NIHR | Innovation Observatory

# HEALTH TECHNOLOGY BRIEFING
# JUNE 2020

# Tucatinib in addition to trastuzumab and capecitabine for advanced breast cancer

| | | | |
|---|---|---|---|
| **NIHRIO ID** | 12139 | **NICE ID** | 10398 |
| **Developer/Company** | Seattle Genetics Inc | **UKPS ID** | 657217 |

| | |
|---|---|
| **Licensing and market availability plans** | Currently in phase II development. |

## SUMMARY


Tucatinib in combination with trastuzumab and capecitabine is in clinical development for the treatment of unresectable or metastatic HER2-positive breast cancer. In HER2-positive breast cancer, the cancer cells have too much of a protein called HER2 on their surface. In normal cells, HER2 helps control cell growth. When it is made in larger than normal amounts by cancer cells, the cells may grow more quickly and are more likely to spread to other parts of the body. Metastatic breast cancer is cancer that has spread beyond the breast and nearby lymph nodes to other organs in the body, unresectable cancer cannot be treated with surgery.

Tucatinib is an oral medicine that is a tyrosine kinase inhibitor of the HER2 protein. By inhibiting HER2, it is hoped tucatinib will inhibit the growth of HER2-positive tumours. If licenced, tucatinib in addition to trastuzumab and capecitabine will provide an additional treatment option for adults with advanced HER2 positive metastatic breast cancer.

# PROPOSED INDICATION

In combination with trastuzumab and capecitabine for the treatment of patients with pre-treated locally advanced, unresectable or metastatic HER2-positive breast carcinoma.[1]

# TECHNOLOGY

## DESCRIPTION

Tucatinib (TUKYSA, ONT-380) is an investigational, oral tyrosine kinase inhibitor that is highly selective for the kinase domain of HER2 with minimal inhibition of epidermal growth factor receptor, which may alter the toxicity profile.[2] In vitro, tucatinib has inhibited phosphorylation of HER2 and HER3, resulting in inhibition of downstream MAPK and AKT signalling and cell growth (proliferation), and showed anti-tumour activity in HER2-expressing tumour cells. In vivo, Tucatinib has inhibited the growth of HER2-expressing tumors.[3]

In the phase II clinical trial (NCT02614794) patients received an oral dose of 300 mg of tucatinib twice daily in addition to 1000mg/m$^2$ of capecitabine twice daily on days 1-14 of each 21-day cycle and 8 mg/kg of trastuzumab intravenously on day 1 of cycle 1, followed by 6 mg/kg on day 1 of each 21-day cycle.[1]

## INNOVATION AND/OR ADVANTAGES

Despite dramatic therapeutic advances over the past 20 years, most patients with HER2-positive metastatic breast cancer ultimately die from their disease. Moreover, as systemic therapies have improved, the incidence of brain metastases, for which effective treatment options are limited, has increased such that brain metastases may develop in up to half of patients. Standard-of-care treatment for patients with HER2-positive metastatic breast cancer is first-line trastuzumab plus pertuzumab and a taxane, followed by second-line trastuzumab emtansine for patients who have disease progression.[2] After progression during treatment with trastuzumab emtansine, no single regimen is considered the standard of care; commonly used regimens include tyrosine kinase inhibitors such as lapatinib with trastuzumab or capecitabine, trastuzumab with chemotherapy, or participation in a clinical trial.[2]

The combination of tucatinib and the anti-HER2 antibody trastuzumab has shown increased anti-tumour activity in vitro and in vivo compared to either medicine alone.[3] In the phase II trial (HER2CLIMB), the estimated progression-free survival in the tucatinib-combination group was 33.1% compared to 12.3% in the placebo group.[2] A proposed advantage of tucatinib is that it is approximately 1000-fold more potent for HER2 than EGFR. Because of its selectivity for HER2, there are fewer EGFR-related toxicities, such as rash and diarrhoea, which are common with many of the other anti-HER TKIs.[4]

If licenced, this combination could provide an option for those patients who progress on previous HER2 targeted treatments.

## DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

In December 2019, the FDA granted Breakthrough Therapy designation for tucatinib in locally advanced or metastatic HER2-positive breast cancer.[5]

In June 2017, tucatinib received Orphan Drug designation from the FDA for the treatment of breast cancer patients with brain metastases.[6]

Tucatinib is in phase II clinical development for HER2+ metastatic colorectal cancer and HER2+ metastatic breast cancer with leptomeningeal disease.[7]

# PATIENT GROUP

## DISEASE BACKGROUND

Breast cancer is the most common malignancy diagnosed in women worldwide.[8] The exact etiology is unknown, but family history is a strong risk factor. Other risk factors for breast cancer include genetic causes, increased age, reproductive history and hormone exposure, lifestyle factors, medical history, and radiation exposure.[9] There are different immune/pathological subtypes of breast cancer. Among them, is HER2, a transmembrane receptor protein that is overexpressed in about 20% of breast cancers and associated with disease that is more aggressive in the absence of HER2 directed therapy. HER2 normally plays a role in cell growth and differentiation.[10]

Metastatic breast cancer (also called stage IV or advanced breast cancer) is breast cancer that has spread to another part of the body, most commonly the liver, brain, bones, or lungs. Cancer cells can break away from the original tumour in the breast and travel to other parts of the body through the bloodstream or the lymphatic system. Breast cancer can come back in another part of the body months or years after the original diagnosis and treatment.[11]

The first symptom of breast cancer most women notice is a lump or an area of thickened tissue in their breast. Other common signs and symptoms include a change in the size or shape of one or both breasts, nipple discharge, dimpling on the skin of the breasts, and rash on or around the nipple.[12] Breast cancer patients experience physical symptoms and psychosocial distress that adversely affect their quality of life (QOL). Treatment, including chemotherapy, can cause physical and psychological problems that adversely affect patient QOL.[13]

## CLINICAL NEED AND BURDEN OF DISEASE

About 1 in 8 women in the UK are diagnosed with breast cancer during their lifetime.[14] In England in 2017, there were 46,109 registrations of newly diagnosed cases of malignant neoplasm of breast (ICD-10 code C50), and the direct age-standardised rate per 100,000 population was 166.7 among females.[15] Incidence rates are projected to rise by 2% in the UK between 2014 and 2035, from 205 per 100,000 (54,833 cases) to 210 per 100,000 (71,022 cases).[16] UK Recommendations for HER2 assessment in breast cancer state between 13% and 20% of women with breast cancer have HER2 positive cancers.[17] This would be approximate to between 5,994 and 9,222 of the newly diagnosed breast cancer cases in England in 2017.[15]

In 2018-19 there were 219,885 finished consultant episodes (FCEs) and 80,435 FCE bed days with a primary diagnosis of malignant neoplasm of breast (ICD-10; C50). There were 215,644 hospital admissions, of which 183,828 were day cases.[18] In England and Wales in 2018, there were 10,314 registrations of death from malignant neoplasm of breast,[19] and the directly age standardised death rate per 100,000 population was 33.6.[15]

# PATIENT TREATMENT PATHWAY

## TREATMENT PATHWAY

The management of breast cancer requires different approaches and involves the use of different therapies. Patients are assigned to a multidisciplinary team to provide the best treatment and care. The main treatments for breast cancer include surgery, radiotherapy, chemotherapy, hormone therapy, and biological therapy (targeted therapy). Patients may have one of these treatments or a combination. The type or combination of treatments will depend on how the cancer was diagnosed and the stage it is at.[20]

For advanced/metastatic HER2-positive breast cancer, NICE pathways recommends a sequence of first-line, second-line and third-line treatment options that combines biological therapies with chemotherapy.[21]

## CURRENT TREATMENT OPTIONS

The second line treatment of advanced HER2-positive breast cancer includes:[21]

- Trastuzumab emtansine is recommended, as an option for treating HER2-positive, unresectable, locally advanced or metastatic breast cancer in adults who previously received trastuzumab and a taxane, separately or in combination. Patients should have either received prior therapy for locally advanced or metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy.

