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# Pertuzumab with trastuzumab and docetaxel for metastatic HER2-positive breast cancer – first line

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# Pertuzumab with trastuzumab and docetaxel for metastatic HER2-positive breast cancer – first line

## Target group

- Breast cancer: metastatic, HER2+ - first line; in combination with trastuzumab and docetaxel.

## Technology description

Pertuzumab (2C4 antibody; R-1273; rhuMAb2C4) is a monoclonal antibody targeting human epidermal growth factor receptor 2 (HER2). Pertuzumab is the first in a new class of anticancer agents called HER dimerisation inhibitors. Pertuzumab binds to the HER2 receptor and prevents the pairing (dimerisation) of HER2 with other HER family receptors, inhibiting intracellular signalling. Pertuzumab and trastuzumab bind to different regions of HER2 and may potentially provide synergistic activity. In trials, pertuzumab was administered by intravenous (IV) infusion with a loading dose of 840mg followed by 420mg every three weeks in combination with trastuzumab and docetaxel.

Pertuzumab is currently in phase III trials in combination with trastuzumab and trastuzumab-DM1 for metastatic breast cancer and phase II trials for HER2+ metastatic breast cancer; locally advanced, inflammatory or early stage HER2+ breast cancer; pancreatic cancer and neuroendocrine tumours.

## Innovation and/or advantages

Pertuzumab is a new monoclonal antibody which may provide an additional treatment option for this patient group. The company anticipate that inhibition of the HER2 receptor with two antibodies will be more effective than treatment with a single antibody.

## Developer

Roche Products Ltd.

## Availability, launch or marketing dates, and licensing plans

In phase III clinical trials.

## NHS or Government priority area

This topic is relevant to the NHS Cancer Plan (2000) and Cancer Reform Strategy (2007).

## Relevant guidance

NICE Technology Appraisals

- In development. Lapatinib and trastuzumab in combination with an aromatase inhibitor for the first line treatment of metastatic hormone receptor positive breast cancer which over-expresses HER2. Expected May 2011[1].
- In development. High dose fulvestrant for the treatment of locally advanced or metastatic breast cancer. Expected June 2011[2].
- In development. Trastuzumab as monotherapy and in combination with a taxane for the treatment of metastatic breast cancer. Expected October 2011[3].
- In development. Lapatinib for breast cancer (for use in women with previously treated advanced or metastatic breast cancer). Expected date of issue to be confirmed[4].
- In development. Bevacizumab in combination with non-taxane chemotherapy for the first line treatment of metastatic breast cancer. Expected date of issue to be confirmed[5].

- Published. Gemcitabine for the treatment of metastatic breast cancer. 2007[6].
- Published. The clinical effectiveness and cost effectiveness of trastuzumab for breast cancer. 2002[7].

NICE Clinical Guidelines

- Advanced breast cancer – diagnosis and treatment. 2009[8].
- Breast cancer (early & locally advanced): diagnosis and treatment. 2009[9].
- Familial breast cancer: the classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care. 2006[10].

NICE Cancer Service Guidance

- NICE cancer service guidance. Improving outcomes in breast cancer[11].

Other Guidelines

- SIGN. Management of breast cancer in women. 2005[12].
- Cancer Services Collaborative Improvement Partnership. Breast cancer service improvement guide. 2003[13].
- European Society for Medical Oncology. Locally recurrent or metastatic breast cancer. Clinical practice guidelines for diagnosis, treatment and follow-up. 2010[14].

**Clinical need and burden of disease**

Breast cancer is the most common cancer in the UK. In England and Wales there were 40,872 new cases and 10,838 deaths in 2007[15] (ICD10:C50). Breast cancer accounts for 31% of all cancers in women, affecting around 120 per 100,000 women[16]. Breast cancer risk is strongly related to age, with 81% of cases occurring in women aged over 50 years, and is greater in those in higher socioeconomic groups[16]. Analysis of breast cancer survival by level of deprivation has consistently shown higher survival for more affluent women[17].

Metastatic breast cancer is the presence of disease at distant sites, most commonly the lymph nodes, bone, liver, lungs and brain[18]. It has been estimated that 5% of women have metastases at diagnosis and a further 35% will develop them over the following 10 years[11]. Estimates of the number of people living with advanced breast cancer vary and population level data for describing the epidemiology of advanced breast cancer is relatively sparse[11]. Over-expression of the product of the HER2 oncogene occurs in about a third of women with metastatic breast cancer and is associated with a worse prognosis[19].

