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Trastuzumab Emtansine for HER2-positive breast cancer - adjuvant

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LAY SUMMARY

Breast cancer is the most common cancer in the UK. One type of breast cancer is called HER2-positive. HER is a protein that is found in large amounts on the surface on some cancer cells where it stimulates their growth. HER2-positive breast cancer tends to grow faster than HER2-negative breast cancer. Treatment of early stage breast cancer usually involves surgery. Most patients will often receive some treatment (e.g. chemotherapy and radiotherapy) both before and after the surgery to improve the success rate of the treatment.

Trastuzumab emtansine is a cancer medicine that is already licensed for some specific types of advanced and metastatic HER2-positive breast cancer. Trastuzumab emtansine is a single intravenous medicine made up of two different products coupled together; trastuzumab (an antibody drug against HER2-positive cells), and emtansine (a cytotoxic chemotherapy). Trastuzumab works by recognising and attaching to the HER2 proteins, stimulating the immune system to kill the cancer cells. Emtansine acts by killing cancer cells when they attempt to grow. Trastuzumab emtansine is being developed as an additional cancer treatment given after the initial treatment for HER2-positive early breast cancer and when there is residual cancer remaining after surgery. If licensed, trastuzumab emtansine will offer additional treatment option for this patient group.

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TARGET GROUP

Breast cancer (HER2-positive, residual following preoperative therapy) - adjuvant

TECHNOLOGY

DESCRIPTION

Trastuzumab emtansine (Kadcyla) is an antineoplastic agent. It 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). Emtansine refers to the MCC-DM1 complex. 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 internalization and subsequent lysosomal degradation, resulting in release of DM1-containing cytotoxic catabolites (primarily lysine-MCC-DM1).

Trastuzumab emtansine has the mechanisms of action of both trastuzumab and DM1:[1]

- Trastuzumab emtansine, like trastuzumab, binds to domain IV of the HER2 extracellular domain (ECD), as well as to Fcγ receptors and complement C1q. In addition, trastuzumab emtansine, like trastuzumab, inhibits shedding of the HER2 ECD, inhibits signalling through the phosphatidylinositol 3-kinase (PI3-K) pathway, and mediates antibody-dependent cell-mediated cytotoxicity (ADCC) in human breast cancer cells that overexpress HER2.
- DM1, the cytotoxic component of trastuzumab emtansine, binds to tubulin. By inhibiting tubulin polymerization, both DM1 and trastuzumab emtansine cause cells to arrest in the G2/M phase of the cell cycle, ultimately leading to apoptotic cell death. Results from in vitro cytotoxicity assays show that DM1 is 20-200 times more potent than taxanes and vinca alkaloids.
- The MCC linker is designed to limit systemic release and increase targeted delivery of DM1, as demonstrated by detection of very low levels of free DM1 in plasma.[1]

Trastuzumab emtansine is being developed as an adjuvant therapy for HER2-positive invasive breast cancer in patients who have residual tumour in the breast or axillary lymph nodes following preoperative treatment. In the phase III clinical trial (KATHERINE; NCT01772472), trastuzumab emtansine is given as an adjuvant therapy at a dose of 3.6 mg/kg intravenously every 3 weeks, 14 cycles. Radiotherapy and/or hormone therapy will be given in addition if indicated.[2]

Trastuzumab emtansine is currently licenced as a single agent for the treatment of adult patients with HER2-positive, 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, or
- Developed disease recurrence during or within six months of completing adjuvant therapy.[1]

The most common adverse reactions of trastuzumab emtansine (occuring in more than one in ten people) are urinary tract infection, insomnia, neuropathy peripheral, epistaxis, cough, stomatitis, diarhhoea, constipation, dry mouth, rash, haemorrhage, pyrexia, dyspnoea, musculoskeletal pain,

arthralgia, myalgia, asthenia, chills, thrombocytopenia, abdominal pain, vomiting, nausea, fatigue, and headache, , anaemia, neutropenia, and hypokalaemia.[1]

Trastuzumab Emtansine is currently in phase III stage of development for HER2 positive early breast cancer and HER2 positive gastric cancer[3] and in phase II stage of development for:

- HER2 positive breast cancer
- HER2 positive gastric cancer
- HER2 positive solid tumours [4]

INNOVATION and/or ADVANTAGES

Amplification of HER2 is associated with shortened survival in breast cancer patients. Combining HER2-targeted agents with standard chemotherapy is an effective therapeutic approach for patients with HER2-positive metastatic breast cancer. When combined with first-line chemotherapy, trastuzumab increases the time to progression and overall survival among patients with metastatic disease. Trastuzumab emtansine incorporates the HER2-targeted antitumor properties of trastuzumab with the cytotoxic activity of DM1. It allows intracellular drug delivery specifically to HER2-overexpressing cells, thereby improving the therapeutic index and minimizing exposure of normal tissue.[5]

If licensed, trastuzumab emtansine will offer additional adjuvant treatment option for patients with HER2-positive breast cancer who have residual tumour in the breast or axillary lymph nodes following preoperative therapy.

