the treatment of breast cancer patients with brain metastases.[8]

Patient Group

Disease Area and Clinical Need

Breast cancer is when abnormal cells in the breast begin to grow and divide in an uncontrolled way and eventually form a growth (tumour). Breast cancer starts in the breast tissue, most commonly in the cells that line the milk ducts of the breast.[9] HER2 is a transmembrane tyrosine kinase receptor that mediates cell growth, differentiation, and survival. Cancers associated with overexpression of HER2 are more aggressive and, before the introduction of HER2 targeted agents, were associated with poorer overall survival compared with HER2 negative cancers.[6] Locally advanced cancer means that the cancer has spread into nearby tissue and lymph nodes around the breast; this includes lymph nodes around the collar bone and breastbone.[10] Whereas metastatic breast cancer has spread to another part of the body, most commonly the bones, lungs, brain, or liver.[11] Unresectable breast cancer is when the cancer is unable to be removed with surgery.[12] Symptoms include hard, uneven, immobile or painless lump in breast, nipple discharge, sudden nipple inversion, changes in the texture of breast skin, unusual breast swelling or tenderness or discomfort in the breast or nipple.[13] Risk factors for breast cancer include being female, a family history of breast cancer (although this does not apply to HER2 positive breast cancers, which are not considered to be hereditary), giving birth for the first time after the age of 30, receiving radiation therapy to the chest, being overweight, living a sedentary lifestyle and using tobacco products. HER2 positive breast cancer is more likely to affect younger women.[14]

Breast cancer is the most common cancer in the UK. It mainly affects women, but men can get it too.[9] Around 55,500 women and around 370 men are diagnosed in the UK each year. 1 in 7 women in the UK develop breast cancer during their lifetime. It is more common in older women. 15% of all newly diagnosed cancers in the UK are breast cancer.[9] 15-25% of women with breast cancer have HER2 positive cancers.[15] Applying this statistic to the yearly UK estimate for breast cancer in women, it can be estimated that between 8,325 and 13,875 women are diagnosed with HER2 positive breast cancer every year.[9,15] In England (2020-21) there were 202,340 finished consultant episodes (FCEs) and 199,226 admissions for malignant neoplasm of breast (ICD-10 code C50), which resulted in 172,062 day cases and 47,613 FCE bed days.[16]

Recommended Treatment Options
NICE recommends the following for the treatment of unresectable, locally-advanced or metastatic HER2+ breast cancer, after previous treatment: • Tucatinib with trastuzumab and capecitabine is recommended, within its marketing authorisation, as an option for treating HER2+ locally advanced or metastatic breast cancer in adults after 2 or more anti-HER2 treatment therapies.[17] • Trastuzumab deruxtecan for use within the Cancer Drugs Fund as an option for treating HER2+ unresectable or metastatic breast cancer in adults after 2 or more anti-HER2 therapies.[18] • Trastuzumab emtansine for treating HER2+, unresectable, locally advanced or metastatic breast cancer in adults who previously received trastuzumab and a taxane, separately or in combination.[5] • Trastuzumab monotherapy for people with tumours expressing HER2 scored at levels of 3+ who have received at least two chemotherapy regimens for metastatic breast cancer. Prior chemotherapy must have included at least an anthracycline and a taxane where these treatments are appropriate. It should also have included hormonal therapy in suitable oestrogen receptor positive patients.[19]

Clinical Trial Information	
Trial	**HER2CLIMB-02; NCT03975647; EudraCT 2019-005017-39;** Randomized, Double-blind, Phase 3 Study of Tucatinib or Placebo in Combination With Ado-trastuzumab Emtansine (T-DM1) for Subjects With Unresectable Locally-advanced or Metastatic HER2+ Breast Cancer (HER2CLIMB-02) **Phase III –** Recruiting **Location(s) –** 10 countries in EU, UK, USA, Australia, Canada and other countries **Primary completion date –** April 2024
Trial Design	Randomized, parallel assignment, quadruple-masked
Population	N = 460 (estimated); Histologically confirmed HER2+ breast carcinoma as determined by a sponsor-designated central laboratory; History of prior treatment with a taxane and trastuzumab in any setting, separately or in combination; 18 years and older
Intervention(s)	Tucatinib 300mg oral, in combination with trastuzumab emtansine 3.6 mg/kg IV
Comparator(s)	Matched placebo in combination with trastuzumab emtansine 3.6 mg/kg IV
Outcome(s)	**Primary outcome** - Progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 by investigator assessment [Time Frame: Up to approximately 5 years] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Tucatinib is already marketed as a combination therapy for UK adult patients with HER2+ locally advanced or metastatic breast cancer who have received at least 2 prior anti-HER2 treatment regimens; the NHS indicative price for 88 x 50mg tablets is £1,968.42 (hospital only), and 84 x 150mg tablets cost £5,636.84 (hospital only).[2,20]

