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HEALTH TECHNOLOGY BRIEFING
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Trastuzumab emtansine in combination with pertuzumab for HER2-positive early breast cancer - adjuvant therapy

NIHRIO ID	15116	**NICE ID**	9839
Developer/Company	Roche Products Ltd	**UKPS ID**	645059

Licensing and market availability plans	Currently in phase III clinical trial.

SUMMARY

Trastuzumab emtansine in addition to pertuzumab is in clinical development as an adjuvant therapy for HER2-positive early breast cancer. 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 of 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 both before and after ('adjuvant' therapy) the surgery to improve the success rate of the treatment.

Trastuzumab emtansine consists of an anti-HER2 therapy (trastuzumab) and a chemotherapy agent (emtansine or DM1) combined together as an antibody-drug conjugate. Trastuzumab specifically binds to cancer cells that are HER2-positive which provides a targeted delivery of the cytotoxic DM1 inside cancer cells, potentially limiting damage to healthy tissue. Pertuzumab, is designed to attach to HER2, and stop HER2 producing signals that cause the cancer cells to grow. The combination is thought to provide a more comprehensive, dual blockade of HER pathways and prevent tumour cell growth and survival, and if licenced, will offer an additional adjuvant treatment option for patients with HER2- positive early breast cancer.

PROPOSED INDICATION

Adjuvant therapy for patients with early operable HER2-positive primary breast cancer.[1]

TECHNOLOGY

DESCRIPTION

Trastuzumab emtansine (Kadcyla) 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. 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 internalization and subsequent lysosomal degradation, resulting in release of DM1-containing cytotoxic catabolites (primarily lysine-MCC-DM1).[2]

Trastuzumab emtansine has the mechanisms of action of both trastuzumab and DM1:[2]

- 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.

Pertuzumab (Perjeta) is a recombinant humanised monoclonal antibody that specifically targets the extracellular dimerization domain (subdomain II) of the human epidermal growth factor receptor 2 protein (HER2), and thereby, blocks ligand-dependent heterodimerisation of HER2 with other HER family members, including EGFR, HER3 and HER4. As a result, pertuzumab inhibits ligand-initiated intracellular signalling through two major signal pathways, mitogen-activated protein (MAP) kinase and phosphoinositide 3-kinase (PI3K). Inhibition of these signalling pathways can result in cell growth arrest and apoptosis, respectively. In addition, pertuzumab mediates antibody-dependent cell-mediated cytotoxicity (ADCC).[3]

Trastuzumab emtansine in addition to pertuzumab is in clinical development as adjuvant therapy for patients with operable HER2-positive breast cancer. In the phase III clinical trial (NCT01966471;KAITLIN), following surgery and anthracycline-based chemotherapy, participants will receive trastuzumab emtansine at a dose of 3.6 mg/kg and pertuzumab at a dose of 420 mg intravenously (IV) every 3 weeks (q3w) for up to a total duration of 1 year (up to 18 cycles).[1]

INNOVATION AND/OR ADVANTAGES

Result from a study has shown that trastuzumab emtansine as a single agent reduced the risk of disease recurrence or death compared to trastuzumab as an adjuvant treatment in people with HER2-positive early breast cancer who have residual disease present following neoadjuvant treatment.[4] Moreso, augmented antitumour activity has been shown with the combination of pertuzumab and trastuzumab.[3] Targeting of HER2-positive tumours with trastuzumab has shown to improve survival in early stage and advanced breast cancer. The addition of pertuzumab, another anti-HER2 antibody, to trastuzumab-containing regimens has demonstrated a modest increase in disease-free survival in the adjuvant setting.[5]

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.[6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

The combination of trastuzumab emtansine and pertuzumab is currently not licenced as an adjuvant treatment of HER-2 positive early breast cancer in the UK/EU.