DEVELOPER

Roche Products Ltd

PATIENT GROUP

BACKGROUND

Breast cancer most commonly starts in the cells that line the ducts of the breast. [6] There are several types of breast cancer described according to the receptors expressed on the surface of tumour cells, stage of diagnosis, and rate of growth.[7] Human Epidermal growth factor Receptor 2 (HER2) is a protein that can affect the growth of some cancer cells which is found on the surface of normal breast cells. Some breast cancer cells have a very high number of HER2 receptors. The extra HER2 receptors stimulate the cancer cells to divide and grow. When there are higher levels of the HER2 protein in a breast cancer, it is called HER2 positive breast cancer. HER2 positive breast cancers tend to grow more quickly than HER2 negative breast cancers.[8]

The causes of breast cancer are not completely understood, however a number of factors are known to increase its likelihood, such as exposure to radiation, increased alcohol consumption, being taller, being overweight or obese, exposure to oestrogen and hormone replacement therapy, greater breast tissue density, and genetic factors. The risk of developing breast cancer is also known to increase markedly with inheritance of certain genes (e.g. BRCA2, BRCA1 and TP53).[9]

Symptoms of breast cancer may include breast lump, change in size, shape or feel of the breast, breast pain, skin changes including puckering, dimpling, a rash, or redness of the skin of the breast, change in the position of the nipple, and fluid leaking from the nipple. Sometimes, in a rare type of breast cancer the whole breast might look red and inflamed and feel sore.[10]

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, and cancer can have other effects including anger, grief, suffering and pain.[11]

CLINICAL NEED and BURDEN OF DISEASE

Breast cancer is the most common cancer in the UK, accounting for 15% of all newly diagnosed cancers. The UK incidence rate is sixth highest in Europe.[12] In females in the UK it is the most common cancer (31% of all new female cancer cases). Age standardised incidence rate of breast cancer in 2015 in England was 90.2 per 100,000.

Breast cancer incidence is strongly related to age, with the highest incidence rates being in older people. In the UK in 2013-2015, on average each year a quarter (25%) of new cases were in people aged 75 years and over.[13] Incidence rates for breast cancer are projected to rise by 2% in the UK between 2014 and 2035, to 210 cases per 100,000 females by 2035.[12]

In England in 2016 there were 45,960 registrations of newly diagnosed cases of malignant neoplasm of breast (ICD-10 code C50), and the directly age-standardised rate per 100,000 population was 169.2 for all cases.[14]

Between 15 and 25 out of every 100 women with breast cancer (15–25%) have HER2 positive cancers.[8] This would be approximate to 6894 and 11,490 of the newly diagnosed breast cancer cases in England in 2016.

The company estimate the UK patient population as 3,290 HER2+ treatment eligible patients in 2021 for post-neoadjuvant adjuvant therapy.[15]

In England in 2016/17 there were 207,043 finished consultant episodes (FCEs) and 85,801 FCE bed days with primary diagnosis of ICD-10 code C50 (malignant neoplasm of breast). There were 203,454 hospital admissions, of which 169,800 were day cases.[16]

Age standardised mortality rate of breast cancer in the UK for 2016 was 34.1 per 100,000. Highest mortality rates are in older people with an average of almost half (47%) of deaths each year in the UK in 2014-2016 were in people aged 75 and over. In England in 2016, there were 9,685 registrations of death from neoplasm of the breast, and the directly age-standardised death rate per 100,000 population was 34.4.[14]

Regarding survival rates for breast cancer, age-standardised one-, five-, and ten-year net survival rates among women aged 15-99 in England and Wales in 2010-2011 was 96%, 86.6%, and 78.4% respectively.[17]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Pertuzumab for adjuvant treatment of early HER2-positive breast cancer (ID1192). Expected publication date: October 2018.
- NICE technology appraisal guidance. Pertuzumab with trastuzumab and docetaxel for treating HER2-positive breast cancer (TA509). March 2018.

- NICE technology appraisal guidance. Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer (TA424). December 2016.