**Existing comparators and treatments**

For women with metastatic disease, the aim of treatment is to ameliorate symptoms, maintain quality of life and prolong survival. The choice of treatment for each patient depends upon many factors including previous treatment, the site of metastases, receptor status of tumour cells, menopausal status, health and informed patient choice. Current treatment options for metastatic breast cancer include[20]:

- Biological therapy
  - Trastuzumab (Herceptin) alone or in combination with chemotherapy e.g. taxanes
  - Bevacizumab (Avastin) - not recommended by NICE
  - Lapatinib (Tyverb) in combination with capecitabine - not recommended by NICE
- Chemotherapy

- Doxorubicin and cyclophosphamide (AC)
- 5-Fluorouracil, epirubicin and cyclophosphamide (FEC)
- Cyclophosphamide, methotrexate and 5-fluorouracil (CMF)
- Docetaxel (Taxotere) or paclitaxel (Taxol)
- Vinorelbine (Navelbine)
- Gemcitabine (Gemzar)
- Capecitabine (Xeloda) - as monotherapy or in combination with docetaxel

- Hormonal therapy (in oestrogen receptor positive (ER+) and/or progesterone receptor positive (PR+) disease)
  - Anti-oestrogens e.g. tamoxifen, fulvestrant (Faslodex)
  - Aromatase inhibitors e.g. anastrozole (Arimidex), letrozole (Femara), exemestane (Aromasin)
  - Progestogens e.g. megestrol acetate (Megace), medroxyprogesterone acetate (Provera)
  - Pituitary downregulators e.g. goserelin (Zoladex)
  - Ovarian ablation
- Bisphosphonates - for patients with symptomatic bone metastases
- Radiotherapy - for local control

**Efficacy and safety**

| Trial | CLEOPATRA, NCT00567190; pertuzumab, docetaxel and trastuzumab vs placebo, docetaxel and trastuzumab; phase III. | NCT00875979; pertuzumab and trastuzumab; phase Ib/II. |
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| Sponsor | Genentech. | Genentech. |
| Status | Ongoing. | Published. |
| Source of information | Trial registry[21]. | Publication[22], trial registry[23]. |
| Location | EU (inc UK), USA and other countries. | EU (inc UK), USA, Canada and other countries. |
| Design | Randomised, placebo-controlled. | Uncontrolled . |
| Participants and schedule | n=808; women ≥18 years; HER2+ metastatic breast cancer.<br>Randomised to:<br>Arm 1: pertuzumab, IV, 840mg loading dose, followed by 420mg, every 3 weeks, plus trastuzumab, IV, 8mg/kg loading dose, followed by 6mg/kg, every 3 weeks and docetaxel, IV, 75mg/m$^2$, every 3 weeks.<br>Arm 2: trastuzumab, IV, 8mg/kg loading dose followed by 6mg/kg, every 3 weeks, plus docetaxel, IV, 75mg/m$^2$, every 3 weeks, and placebo, IV, every 3 weeks. | n=66; women ≥18 years; HER2+ locally advanced or metastatic breast cancer.<br>Trastuzumab administered according to dose schedule prior to study entry: loading dose 4mg/kg 28 days before cycle 1, followed by 2mg/kg on days 1,8 and 15 of each 21 day cycle or loading dose of 8mg/kg 28 days before cycle 1, followed by 6mg/kg on day 1 of each cycle.<br>For the first cycle, a loading dose of pertuzumab of 840mg administered IV, on days 1 and 2; in cycles 2 and thereafter, pertuzumab 420mg administered IV, on day 1 (trastuzumab administered first). Treatment period 8 cycles, but patients could continue treatment if free from progressive disease. |
| Follow-up | Active treatment period until disease progression or unacceptable toxicity; follow-up every 18 weeks until death. | Active treatment period 24 weeks; follow-up every 3 months until disease progression. |
| Primary outcome | Progression-free survival (PFS). | Adverse events; cardiac function; objective response rate based on |

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| | | investigator assessment. |
| Secondary outcomes | Overall survival; incidence of congestive heart failure and reduced left ventricular ejection fraction. | PFS; duration of response. |
| Key results | - | Complete response: 7.6% (80% CI: 3.7-13.6); partial response: 16.7% (80% CI: 10.9-24.1); stable disease ≥6months: 25.8% (80% CI: 18.8-33.9); progressive disease 50% (80% CI: 41.5-58.5); median time to response: 2.6 months (range: 1.1 – 8.6 months); median PFS: 5.5 months (range: 0.9 – 17.0 months); median duration of response: 5.8 months (range: 2.9 – 15.3 months); median time to progression: 3.9 months (range: 0.9 – 17.0 months). |
| Expected reporting date | First efficacy data expected 2011. | - |
| Adverse effects (AEs) | - | Most commonly reported AEs: diarrhoea 65%; fatigue 33%; nausea 27%, rash 26%, headache 20%, arthralgia 17%, cough 14%, anorexia 14%, asthenia 12%, dizziness 12%, muscle spasms 12%, myalgia 12%, paresthesia 11%, pruritus 11%, vomiting 11%. |

**Estimated cost and cost impact**

The cost of pertuzumab is not yet known. The cost of treatment with trastuzumab is approximately £1,630 for the loading dose of 8mg/kg and £1,225 for subsequent doses of 6mg/kg[a]. Docetaxel costs around £1,230 per 100mg/m$^2$ dose[b,24].