Trastuzumab emtansine is currently licenced in the UK as a monotherapy for the treatment of HER2-positive, unresectable locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination.[2]

The most common side effects with trastuzumab emtansine (> 0.5% of patients include haemorrhage, pyrexia, dyspnoea, musculoskeletal pain, thrombocytopenia, abdominal pain and vomiting, nausea,fatigue and headache.[2]

Pertuzumab is currently licenced in the UK for the following indications:[3]

- In combination with trastuzumab and chemotherapy for neoadjuvant and adjuvant treatments of HER2-positive early breast cancer
- In combination with trastuzumab and docetaxel for HER2-positive metastatic breast cancer

The most common side effects with pertuzumab (which may affect more than 1 in 10 people) include diarrhoea, alopecia, nausea, fatigue, neutropenia,vomiting and febrile neutropenia.[3]

Pertuzumab and trastuzumab emtansine separately are in phase II and III clinical development in combination with other treatments for advanced solid tumours and breast cancer.[7,8]

PATIENT GROUP

DISEASE BACKGROUND

Breast cancer is the most common malignancy diagnosed in women worldwide.[9] The exact etiology is unknown, but family history is a strong risk factor.[10] There are some factors known to increase its likelihood, such as exposure to radiation, increased alcohol consumption, 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).[11]

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.[12]

The first symptom of breast cancer 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, lump or swelling in either of the armpits, nipple discharge, dimpling on the skin of your breasts, and rash on or around your nipple.[13,14]

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.[15]

CLINICAL NEED AND BURDEN OF DISEASE

In England, in 2017 there were 46,109 registrations of newly diagnosed cases of malignant neoplasm of breast (ICD-10 code C50).[16] In 2017, the direct age-standardised incidence rate per 100,000 population was 166.7 among females.[17] 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).[18]

Between 15 and 25 of every 100 women with breast cancer (15 to 25%) have HER2-positive cancers.[19] Based on the 2017 registration, this would approximate to 6,916 and 11,587 newly diagnosed breast cancer cases in England in 2017.
The company estimated that there might be about 3,290 HER2+ eligible patients in 2021 for the post-neoadjuvant, adjuvant therapy.[a]

In 2017-18 there were 212,840 finished consultant episodes (FCEs) and 209,061 admissions which led to 80,769 FCE bed days and 177,174 day cases with a primary diagnosis of malignant neoplasm of breast (ICD-10; C50).[20] In England in 2017, there were 10,219 registrations of death from malignant neoplasm of breast and the directly age-standardised death rate per 100,000 population was 33.6.[21,17]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment of breast cancer should be carried out in specialised breast units/centres and provided by a multidisciplinary team specialised in breast cancer, consisting of at least medical oncologists, breast surgeons, radiation oncologists, breast radiologists, breast pathologists and breast nurses (or similarly trained and specialised health care practitioners).

Adjuvant systemic therapy should be started without undue delays, as data show an important decrease in efficacy when it is administered >12 weeks after surgery. The decision on adjuvant systemic therapies should be based on an individual's risk of relapse (which depends on tumour burden and tumour biology), the predicted sensitivity to particular types of treatment, the benefit from their use and their associated short- and long-term toxicities, the patient's biological age, general health status, comorbidities and preferences.

[a] Information provided by Roche Ltd on UK PharmaScan

It is recommended that HER2-positive tumours should be treated with chemotherapy, endocrine therapy and anti-HER2 therapy. Anti-HER2 therapy may routinely be combined with nonanthracycline-based chemotherapy, endocrine therapy and radiotherapy.[22]

CURRENT TREATMENT OPTIONS

The following are recommended in the treatment of early breast cancer:[23,24]

- Adjuvant chemotherapy
  - A regimen which contains both a taxane and anthracyclin is recommended for people of sufficient risk that chemotherapy is indicated.

- Biological therapy
  - Adjuvant trastuzumab is recommended for people with T1a/T1b,T1c and above HER2-positive in combination with surgery, chemotherapy and radiotherapy as appropriate
  - Adjuvant bisphosphonate therapy (zoledronic acid or sodium clodronate) is also recommended for postmenopausal women.
  - Pertuzumab, with intravenous trastuzumab and chemotherapy is recommended in patients with HER2-positive and lymph-node-positive disease.

