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HEALTH TECHNOLOGY BRIEFING OCTOBER 2019

Pertuzumab and trastuzumab (fixed-dose combination) in addition to chemotherapy for breast cancer

NIHRIO ID	24201	**NICE ID**	10255
Developer/Company	Roche Products Ltd	**UKPS ID**	653345

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Pertuzumab/trastuzumab (fixed-dose combination (FDC) in addition to chemotherapy is in clinical development as a subcutaneous formulation (SC) for the adjuvant treatment of adults with the human epidermal growth factor receptor 2 (HER2) positive early and metastatic breast cancer. HER2 positive breast cancer is a subtype in which the HER2 receptor is over expressed on the cell surface. HER2 promotes the growth of cancer cells and this breast cancer subtype tends to be more aggressive than other types. Metastatic breast cancer is when cancer has spread beyond the breast and nearby lymph nodes to other organs in the body. Treatment of the disease often involves the use of anti-HER2 therapies, chemotherapy or a combination of both.

Pertuzumab, is a monoclonal antibody, a type of protein that attaches to HER2 and activates the immune system (the body's natural defences) which result in growth arrest and death of cancer cells. Trastuzumab is a monoclonal antibody that attaches to the HER2 protein and activates cells of the immune system which results in growth inhibition and death of cancer cells. Pertuzumab provides additional benefits when added to other medicines for HER-positive cancer, notably trastuzumab. Pertuzumab in combination with trastuzumab and chemotherapy is a treatment option for HER2-positive early and metastatic breast cancer as either in subcutaneous (SC) or intravenous (IV) formulation. However, pertuzumab and trastuzumab in a FDC with chemotherapy given subcutaneously will offer a new formulation for patients with HER2-positive early and metastatic breast cancer.

PROPOSED INDICATION

All current breast cancer indications for pertuzumab in combination with trastuzumab and chemotherapy for adults with HER2-positive early and metastatic breast cancer.[1,a]

TECHNOLOGY

DESCRIPTION

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).[2]

Trastuzumab (Herceptin) is a recombinant humanised IgG1 monoclonal antibody against the HER2. Trastuzumab binds with high affinity and specificity to sub-domain IV, a juxta-membrane region of HER2's extracellular domain. Binding of trastuzumab to HER2 inhibits ligand-independent HER2 signalling and prevents the proteolytic cleavage of its extracellular domain, an activation mechanism of HER2. As a result, trastuzumab has been shown, in both in vitro assays and in animals, to inhibit the proliferation of human tumour cells that overexpress HER2.[3]

Pertuzumab in combination with trastuzumab and chemotherapy is already licensed for treating patients with HER2-positive early or metastatic breast cancer.[2] A new formulation has been developed offering pertuzumab and trastuzumab together in a FDC given through a SC route of administration. This is being used in the phase III clinical trial (NCT03493854), where patients will receive the FDC as a fixed non-weight-based dose. A loading dose of 1200 mg subcutaneous (SC) pertuzumab and 600 mg SC trastuzumab is then followed by a maintenance dose of 600 mg SC pertuzumab and 600 mg SC trastuzumab Q3W.[4,b]

INNOVATION AND/OR ADVANTAGES

The FDC of pertuzumab and trastuzumab is a new SC formulation which contains the permeation-enhancer recombinant human hyaluronidase (PH20), an enzyme that allows absorption and dispersion of large fluid volumes by temporarily degrading hyaluronan at the local injection site.[5,6] The SC route of administration is preferred by patients over separate intravenous infusions and is also associated with a reduction in patients' infusion chair time, healthcare professionals' time, other hospital resources and lower adverse events compared with intravenous administration.[6]

[a] Information provided by Roche Products Ltd
[b] Information provided by Roche Products Ltd on UK PharmaScan

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Pertuzumab in combination with trastuzumab and chemotherapy is licensed in the EU/UK for the following indications:[2]

- Neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early-stage breast cancer at high risk of recurrence
- Adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence

Pertuzumab in combination with trastuzumab and docetaxel is indicated in the EU/UK for adult patients with HER-2 positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.[7]

The most common side effects (affecting more than 3 in 10 people) with pertuzumab, when given with trastuzumab and chemotherapy, are neutropenia (low levels of neutrophils, a type of white blood cell important for fighting infections), diarrhoea, nausea (feeling sick), vomiting, hair loss and tiredness. The most common severe side effect (affecting more than 1 in 10 people) is neutropenia, with or without fever.[1]

PATIENT GROUP

DISEASE BACKGROUND

Breast cancer is the most common cancer in the UK, and mainly affects women, although men can also have the condition. It usually starts in the cells that line the ducts of the breast.[8] Early-stage breast cancer is defined as disease confined to the breast with or without regional lymph node involvement and the absence of distant metastatic disease. Early-stage breast cancer is potentially curable while metastatic breast can means that the cancer has spread to other parts of the body, such as liver and bones.[9,10] There are different immune/pathological subtypes of breast cancer. Among them, HER2, a transmembrane receptor protein that is overexpressed in about 20% of breast cancers and associated with more aggressive disease in the absence of HER2 directed therapy. HER2 plays a role in cell growth and differentiation.[11]