Trastuzumab emtansine is already marketed in the UK for the adjuvant treatment of adult patients with HER2+ early breast and HER2+, unresectable locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane separately or in combination; the NHS indicative price for one 100mg powder for concentrate for solution for infusion vial is £1,641.01, and one 160mg powder for concentrate for solution for infusion vial is £2,625.62.[3,21]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after trastuzumab and a taxane (GID-TA10804). Expected date of issue January 2023.
- NICE technology appraisal. Tucatinib with trastuzumab and capecitabine for treating HER2-positive advanced breast cancer after 2 or more anti-HER2 therapies (TA786). April 2022.
- NICE technology appraisal. Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies (TA704). May 2021.
- NICE technology appraisal. Trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane (TA458). November 2017.
- NICE technology appraisal. Gemcitabine for the treatment of metastatic breast cancer (TA116). January 2007.
- NICE technology appraisal. Guidance on the use of trastuzumab for the treatment of advanced breast cancer (TA34). March 2002.
- 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

- European Society of Medical Oncology (ESMO). ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. December 2021.[22]
- American Society of Clinical Oncology. Current and Future Management of HER2-Positive Metastatic Breast Cancer. October 2021.[23]
- National Comprehensive Cancer Network (NCCN). Breast Cancer, Version 3.2020, NCCN Clinical Practice Guidelines in Oncology. April 2020.[24]

- American Society of Clinical Oncology. Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: ASCO Clinical Practice Guideline Update. September 2018.[25]

Additional Information

References

1 ClinicalTrials.gov. *A Study of Tucatinib vs. Placebo in Combination With Ado-trastuzumab Emtansine (T-DM1) for Patients With Advanced or Metastatic HER2+ Breast Cancer. Trial ID: NCT03975647*. 2019. Available from: https://clinicaltrials.gov/ct2/show/NCT03975647 [Accessed 10th June 2022].

2 Electronic Medicines Compendium. *TUKYSA 150 mg film-coated tablets.* 2022. Available from: https://www.medicines.org.uk/emc/product/12952/smpc [Accessed 10th June 2022].

3 Electronic Medicines Compendium. *Kadcyla 100 mg Powder for Concentrate for Solution for Infusion.* 2022. Available from: https://www.medicines.org.uk/emc/product/5252/smpc [Accessed 10th June 2022].

4 Borges VF, Ferrario C, Aucoin N, Falkson C, Khan Q, Krop I, et al. Tucatinib Combined With Ado-Trastuzumab Emtansine in Advanced ERBB2/HER2-Positive Metastatic Breast Cancer: A Phase 1b Clinical Trial. *JAMA Oncology*. 2018;4(9):1214-20. Available from: https://doi.org/10.1001/jamaoncol.2018.1812.

5 National Institute for Health and Care Research. *Trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane.* 2017. Available from: https://www.nice.org.uk/guidance/ta458/chapter/1-Recommendations [Accessed 13th June 2022].

6 Seagen. *Seattle Genetics Announces Initiation of Phase 3 Clinical Trial of Tucatinib in Combination with Ado-trastuzumab Emtansine (T-DM1, Kadcyla®) for Patients with Advanced or Metastatic HER2-Positive Breast Cancer.* 2019. Available from: https://investor.seagen.com/press-releases/news-details/2019/Seattle-Genetics-Announces-Initiation-of-Phase-3-Clinical-Trial-of-Tucatinib-in-Combination-with-Ado-trastuzumab-Emtansine-T-DM1-Kadcyla-for-Patients-with-Advanced-or-Metastatic-HER2-Positive-Breast-Cancer/default.aspx [Accessed 13th June 2022].