The third line treatment of advanced HER2-positive breast cancer includes:[21]

- Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens.

## PLACE OF TECHNOLOGY

If licenced, tucatinib in addition to trastuzumab and capecitabine will provide an additional treatment option for the treatment of adult patients with pre-treated locally advanced unresectable or metastatic HER2-positive breast cancer.[1]

# CLINICAL TRIAL INFORMATION

| | |
|---|---|
| **Trial** | **HER2CLIMB**, NCT02614794, 2015-002801-12; Phase 2 Randomized, Double-Blinded, Controlled Study of Tucatinib vs Placebo in Combination With Capecitabine and Trastuzumab in Patients With Pre-treated Unresectable Locally Advanced or Metastatic HER2+ Breast Carcinoma<br>**Phase II - ongoing**<br>**Location:** EU countries (inc UK), United States, Canada and other countries. |
| **Trial design** | Randomised, parallel assignment, double-blind |
| **Population** | N=612, aged 18 years and older, advanced HER2+ breast carcinoma, previous treated with trastuzumab, pertuzumab, and T-DM1. |
| **Intervention(s)** | Tucatinib 300mg orally twice daily in combination with capecitabine 1000mg/m$^2$ administered twice per day, orally in Days 1-14 of each 21-day cycle and trastuzumab administered 8 mg/kg intravenously (IV) on Day 1 of Cycle 1, followed by 6 mg/kg on Day 1 of each 21-day cycle. |
| **Comparator(s)** | Placebo in combination with capecitabine and trastuzumab. |
| **Outcome(s)** | Primary Outcome Measure(s) : |

| | |
|---|---|
| | • Progression-free survival (PFS) per RECIST 1.1 as determined by blinded independent central review (BICR) (Double-blind Phase) [Time frame: 48 months]<br><br>See trial record for full list of outcomes. |
| **Results (efficacy)** | At 1 year, the estimated progression-free survival was 33.1% (95% confidence interval [CI], 26.6 to 39.7) in the tucatinib-combination group and 12.3% (95% CI, 6.0 to 20.9) in the placebo combination group, and the median duration of progression-free survival was 7.8 months (95% CI, 7.5 to 9.6) and 5.6 months (95% CI, 4.2 to 7.1), respectively.[2] |
| **Results (safety)** | Adverse events led to the discontinuation of tucatinib in 5.7% of the patients, to the discontinuation of placebo in 3.0% of the patients.<br>Adverse events that were reported in at least 20% of the patients in the tucatinib-combination group were diarrhoea, PPE syndrome, nausea, fatigue, vomiting, stomatitis, decreased appetite, and headache.[2] |

| | |
|---|---|
| **Trial** | NCT02025192; A Phase 1b, Open-label Study to Assess the Safety and Tolerability of Tucatinib (ONT-380) Combined With Capecitabine and Trastuzumab, Alone and in Combination in HER2+ Metastatic Breast Cancer<br>**Phase I - completed**<br>**Location:** United States |
| **Trial design** | Open label, parallel assignment, non-randomised. |
| **Population** | N=60, aged 18 years and older, metastatic HER2+ breast carcinoma, previous treated with trastuzumab and T-DM1. |
| **Intervention(s)** | Tucatinib 300mg orally twice daily in combination with capecitabine 1000mg/m$^2$ administered twice per day, orally in Days 1-14 of each 21-day cycle and trastuzumab administered at a loading dose of 8 mg/kg IV followed by 6 mg/kg once every 21 days. |
| **Comparator(s)** | Tucatinib in combination with capecitabine or trastuzumab. |
| **Outcome(s)** | Primary Outcome Measure(s):<br>• Incidence of adverse events [Time frame: up to approximately 4 years]<br>• Severity of adverse events [Time frame: up to approximately 4 years]<br><br>See trial record for full list of outcomes. |
| **Results (efficacy)** | The proportion of patients with measurable disease achieving objective response was 83% (five of six patients) in the combination of tucatinib with capecitabine, 40% (six of 15 patients) in the combination of tucatinib with trastuzumab, and 61% (14 of 23 patients) in the combination of tucatinib with both capecitabine and trastuzumab.[22] |
| **Results (safety)** | Adverse events seen at the recommended phase 2 dose regardless of causality, grade, and treatment group included diarrhoea (35 [67%] of 52 patients), nausea (31 [60%] patients), palmar-plantar erythrodysaesthesia syndrome (23 [44%] patients), fatigue (20 [38%] patients), and vomiting (20 [38%] patients).[22] |