The exact aetiology is unknown, but family history is a strong risk factor (hereditary factors).[12] Other risk factors for breast cancer include genetic causes, increased age, reproductive history and hormone exposure, lifestyle factors, medical history, and radiation exposure.[13]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 breast, nipple discharge, dimpling on the skin of your breasts, and rash on or around your nipple.[14,15]

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), and the direct age-standardised rate per 100,000 population was 166.7 among females.[16] Incidence rates among females 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).[17]

Between 15 and 25 of every 100 women with breast cancer (15 to 25%) have HER2 positive cancers.[18] This would be approximate to 6,916 and 11,527 of the newly diagnosed breast cancer cases in England in 2017.

In 2017-18 there were 212,840 finished consultant episodes (FCEs) and 80,769 FCE bed days with a primary diagnosis of malignant neoplasm of breast (ICD-10; C50). There were 209,061 hospital admissions, of which 177,174 were day cases.[19] In England in 2017, there were 10,219 registrations of death from malignant neoplasm of breast,[20] and the directly age-standardised death rate per 100,000 population was 0.3 and 33.3 among males and females respectively.[16]

The latest published survival statistics for breast cancer for women in England (2018, patients diagnosed 2013-2017) report a 1-year survival rate of 95.8% and a 5-year survival rate of 85% (age-standardised).[21]

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, 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 of the disease.[22]

CURRENT TREATMENT OPTIONS

There are some biological therapy approaches for the treatment of early and metastatic breast cancer which includes:[7,23,24]

- Trastuzumab, for patients with T1c and above HER2-positive invasive cancer, given at 3-week intervals for 1 year in combination with surgery, chemotherapy and radiotherapy as appropriate
- Pertuzumab, with intravenous trastuzumab and chemotherapy, is recommended for the adjuvant treatment of HER2-positive early-stage breast cancer in adults only if:
    - They have a lymph-node-positive disease
    - The company provides it according to the commercial arrangement
- Pertuzumab in combination with trastuzumab and docetaxel is recommended for treating HER2-positive metastatic or locally recurrent unresectable breast cancer, in adults who have not had previous anti-HER2 therapy or chemotherapy for their metastatic disease, only if the company provides pertuzumab within the agreed commercial access arrangement

PLACE OF TECHNOLOGY

If approved, the FDC of pertuzumab and trastuzumab in addition to chemotherapy will offer an additional treatment route of administration (subcutaneous) for patients with HER2-positive early and metastatic breast cancer.

CLINICAL TRIAL INFORMATION

Trial	NCT03493854, **WO40324,** EudraCT-2017-004897-32; adults ≥ 18 years; pertuzumab IV + trastuzumab IV + chemotherapy vs FDC of pertuzumab and trastuzumab SC + chemotherapy; phase III
Sponsor	Hoffman-La Roche
Status	Ongoing
Source of Information	Trial registry[4,25]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, parallel assignment, open-label
Participants	n= 500; aged ≥ 18 years old: female and male patients with Stage II – IIIC; locally advanced, inflammatory, or early-stage, unilateral, invasive breast cancer, primary tumour >2 cm in diameter, or node-positive disease, and HER2-positive breast cancer confirmed.
Schedule	Patients were randomised to: Arm A (Comparator): pertuzumab IV + trastuzumab IV + chemotherapy • Participants will receive 8 cycles of investigator's choice of neoadjuvant chemotherapy. This will include either: 1) 4 cycles of dose-dense doxorubicin plus cyclophosphamide (ddAC) once every 2 weeks (Q2W) (given with granulocyte colony-stimulating factor [G-CSF] support as needed according to local guidelines) followed by paclitaxel Q1W for 12 weeks; or 2) 4 cycles of doxorubicin plus cyclophosphamide (AC) once every 3 weeks (Q3W) followed by docetaxel Q3W for 4 cycles. Pertuzumab and trastuzumab will be given intravenously (IV) for 4 cycles Q3W concurrently with the taxane component of chemotherapy. After completing their neoadjuvant therapy, participants will undergo surgery. Thereafter, participants will receive an additional 14 cycles of pertuzumab IV and trastuzumab IV for a total of 18 cycles. o Cyclophosphamide 600 mg/m2 will be administered IV on day 1 of each cycle of treatment (as part of ddAC Q2W or AC Q3W) for cycles 1-4 o Doxorubicin 60 mg/m2 will be administered IV on day 1 of each cycle of treatment (as part of either ddAC Q2W or AC Q3W) for cycles 1-4 o Docetaxel 75 mg/m2 will be administered IV on day 1 of cycle 5 and then 100 mg/m2 IV at the discretion of the investigator for cycles 6-8 (Q3W), if no dose-limiting toxicity occurs o Paclitaxel 80 mg/m2 will be administered IV QW for 12 weeks o Pertuzumab will be administered as a fixed non-weight-based dose of 840-mg IV loading dose and then 420-mg IV maintenance dose Q3W o Trastuzumab will be administered as an 8-mg/kg IV loading dose and then 6 mg/kg IV maintenance dose Q3W o After surgery (from cycle 9 onwards), participants in arm A will be allowed to switch from trastuzumab IV to trastuzumab SC, at the discretion of the investigator, in the countries where trastuzumab SC is routinely used. For participants who switch, a fixed dose of 600 mg trastuzumab SC (irrespective of the patient's weight) will be administered in the adjuvant phase