**Claimed or potential impact – speculative**

Patients

- ☑ Reduced mortality or increased length of survival
- ☑ Reduction in associated morbidity or Improved quality of life for patients and/or carers
- ☐ Quicker, earlier or more accurate diagnosis or identification of disease
- ☐ Other:
- ☐ None identified

Services

- ☑ Increased use: additional IV infusion
- ☐ Service organisation
- ☐ Staff requirements
- ☐ Decreased use
- ☐ Other:
- ☐ None identified

Costs

- ☐ Increased unit cost compared to alternative
- ☐ Increased costs: more patients coming for treatment
- ☐ Increased costs: capital investment needed
- ☑ New costs: additional treatment option
- ☐ Savings:
- ☐ Other:

[a] Based on female average weight of 70.2kg. Assumes wastage.
[b] Based on average surface area of 1.7m$^2$. Assumes wastage.

Other issues

☐ Clinical uncertainty or other research question identified: ☑ None identified

## References

[1] National Institute for Health and Clinical Excellence. Technology appraisal in development. Lapatinib and trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone receptor positive breast cancer which over-expresses HER2. Expected May 2011.
[2] National Institute for Health and Clinical Excellence. Technology appraisal in development. High dose fulvestrant for the treatment of locally advanced or metastatic breast cancer. Expected June 2011.
[3] National Institute for Health and Clinical Excellence. Trastuzumab as monotherapy and in combination with a taxane for the treatment of metastatic breast cancer. Technology appraisal in development. Expected October 2011.
[4] National Institute for Health and Clinical Excellence. Technology appraisal in development. Lapatinib for breast cancer (for use in women with previously treated advanced or metastatic breast cancer). Expected date of issue to be confirmed.
[5] National Institute for Health and Clinical Excellence. Technology appraisal in development. Bevacizumab in combination with non-taxane chemotherapy for the first-line treatment of metastatic breast cancer. Expected date of issue to be confirmed.
[6] National Institute for Health and Clinical Excellence. Breast cancer - gemcitabine for the treatment of metastatic breast cancer. Technology appraisal TA116. London: NICE; January 2007.
[7] National Institute for Health and Clinical Excellence. The clinical effectiveness and cost effectiveness of trastuzumab for breast cancer. Technology appraisal TA34. London: NICE; March 2002.
[8] National Institute for Health and Clinical Excellence. Advanced breast cancer – diagnosis and treatment. Clinical guideline CG81. London: NICE; February 2009.
[9] National Institute for Health and Clinical Excellence. Breast cancer (early & locally advanced): diagnosis and treatment. Clinical guideline CG80. London: NICE; February 2009.
[10] National Institute for Health and Clinical Excellence. Familial breast cancer. Clinical guideline CG41. London: NICE; October 2006.
[11] National Institute for Health and Clinical Excellence. Improving outcomes in breast cancer. Cancer service guidance CSGBC. London: NICE; August 2002.
[12] Scottish Intercollegiate Guidelines Network. Management of breast cancer in women. Clinical guideline No. 84. Edinburgh: SIGN; December 2005.
[13] Cancer Services Collaborative Improvement Partnership. Breast cancer service improvement guide. October 2003.
[14] European Society for Medical Oncology. Locally recurrent or metastatic breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2010;21(suppl 5):v15-v19.
[15] Office for National Statistics. Cancer incidence and mortality 2005-07 statistical bulletin. 2010. www.statistics.gov.uk Accessed 26 October 2010.
[16] Cancer Research UK. http://info.cancerresearchuk.org/cancerstats/types/breast/incidence/ Accessed 16 November 2010.
[17] Cancer Research UK. http://info.cancerresearchuk.org/cancerstats/types/breast/index.htm?script=true Accessed 16 November 2010.
[18] Map of Medicine. http://app.mapofmedicine.com/mom/58/page.html?department-id=3&specialty-id=1007&pathway-id=11314&page-id=11322 Accessed 26 October 2010.
[19] Stebbing J, Slater S and Slevin M. Breast cancer (metastatic). Clinical Evidence Handbook. BMJ Publishing Group Limited. London; June 2009.
[20] Macmillan Cancer Support. Secondary breast cancer. http://www.macmillan.org.uk/Cancerinformation/Cancertypes/Breastsecondary/Secondarybreastcancer.aspx Accessed 26 October 2010.
[21] ClinicalTrials.gov. A study to evaluate pertuzumab and trastuzumab and docetaxel vs placebo and trastuzumab and docetaxel in previously untreated HER2-positive metastatic breast cancer (CLEOPATRA). http://clinicaltrials.gov/ct2/show/NCT00567190?term=nct00567190&rank=1 Accessed 1 November 2010.
[22] Baselga J, Gelmon KA, Verma S *et al*. Phase II trial of pertuzumab and trastuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer that progressed during prior trastuzumab therapy. Journal of Clinical Oncology 2010;28(7):1138-1144.
[23] ClinicalTrials.gov. A study of trastuzumab-MCC-DM1 (T-DM1) in combination with pertuzumab administered to patients with HER2-positive locally advanced or metastatic breast cancer who have previously received trastuzumab. http://clinicaltrials.gov/ct2/show/NCT00875979?term=pertuzumab&cond=breast+cancer&intr=trastuzumab&rank=1 Accessed 28 October 2010.

[24] British Medical Association and Royal Pharmaceutical Society of Great Britain. British National Formulary. BMJ Group and RPS Publishing. London; September 2010.

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