Trastuzumab subcutaneous (Herceptin SC) for early and metastatic HER2-positive breast cancer

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Trastuzumab subcutaneous (Herceptin SC) for early and metastatic HER2-positive breast cancer

Target group
All breast cancer indications for which trastuzumab is currently licensed:
- (HER2-positive) metastatic breast cancer
  - Monotherapy for patients who have received at least two chemotherapy regimens for metastatic disease.
  - In combination with paclitaxel for patients who have not received chemotherapy for metastatic disease and for whom an anthracycline is unsuitable.
  - In combination with docetaxel for patients who have not received chemotherapy for metastatic disease.
  - In combination with an aromatase inhibitor for post-menopausal patients with hormone-receptor positive metastatic breast cancer, not previously treated with trastuzumab.
- Early breast cancer
  - HER2+ early breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable).

Technology description
Trastuzumab subcutaneous (SC) (Herceptin SC; reformulated Herceptin; RG597 [SC formulation]; recombinant human hyaluronidase/trastuzumab) is a recombinant, humanised monoclonal antibody directed against the extracellular domain of the human epidermal growth factor receptor 2 (HER2) combined with a hyaluronidase enzyme. This produces a co-formulation which opens up channels in the extracellular matrix of the skin to allow large molecules to enter the bloodstream, enabling the drug to be administered via SC injection. Trastuzumab has activity against tumour cells with over-expression of the product of the HER2 oncogene. Trastuzumab SC will be administered at 600mg/5ml every 3 weeks.

Trastuzumab is currently licensed in the EU for the breast cancer indications listed above and for metastatic gastric cancer. IV administration of trastuzumab is associated with a number of common or very common adverse effects, including cardiotoxicity, infusion reactions (typically mild or moderate), febrile neutropenia and other cytopenias, gastrointestinal effects, dyspnoea, wheezing, and other respiratory disorders.

Innovation and/or advantages
If licensed, trastuzumab SC may offer an alternative to IV treatment, with a shorter administration time than current therapy and the potential for a reduction in infusion related reactions.

Developer
Roche Products Ltd (EU licence holder); Halozyme Therapeutics.

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.
- In development. High dose fulvestrant for the treatment of locally advanced or metastatic breast cancer. Expected date of issue to be confirmed.
- 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.
- 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.
- In development. Eribulin monotherapy for the treatment of people with breast cancer who have received two or more chemotherapy regimens for locally advanced or metastatic disease. Expected date of issue to be confirmed.
- Docetaxel for the adjuvant treatment of early node-positive breast cancer. 2006.
- Paclitaxel for the adjuvant treatment of early node-positive breast cancer. 2006.

NICE Clinical Guidelines


NICE cancer service guidance

- National Cancer Research Institute. UK clinical guidelines for the use of adjuvant trastuzumab (Herceptin) with or following chemotherapy in HER2-positive early breast cancer. 2005.

Clinical need and burden of disease

Breast cancer is the most common cancer in the UK. In 2008, there were 39,681 new cases diagnosed in England, accounting for 173,815 hospital admissions and 173,653 bed days. In 2009, 10,374 deaths occurred in England and Wales, equating to 4.1% of all female deaths (ICD10: C50). Breast cancer accounts for 31% of all cancers in women, affecting around 120 per 100,000 women. Breast cancer risk is strongly related to age, with 81% of cases occurring in women aged over 50 years, and is greater in those...
from higher socioeconomic groups\textsuperscript{26}. Analysis of breast cancer survival by level of deprivation has consistently shown higher survival for more affluent women\textsuperscript{26}.

Breast cancer is described as ‘early’ if it is confined to the breast only, or the breast and adjacent lymph nodes (most often axillary) without spread to other parts of the body\textsuperscript{15}. Metastatic breast cancer is the presence of disease at distant sites. The most common sites for metastases are the lymph nodes, bone, liver, lungs and brain\textsuperscript{27}. An estimated 5\% of women have metastases at diagnosis and a further 35\% will develop them over the following 10 years\textsuperscript{14}. 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\textsuperscript{14}. 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\textsuperscript{28}.

**Existing comparators and treatments**

For breast cancer, the choice of treatment depends upon factors including stage and grade of cancer, previous treatment, site of tumour or metastases, receptor status of tumour cells, menopausal status, health and informed patient choice.