	Arm B (Experimental): FDC of Pertuzumab and Trastuzumab SC + Chemotherapy • Participants will receive 8 cycles of investigator's choice of neoadjuvant chemotherapy. This will include either: 1) 4 cycles of ddAC Q2W (given with G-CSF support as needed according to local guidelines) followed by paclitaxel once every week (QW) for 12 weeks; or 2) 4 cycles of AC Q3W followed by docetaxel Q3W for 4 cycles. The fixed-dose combination (FDC) of pertuzumab and trastuzumab will be given subcutaneously (SC) for 4 cycles (Q3W) concurrently with the taxane component of chemotherapy. After completing their neoadjuvant therapy, participants will undergo surgery. Thereafter, participants will receive an additional 14 cycles of the FDC of pertuzumab and trastuzumab SC for a total of 18 cycles. o Cyclophosphamide 600 mg/m2 will be administered IV on day 1 of each cycle of treatment (as part of ddAC Q2W or AC Q3W) for cycles 1-4 o Doxorubicin 60 mg/m2 will be administered IV on day 1 of each cycle of treatment (as part of either ddAC Q2W or AC Q3W) for cycles 1-4 o Docetaxel 75 mg/m^2 will be administered IV on day 1 of cycle 5 and then 100 mg/m^2 IV at the discretion of the investigator for cycles 6-8 (Q3W), if no dose-limiting toxicity occurs o Paclitaxel 80 mg/m^2 will be administered IV QW for 12 weeks o FDC of pertuzumab and trastuzumab will be administered SC at a fixed non-weight-based dose. A loading dose of 1200 mg SC pertuzumab and 600 mg SC trastuzumab is then followed by a maintenance dose of 600 mg SC pertuzumab and 600 mg SC trastuzumab Q3W
Follow-up	From baseline up to 5.5 years
Primary Outcomes	• Trough Serum Concentration (Ctrough) of pertuzumab during cycle 7 [Time frame: pre-dose on cycle 8, day 1 (up to 21 weeks)]
Secondary Outcomes	• Ctrough of trastuzumab during cycle 7 [Time frame: pre-dose on cycle 8, day 1 (up to 21 weeks)] • Percentage of participants with total pathological complete response (tpCR), according to local pathologist assessment [Time frame: following completion of surgery (up to 33 weeks)] • Kaplan-Meier estimate of the percentage of participants who are event-free according to invasive disease-free survival (iDFS; Excluding second primary non-breast cancer [SPNBC]) criteria [Time frame: up to 5.5 years] • Kaplan-Meier estimate of the percentage of participants who are event-free according to iDFS (Including SPNBC) criteria [Time frame: Up to 5.5 years] • Kaplan-Meier estimate of the percentage of participants who are event-free according to event-free survival (EFS; including SPNBC) Criteria [Time frame: Up to 5.5 years] • Kaplan-Meier estimate of the percentage of participants who are event-free according to EFS (Including SPNBC) criteria [Time frame: up to 5.5 years]

	• Kaplan-Meier estimate of the percentage of participants who are event-free according to distant recurrence-free interval (DRFI) Criteria [Time frame: up to 5.5 years] • Kaplan-Meier estimate of the percentage of participants in overall survival [Time frame: up to 5.5 years] • Percentage of participants with adverse events (including serious adverse events), severity determined according to national cancer institute common terminology criteria for adverse events version 4 (NCI CTCAE v4) [Time frame: Up to 5.5 years] • Percentage of participants with a primary cardiac event [Time frame: from baseline up to 5.5 years] • Percentage of participants with a secondary cardiac event [Time frame: from baseline up to 5.5 years]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date reported as July 2019 Estimated study completion date reported as February 2024

ESTIMATED COST

Pertuzumab is already marketed in the UK for HER2-positive breast cancers; a 420/14 ml mg vial costs £2395.[7,26] Trastuzumab is already marketed in the UK; a 600mg/5ml vial costs £1222.20.[27]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Pertuzumab for adjuvant treatment of HER2-positive early stage breast cancer (TA569). March 2019.
- NICE technology appraisal guidance. Pertuzumab with trastuzumab and docetaxel for treating HER2-positive breast cancer. March 2018.
- NICE Technology appraisal guidance. Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer. August 2006.

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. Early breast cancer. ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2019.[28]
- National Comprehensive Cancer Network (NCCN). Breast Cancer, Version 4.2017, NCCN Clinical Practice guidelines in Oncology. 2018.[29]

ADDITIONAL INFORMATION

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