NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Tucatinib with trastuzumab and capecitabine for treating HER2-positive unresectable or metastatic advanced breast cancer after 2 or more anti-HER2 therapies

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of tucatinib with trastuzumab and capecitabine within its marketing authorisation for treating HER2-positive unresectable or metastatic advanced breast cancer after 2 or more anti-HER2 therapies.

Background

Breast cancer arises from the tissues of the ducts or lobules of the breast. Metastatic breast cancer is when the cancer has spread beyond the breast and nearby lymph nodes to other organs in the body. Unresectable means that the cancer cannot be treated by surgery. Human epidermal growth factor receptor 2 (HER2) is a receptor for a growth factor which occurs naturally in the body. When human epidermal growth factor attaches itself to HER2 receptors on breast cancer cells, it can stimulate the cells to divide and grow. Some breast cancer cells have more HER2 receptors than others. In this case, the tumour is described as being HER2-positive.

In 2017, there were 46,109 new diagnoses of breast cancer in England.[1] There were approximately 2,300 cases of stage IV breast cancer in the UK in 2016 according to the National Cancer Registration and Analysis Service.[2] In 2017 in England, there were 10,219 deaths from breast cancer.[3] It is estimated that approximately 15 to20% of women with breast cancer will have HER2-positive tumours.[4] Brain metastases may develop in up to half of patients with HER2-positive tumours.[5]

Current treatments for advanced breast cancer aim to relieve symptoms, prolong survival and maintain a good quality of life with few adverse events. Treatment depends on whether the cancer cells have particular receptors (hormone receptor status or HER2 status), the extent of the disease and previous treatments.

For people with HER2-positive unresectable or metastatic breast cancer who have not had previous anti-HER2 treatment or chemotherapy for their metastatic disease, NICE technology appraisal guidance 509 recommends pertuzumab with trastuzumab and docetaxel as first line treatment. In addition, NICE technology appraisal guidance 34 recommends trastuzumab with paclitaxel as an option for people with tumours expressing HER2 who have not received chemotherapy for metastatic breast cancer and in whom anthracycline is not appropriate. For disease that has progressed, NICE technology appraisal guidance 458 recommends trastuzumab emtansine as an option for treating HER2-positive unresectable, locally advanced or metastatic breast cancer after trastuzumab and a taxane. There is currently no standard of care for HER2-targeted therapy in people with metastatic HER2-positive breast cancer whose disease has progressed on or after trastuzumab emtansine. NICE clinical guideline (CG81) recommends that patients may receive treatment with non-targeted

chemotherapies such as capecitabine or vinorelbine. NICE technology appraisal guidance 423 recommends eribulin for locally advanced or metastatic breast cancer after 2 or more lines of chemotherapy regimens. In addition, lapatinib is a HER2 targeted treatment which in combination with capecitabine or trastuzumab is also licensed for use at this point in the treatment pathway. Lapatinib is not funded for this indication in England.

The technology

Tucatinib (Tukysa, Seattle Genetics Inc.) is a selective tyrosine kinase inhibitor of the HER2 receptor protein on the surface of the cancer cell. By inhibiting HER2, tucatinib interrupts cell signalling pathways and in turn stops the growth of HER2-positive tumours. It is given orally.

Trastuzumab (Herceptin, Roche) is a recombinant, humanized monoclonal antibody, which specifically targets the HER2 protein expressed on the cell-surface, inhibiting cell proliferation. It is given intravenously.

Capecitabine (Xeloda, Roche) is a fluoropyrimidine carbamate precursor of the chemotherapy drug fluorouracil (5-FU). Enzymes principally located in the liver and tumour tissue change capecitabine into 5-FU, which stops cells making and repairing DNA. It is given orally.

Tucatinib with trastuzumab and capecitabine does not currently have a marketing authorisation in the UK for treating HER2-positive advanced breast cancer after 2 or more anti-HER2 therapies. It has been studied in a randomised controlled trial compared with placebo with trastuzumab and capecitabine in adults previously treated with trastuzumab, pertuzumab, and trastuzumab emtansine, with unresected locally advanced or metastatic HER2 positive breast cancer.

Intervention(s)	Tucatinib with trastuzumab and capecitabine
Population(s)	People with HER2-positive, unresectable locally advanced or metastatic breast cancer who have had 2 or more prior anti-HER2 therapies
Comparators	• capecitabine • vinorelbine • eribulin

Outcomes	The outcome measures to be considered include: • progression free survival • overall survival • response rate • duration of response • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.
Other considerations	If the evidence allows the following subgroups will be considered. These include: • People with brain metastases Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. The availability and cost of biosimilar and generic products should be taken into account.
Related NICE recommendations and NICE Pathways	**Related Technology Appraisals:** Trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane (2017) NICE technology appraisal guidance 458. Review date 2020 Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens (2016) NICE technology appraisal guidance TA423. Review date TBC.

	Guidance on the use of trastuzumab for the treatment of advanced breast cancer (2002) NICE technology appraisal guidance TA34. Review date TBC. Appraisals in development (including suspended appraisals) Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies [ID2697]. Technology appraisal in development. Expected publication date 19 May 2021 Pertuzumab–trastuzumab with chemotherapy for treating HER2-positive breast cancer [ID2724].Technology appraisal in development. Expected publication date 23 June 2021 Neratinib for treating HER2-positive breast cancer after 2 therapies [ID1381] NICE technology appraisal in development. Publication expected December 2021 **Related Guidelines:** Advanced breast cancer: diagnosis and treatment (2009) NICE guideline CG81 last updated August 2017 Early and locally advanced breast cancer (update) (2018) NICE guideline 101. Reviewed 2020. **Related Quality Standards:** Breast cancer (2011, updated 2016) NICE quality standard QS12 **Related NICE Pathways:** Advanced breast cancer (2018) NICE pathway
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) Specialist cancer services (adults) Chapter 105 Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 1 and 2. Department of Health, Improving Outcomes: A Strategy for Cancer, fourth annual report, Dec 2014

Questions for consultation

Have all relevant comparators for tucatinib with trastuzumab and capecitabine been included in the scope?

Would trastuzumab monotherapy or trastuzumab with chemotherapy be used in this population in clinical practice?

As trastuzumab is included in the NICE recommended combinations for both untreated HER2-positive breast cancer and after one prior therapy, would it be used again in a different combination after two prior therapies and beyond?

Are the outcomes listed appropriate?

Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom tucatinib with trastuzumab and capecitabine is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Would the comparators for people with brain metastases differ to those listed in the scope?

Where do you consider tucatinib with trastuzumab and capecitabine will fit into the existing NICE pathway, advanced breast cancer?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which tucatinib with trastuzumab and capecitabine will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider tucatinib with trastuzumab and capecitabine to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of tucatinib with trastuzumab and capecitabine can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

References

1. Office for National Statistics. Cancer registration statistics, England 2017. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland Accessed September 2020

2. National Cancer Registration and Analysis Service (NCRAS). Stage breakdown by CCG 2016. London: Public Health England, 2016. Available from: http://www.ncin.org.uk/view?rid=3604 Accessed September 2020

3. Office for National Statistics. Death Registrations Summary Statistics, England and Wales, 2017. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathregistrationssummarytablesenglandandwalesreferencetables Accessed September 2020

4. Macmillan Cancer Support Receptors for HER2. Available from https://www.macmillan.org.uk/cancer-information-and-support/breast-cancer/receptors-for-breast-cancer Accessed September 2020

5. Rashmi K., Murthy, M.D., Sherene Loi, M.D.*et al.* Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. New England Journal of Medicine 2020. 382:597-609.