## ESTIMATED COST

The cost of tucatinib is not known yet.

# RELEVANT GUIDANCE

## NICE GUIDANCE

- NICE technology appraisal guidance. Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer (TA632). June 2020.
- NICE technology appraisal guidance. Pertuzumab with trastuzumab and docetaxel for treating HER2-positive breast cancer (TA509). March 2018.
- NICE technology appraisal guidance. Trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane (TA458). November 2017.
- NICE technology appraisal guidance. Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens (TA423). December 2016.
- NICE technology appraisal guidance. Trastuzumab emtansine for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane (TA371). December 2015.
- NICE technology appraisal guidance. Lapatinib or trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2. (TA257) June 2012.
- NICE clinical guideline. Advanced breast cancer: diagnosis and treatment (CG81). August 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 School of Oncology (ESO) and the European Society for Medical Oncology (ESMO). 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). 2018.[23]
- National Comprehensive Cancer Network (NCCN). Breast Cancer, Version 4.2017, NCCN Clinical Practice Guidelines in Oncology. 2018.[24]

# ADDITIONAL INFORMATION

# REFERENCES


1 Clinicaltrials.gov. A Study of Tucatinib vs. Placebo in Combination With Capecitabine & Trastuzumab in Patients With Advanced HER2+ Breast Cancer (HER2CLIMB). *Trial ID: NCT02614794*. 2015;Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT02614794.

2 Murthy RK, Loi S, Okines A, Paplomata E, Hamilton E, Hurvitz SA, et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. *N Engl J Med*. 2020 Feb 13;382(7):597-609. Available from: https://doi.org/10.1056/NEJMoa1914609.

3 BioSpace. *Seattle Genetics Announces U.S. FDA Approval of TUKYSA™ (tucatinib) for People with Advanced Unresectable or Metastatic HER2-Positive Breast Cancer*. 2020. Available from: https://www.biospace.com/article/releases/seattle-genetics-announces-u-s-fda-approval-of-tukysa-tucatinib-for-people-with-advanced-unresectable-or-metastatic-her2-positive-breast-cancer/?s=74 [Accessed 05 May 2020].

4 Pernas S, Tolaney SM. HER2-positive breast cancer: new therapeutic frontiers and overcoming resistance. *Therapeutic Advances in Medical Oncology*. 2019;11:1758835919833519-. Available from: https://doi.org/10.1177/1758835919833519.

5 Genetics S. *Seattle Genetics Announces U.S. FDA Grants Breakthrough Therapy Designation for Tucatinib in Locally Advanced or Metastatic HER2-Positive Breast Cancer*. 2019. Available from: https://investor.seattlegenetics.com/press-releases/news-details/2019/Seattle-Genetics-Announces-US-FDA-Grants-Breakthrough-Therapy-Designation-for-Tucatinib-in-Locally-Advanced-or-Metastatic-HER2-Positive-Breast-Cancer/default.aspx [Accessed 05 May 2020].

6 BioSpace. *Cascadian Therapeutics' Lead Candidate, Tucatinib, Receives Orphan Drug Designation From FDA For Treatment Of Breast Cancer Patients With Brain Metastases.* 2017. Available from: https://www.biospace.com/article/releases/cascadian-therapeutics-lead-candidate-tucatinib-receives-orphan-drug-designation-from-fda-for-treatment-of-breast-cancer-patients-with-brain-metast/ [Accessed 06 May 2020].