NHS ENGLAND and POLICY 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

- National Comprehensive Cancer Network (NCCN). Breast Cancer, Version 4.2017, NCCN Clinical Practice Guidelines in Oncology. March 2018.[18]
- European School of Oncology (ESO) and European Society for Medical Oncology (ESMO). ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). 2014.[19]

CURRENT TREATMENT OPTIONS

NICE recommends to consider adjuvant therapy for all patients with early invasive breast cancer after surgery. Adjuvant chemotherapy or radiotherapy needs to be started as soon as clinically possible, within 31 days of completion of surgery in patients with early breast cancer having these treatments.[20]

Trastuzumab, given at three-week intervals for one year or until disease recurrence (whichever is the shorter period), is recommended by NICE as a treatment option for women with early-stage HER2-positive breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable).[21]

For patients with lymph node-positive breast cancer, NICE recommends docetaxel as part of an adjuvant chemotherapy regimen. Docetaxel, when given concurrently with doxorubicin and cyclophosphamide (the TAC regimen) as per its licensed indication, is recommended as an option for the adjuvant treatment of women with early node-positive breast cancer.[22]

For patients with early invasive breast cancer who have had a mastectomy and are at a high risk of local recurrence (include those with four or more positive axillary lymph nodes or involved resection margins), NICE recommends offering adjuvant chest wall radiotherapy.[23]

EFFICACY and SAFETY

Trial	KATHERINE, NCT01772472, BO27938; 18 years and older; trastuzumab emtansine vs trastuzumab; phase III
Sponsor	Hoffmann-La Roche
Status	Ongoing
Source of Information	Trial registry[2]
Location	EU (incl UK), USA, Canada and other countries.
Design	Randomised, active-controlled, parallel assignment, open label
Participants	n=1487; aged 18 years and older; males and females; invasive breast carcinoma; HER2-positive; clinical stage T1-4/N0-3/M0 at presentation

	(Tumour (T), Node (N), Metastasis (M)); residual tumour present pathologically in the breast or axillary lymph nodes following preoperative therapy.
Schedule	Randomised to: • Trastuzumab emtansine at a dose of 3.6 mg/kg intravenously every 3 weeks for 14 cycles; or • Trastuzumab at a dose of 6 mg/kg intravenously every 3 weeks for 14 cycles
Follow-up	Active treatment period: 14 cycles (duration of the cycle is not reported) Follow up period: up to 10 years
Primary Outcomes	Invasive disease-free survival (IDFS) [Time Frame: up to 10 years]
Secondary Outcomes	Time frame: up to 10 years • Invasive disease-free survival including second non-breast cancers • Disease-free survival • Overall survival • Distant recurrence-free interval • Safety: Incidence of adverse events • Incidence of cardiac events • Patient reported outcomes: European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Quetionnaire QLQ-C30/QLQ-BR23, EuroQol EQ-5d Questionnaire
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as April 2023.

ESTIMATED COST and IMPACT

COST

- The NHS indicative price for trastuzumab emtansine (Kadcyla) 100mg powder for concentrate for solution for infusion vials (one vial) (Roche Products Ltd) is £1641.01.[24]

The NHS indicative price for trastuzumab emtansine (Kadcyla) 160mg powder for concentrate for solution for infusion vials (one vial) (Roche Products Ltd) is £2625.62.[24]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other: *specify*

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other: *specify*

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs: *specify*

☐ Other reduction in costs

☐ Other: *specify*

☒ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified: *specify*

☒ None identified

REFERENCES

[1] electronic Medicines Compendium (eMC). *Kadcyla 100 mg & 160 mg Powder for Concentrate for Solution for Infusion.* Available from: https://www.medicines.org.uk/emc/product/5252#PRODUCTINFO [Accessed 18th Jun 2018].

[2] ClinicalTrials.gov. *A Study of Trastuzumab Emtansine Versus Trastuzumab as Adjuvant Therapy in Patients With HER2-Positive Breast Cancer Who Have Residual Tumor in the Breast or Axillary Lymph Nodes Following Preoperative Therapy (KATHERINE): NCT01772472.* Available from: https://clinicaltrials.gov/ct2/show/study/NCT01772472 [Accessed 18th Jun 2018].

[3] ClinicalTrials.gov. *Search results: Trastuzumab Emtansine |roche |Phase 3*. Available from: https://clinicaltrials.gov/ct2/results?cond=&term=&type=&rslt=&age_v=&gndr=&intr=Trastuzumab+Emtansine&titles=&outc=&spons=roche&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=2&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&lupd_s=&lupd_e= [Accessed 18th Jun 2018].

[4] ClinicalTrials.gov. *Search results: Trastuzumab Emtansine |roche |Phase 2.* Available from: https://clinicaltrials.gov/ct2/results?cond=&term=&type=&rslt=&age_v=&gndr=&intr=Trastuzumab+Emtansine+&titles=&outc=&spons=roche&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=1&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&lupd_s=&lupd_e= [Accessed 18th Jun 2018].