PLACE OF TECHNOLOGY

If licenced, trastuzumab emtansine in combination with pertuzumab will offer an additional therapy as an adjuvant treatment for patients with early primary invasive, operable HER2-positive breast cancer.

CLINICAL TRIAL INFORMATION

Trial	**NCT01966471; EudraCT-2012-004902-82; KAITLIN; adults aged 18 yrs and older; trastuzumab emtansine vs trastuzumab in addition to chemotherapy both in combination with pertuzumab; phase III**
Sponsor	Hoffmann-La Roche
Status	Ongoing
Source of Information	Trial registry[1,25]
Location	13 EU countries (incl UK), USA, Canada and other countries
Design	Randomised, open label, parallel assignment,
Participants	N=1846: aged 18 yrs and older; non-metastatic; primary invasive; operable; breast cancer; HER2-positive; under gone breast surgery
Schedule	Participants are randomised to: • Active comparator: Anthracycline followed by trastuzumab, pertuzumab, and taxane Trastuzumab and pertuzumab will be administered concurrently for up to a total duration of 1 yr (up to 18 cycles [1 cycle = 21 days]) with the taxane (docetaxel or paclitaxel) component of chemotherapy following anthracycline [5 fluorouracil, epirubicin, and cyclophosphamide or epirubicin and cyclophosphamide or doxorubicin and cyclophosphamide based chemotherapy. • Experimental: Anthracycline followed by trastuzumab emtansine and pertuzumab Trastuzumab emtansine and pertuzumab will continue for up to a total duration of 1 yr (up to 18 cycles [1 cycle = 21 days]) following anthracycline [5

	fluorouracil, epirubicin, and cyclophosphamide or epirubicin and cyclophosphamide (or doxorubicin and cyclophosphamide based chemotherapy.
Follow-up	Up to 10 yrs
Primary Outcomes	Time frame: Baseline up to approximately 10 yrs • Invasive disease-free survival (IDFS) • IDFS in the node-positive subpopulation
Secondary Outcomes	Time frame: Baseline up to approximately 10 yrs • IDFS plus second primary non-breast cancer, excluding non-melanoma skin cancers and carcinoma in situ of any site • Disease-free survival (DFS)) • Distant recurrence-free interval (DRFI) • Overall Survival (OS) • Percentage of participants with adverse events • Percentage of participants with decrease in left ventricular ejection fraction from baseline over time Time frame: Up to approximately 3 yrs • European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ C30) score • EORTC Quality of Life Questionnaire-Breast Cancer 23 (QLQ-BR23) score • Time to clinically meaningful deterioration in the global health status/ quality of life and functional (physical, role, and cognitive) subscales of the QLQ-C30 from first HER2-targeted treatment
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as Jan 2024.

ESTIMATED COST

Pertuzumab is already marketed in the UK; a 420mg/14ml concentrate for solution for infusion costs £2,395.[26]

Trastuzumab emtansine is already marketed in the UK; a 100mg and 160mg powder for concentrate for infusion vials cost £1,641.01 and £2,625.62 respectively.[27]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development . Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer (ID1516). Expected publication date: June 2020.

- NICE technology appraisal guidance. Pertuzumab for adjuvant treatment of HER2-positive early stage breast cancer (TA569). March 2019.
- NICE clinical guideline. Early and locally advanced breast cancer: diagnosis and management (NG101). July 2018.
- NICE quality standard. Breast cancer (QS12). June 2016.
- NICE diagnostics guidance. Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer (DG34). December 2018.

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 for Medical Oncology (ESMO). Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2019[22]
- National Comprehensive Cancer Network (NCCN). Breast Cancer, Version 4.2017, NCCN Clinical Practice Guidelines in Oncology. March 2018.[28]

ADDITIONAL INFORMATION

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