7 Clinicaltrials.gov. *Search: Tucatinib | Phase 2, 3*. 2020. Available from: https://clinicaltrials.gov/ct2/results?term=Tucatinib&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 05 May 2020].

8 Harbeck N, Gnant M. Breast cancer. *The Lancet*. 2017 2017/03/18;389(10074):1134-50. Available from: https://doi.org/10.1016/S0140-6736(16)31891-8.

9 National Health Service. *Causes - Breast cancer in women*. 2019. Available from: https://www.nhs.uk/conditions/breast-cancer/causes/ [Accessed 06 May 2020].

10 Ahmed S, Sami A, Xiang J. HER2-directed therapy: current treatment options for HER2-positive breast cancer. *Breast Cancer*. 2015 2015/03/01;22(2):101-16. Available from: https://doi.org/10.1007/s12282-015-0587-x.

11 BreastCancer.org. *Metastatic Breast Cancer*. 2020. Available from: https://www.breastcancer.org/symptoms/types/recur_metast [Accessed 06 May 2020].

12 American Cancer Society. *Breast Cancer Signs and Symptoms*. 2019. Available from: https://www.cancer.org/cancer/breast-cancer/about/breast-cancer-signs-and-symptoms.html [Accessed 05 May 2020].

13 Perry S, Kowalski TL, Chang C-H. Quality of life assessment in women with breast cancer: benefits, acceptability and utilization. *Health and Quality of Life Outcomes*. 2007 2007/05/02;5(1):24. Available from: https://doi.org/10.1186/1477-7525-5-24.

14 National Health Service. *Overview - Breast cancer in women*. 2019. Available from: https://www.nhs.uk/conditions/breast-cancer/ [Accessed 06 May 2020].

15 Office for National Statistics. *Cancer Registration Statistics, England*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland

16 Cancer Research UK. *Cancer incidence for common cancers*. 2019. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/common-cancers-compared#heading-Four [Accessed 05 May 2020].

17 Rakha EA, Pinder SE, Bartlett JMS, Ibrahim M, Starczynski J, Carder PJ, et al. Updated UK Recommendations for HER2 assessment in breast cancer. *Journal of Clinical Pathology*. 2015;68(2):93. Available from: https://doi.org/10.1136/jclinpath-2014-202571.

18 NHS Digital. *Hospital Episode Statistics for England. Admitted Patient Care statistics, 2018-19*. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19

19 Office for National Statistics. *Deaths registered in England and Wales – 21st century mortality: 2018*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/the21stcenturymortalityfilesdeathsdataset

20 National Health Service. *Treatment - Breast cancer in women*. 2019. Available from: https://www.nhs.uk/conditions/breast-cancer/treatment/ [Accessed 05 May 2020].

21 National Institute for Health and Care Excellence. *Managing advanced breast cancer* 2020. Available from: https://pathways.nice.org.uk/pathways/advanced-breast-cancer/managing-advanced-breast-cancer [Accessed 12 May 2020].

22 Murthy R, Borges VF, Conlin A, Chaves J, Chamberlain M, Gray T, et al. Tucatinib with capecitabine and trastuzumab in advanced HER2-positive metastatic breast cancer with and without brain metastases: a non-randomised, open-label, phase 1b study. *The Lancet Oncology*. 2018 2018/07/01;19(7):880-8. Available from: https://doi.org/10.1016/S1470-2045(18)30256-0.

23 Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, Andre F, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)dagger. *Ann Oncol*. 2018 Aug 1;29(8):1634-57. Available from: https://doi.org/10.1093/annonc/mdy192.

24 Gradishar WJ, Anderson BO, Balassanian R, Blair SL, Burstein HJ, Cyr A, et al. Breast Cancer, Version 4.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2018 Mar;16(3):310-20. Available from: https://doi.org/10.6004/jnccn.2018.0012.