[5] Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, Pegram M, Oh DY, Diéras V, Guardino E, Fang L. Trastuzumab emtansine for HER2-positive advanced breast cancer. *New England Journal of Medicine*. 2012 Nov 8;367(19):1783-91. Available from: https://doi.org/10.1056/NEJMoa1209124

[6] Cancer Research UK. *Breast cancer*. 21st Sep 2017. Available from: http://www.cancerresearchuk.org/about-cancer/breast-cancer/about [Accessed 18th Jun 2018].

[7] American Cancer Society. *Breast cancer facts & figures 2017-2018.* Available from: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2017-2018.pdf [Accessed 18th Jun 2018].

[8] Macmillan Cancer Support. *HER2 positive breast cancer.* Available from: https://www.macmillan.org.uk/cancerinformation/cancertypes/breast/aboutbreastcancer/typesandrelatedconditions/her2%20positive.aspx [Accessed 18th Jun 2018].

[9] NHS Choices. *Breast cancer in women*. 29th Sep 2016. Available from: https://www.nhs.uk/conditions/breast-cancer/causes/#lifestyle-factors [Accessed 18th Jun 2018].

[10] Cancer Research UK. *Breast cancer: symptoms. 26th Sep 2017.* Available from: http://www.cancerresearchuk.org/about-cancer/breast-cancer/symptoms [Accessed 18th Jun 2018].

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

[12] Cancer Research UK. *Breast cancer statistics.* Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer#heading-Zero [Accessed 18th Jun 2018].

[13] Cancer Research UK. *Breast cancer incidence (invasive) statistics.* Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive#heading-One [Accessed 18th Jun 2018].

[14] Office for National Statistics. *Cancer Registration Statistics, England 2016.* Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 18th Jun 2018].

[15] UK PharmaScan. *Technology Summary (644993).* Available from: https://www.ukpharmascan.org.uk/HS/technology/644993 [Accessed 25 July 2018]. Login Required.

[16] NHS Digital. *Hospital Admitted Patient Care Activity, 2016-17*. Available from: https://digital.nhs.uk/catalogue/PUB30098 [Accessed 23 October 2017]

[17] Cancer Research UK. *Breast cancer survival statistics*. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/survival#heading-Zero [Accessed 28th Jun 2018].

[18] Gradishar WJ, Anderson BO, Balassanian R, Blair SL, Burstein HJ, Cyr A, Elias AD, Farrar WB, Forero A, Giordano SH, Goetz MP. Breast Cancer, Version 4.2017, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network*. 2018 Mar 1;16(3):310-20. Available from: https://doi.org/10.6004/jnccn.2018.0012

[19] Cardoso F, Costa A, Norton L, Senkus E, Aapro M, Andre F, Barrios CH, Bergh J, Biganzoli L, Blackwell KL, Cardoso MJ. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). *Annals of oncology.* 2014 Sep 18;25(10):1871-88. Available from: https://doi.org/10.1093/annonc/mdu385

[20] National Institute for Health and Care Excellence. *NICE pathway: adjuvant therapy for early and locally advanced breast cancer.* Available from: https://pathways.nice.org.uk/pathways/early-and-locally-advanced-breast-cancer/adjuvant-therapy-for-early-and-locally-advanced-breast-cancer#content=view-node%3Anodes-adjuvant-therapy-planning [Accessed 28th Jun 2018].

[21] National Institute for Health and Care Excellence. *NICE pathway: adjuvant therapy for early and locally advanced breast cancer: biological therapy.* Available from: https://pathways.nice.org.uk/pathways/early-and-locally-advanced-breast-cancer/adjuvant-therapy-for-early-and-locally-advanced-breast-cancer#content=view-node%3Anodes-biological-therapy [Accessed 28th Jun 2018].

[22] National Institute for Health and Care Excellence. *NICE pathway: adjuvant therapy for early and locally advanced breast cancer: chemotherapy.* Available from: https://pathways.nice.org.uk/pathways/early-and-locally-advanced-breast-cancer/adjuvant-therapy-for-early-and-locally-advanced-breast-cancer#content=view-node%3Anodes-chemotherapy [Accessed 28th Jun 2018].

[23] National Institute for Health and Care Excellence. *NICE pathway: adjuvant therapy for early and locally advanced breast cancer: radiotherapy.* Available from: https://pathways.nice.org.uk/pathways/early-and-locally-advanced-breast-cancer/adjuvant-therapy-for-early-and-locally-advanced-breast-cancer#content=view-node%3Anodes-radiotherapy [Accessed 28th Jun 2018].

[24] National Institute for Health and Care Excellence. *BNF: trastuzumab emtansine.* Available from: https://bnf.nice.org.uk/medicinal-forms/trastuzumab-emtansine.html [Accessed 28th Jun 2018].