7 ClinicalTrials.gov. *tucatinib, trastuzumab emtansine, Ado-trastuzumab Emtansine, T-DM1, breast cancer | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Phase 2, 3.* 2022. Available from: https://www.clinicaltrials.gov/ct2/results?term=tucatinib%2C+trastuzumab+emtansine%2C+Ado-trastuzumab+Emtansine%2C+T-DM1%2C+breast+cancer&Search=Apply&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=&rslt=&phase=1&phase=2 [Accessed 13th June 2022].

8 US Food and Drug Administration. *Search Orphan Drug Designations and Approvals.* 2022. Available from: https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=570716 [Accessed 13th June 2022].

9 Cancer Research UK. *What is breast cancer?* 2021. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/about [Accessed 13th June 2022].
10 Cancer Research UK. *What is secondary breast cancer?* 2021. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/secondary/what-is [Accessed 14th June 2022].
11 BreastCancer.org. *Metastatic Breast Cancer.* 2022. Available from: https://www.breastcancer.org/types/metastatic [Accessed 14th June 2022].
12 National Cancer Institute. *unresectable.* 2022. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/unresectable [Accessed 14th June 2022].
13 Moffitt Cancer Center. *HER2 Positive Breast Cancer Symptoms.* 2022. Available from: https://moffitt.org/cancers/her2-positive-breast-cancer/symptoms/ [Accessed 13th June 2022].
14 Moffitt Cancer Center. *HER2 Positive Breast Cancer Risk Factors.* 2022. Available from: https://moffitt.org/cancers/her2-positive-breast-cancer/diagnosis/risk-factors/ [Accessed 13th June 2022].
15 MacMillan Cancer Support. *HER2 POSITIVE BREAST CANCER.* 2015. Available from: https://www.nhs.uk/ipgmedia/national/Macmillan%20Cancer%20Support/Assets/HER2positivebreastcancerMCS6pages.pdf [Accessed 13th June 2022].
16 NHS Digital. *Hospital Admitted Patient Care Activity 2020-21: Diagnosis.* 2021. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2020-21 [Accessed 14th June 2022].
17 National Institute for Health and Care Research. *Tucatinib with trastuzumab and capecitabine for treating HER2-positive advanced breast cancer after 2 or more anti-HER2 therapies.* 2022. Available from: https://www.nice.org.uk/guidance/ta786/chapter/1-Recommendations [Accessed 13th June 2022].
18 National Institute for Health and Care Research. *Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies.* 2021. Available from: https://www.nice.org.uk/guidance/ta704/chapter/1-Recommendations [Accessed 13th June 2022].
19 National Institute for Health and Care Research. *Guidance on the use of trastuzumab for the treatment of advanced breast cancer.* 2002. Available from: https://www.nice.org.uk/guidance/ta34/chapter/1-Guidance [Accessed 13th June 2022].
20 British National Formulary. *Tucatinib - Medicinal forms.* 2022. Available from: https://bnf.nice.org.uk/drugs/tucatinib/medicinal-forms/ [Accessed 13th June 2022].
21 British National Formulary. *Trastuzumab emtansine - Medicinal forms.* 2022. Available from: https://bnf.nice.org.uk/drugs/trastuzumab-emtansine/medicinal-forms/ [Accessed 13th June 2022].
22 Gennari A, André F, Barrios CH, Cortés J, de Azambuja E, DeMichele A, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Annals of Oncology*. 2021;32(12):1475-95. Available from: https://doi.org/10.1016/j.annonc.2021.09.019.
23 Martínez-Sáez O, Prat A. Current and Future Management of HER2-Positive Metastatic Breast Cancer. *JCO Oncology Practice*. 2021;17(10):594-604. Available from: https://doi.org/10.1200/OP.21.00172.
24 Gradishar WJ, Anderson BO, Abraham J, Aft R, Agnese D, Allison KH, et al. Breast Cancer, Version 3.2020, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2020;18(4):452-78. Available from: https://doi.org/10.6004/jnccn.2020.0016.

25 Giordano SH, Temin S, Chandarlapaty S, Crews JR, Esteva FJ, Kirshner JJ, et al. Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: ASCO Clinical Practice Guideline Update. *Journal of Clinical Oncology*. 2018;36(26):2736-40. Available from: https://doi.org/10.1200/JCO.2018.79.2697.

NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.