**Current management options for early HER2+ breast cancer include\textsuperscript{12, 29}**:

- Surgery – lumpectomy or mastectomy.
- Radiotherapy – to the remainder of the breast tissue or the chest wall.
- Standard chemotherapy regimens – adjuvant or neoadjuvant.
  - 5-fluorouracil (5FU), epirubicin and cyclophosphamide (FEC).
  - Doxorubicin and cyclophosphamide (AC).
  - Cyclophosphamide, methotrexate and 5FU (CMF).
  - Epirubicin and CMF (E-CMF).
  - FEC plus docetaxel (FEC-T).
- Hormonal therapy – oestrogen receptor positive (ER+).
  - Anti-oestrogens e.g. tamoxifen, fulvestrant (Faslodex).
  - Aromatase inhibitors e.g. anastrozole (Arimidex), letrozole (Femara), exemestane (Aromasin).
  - Pituitary downregulators e.g. goserelin (Zoladex).
  - Ovarian ablation.
- Biological therapy e.g. trastuzumab after surgery and adjuvant chemotherapy (and radiotherapy, if appropriate).

For women with metastatic disease the aim of treatment is to ameliorate symptoms, maintain quality of life and prolong survival. Current treatment options for metastatic breast cancer include\textsuperscript{14}:

- Biological therapy
  - Trastuzumab alone or in combination with chemotherapy e.g. taxanes.
  - Bevacizumab (Avastin) - not recommended by NICE.
- Chemotherapy
  - Doxorubicin and cyclophosphamide (AC).
  - 5-Fluorouracil, epirubicin and cyclophosphamide (FEC).
  - Cyclophosphamide, methotrexate and 5-fluoruracil (CMF).
  - Docetaxel (Taxotere) or paclitaxel (Taxol).
  - Vinorelbine (Navelbine).
  - Gemcitabine (Gemzar).
  - Capecitabine (Xeloda) - as monotherapy or in combination with docetaxel.
Lapatinib (Tyverb) in combination with capecitabine - not recommended by NICE.

- **Hormonal therapy** – 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 bony metastases.
- **Radiotherapy** - for local control.

**Efficacy and safety**

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT00950300, BO22227; trastuzumab SC or IV, with docetaxel, 5-fluorouracil, epirubicin and cyclophosphamide; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Hoffmann-La Roche.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry.</td>
</tr>
<tr>
<td>Location</td>
<td>EU, Canada and other countries.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, active-controlled.</td>
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<tr>
<td>Participants and schedule</td>
<td>n=552 (planned); women ≥18 years; non-metastatic primary invasive breast cancer stage I-IIIC, including inflammatory and multicentric; HER2+. Randomised to: trastuzumab, SC, pre-surgery, 12mg/kg loading dose followed by 9mg/kg maintenance dose every 3 weeks, and post-surgery, 700mg every 3 weeks; or trastuzumab, IV, 8mg/kg loading dose followed by 6mg/kg maintenance dose every 3 weeks. Both arms with docetaxel, IV, 75mg/m², 3 weekly, cycles 1-4, and 5-fluorouracil, IV, 500mg/m², 3 weekly, cycles 5-8, and epirubicin, IV, 75mg/m², 3 weekly, cycles 5-8, and cyclophosphamide, IV, 500mg/m², 3 weekly, cycles 5-8.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment period 12 months; 24 month follow-up.</td>
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<tr>
<td>Primary outcomes</td>
<td>Trastuzumab serum concentrations; complete response.</td>
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<tr>
<td>Secondary outcomes</td>
<td>Overall response rate; progression and recurrence free survival; overall survival; immunogenicity.</td>
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<tr>
<td>Expected reporting date</td>
<td>Not reported.</td>
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</tbody>
</table>

**Estimated cost and cost impact**

The cost of trastuzumab SC is not yet known.

**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: shorter administration time and reduced time in clinic.

☐ Other:  ☐ Quicker, earlier or more accurate diagnosis or identification of disease

☐ None identified
Services

- Increased use
- Service organisation
- Staff requirements

☑ Decreased use: SC administration, shorter administration time and reduced time in clinic.

☐ Other:

☐ None identified

Costs

- Increased unit cost compared to alternative

☐ New costs:

☑ Savings: reduced IV administration and time in clinic.

☐ Increased costs: capital investment needed

☐ Increased costs: more patients coming for treatment.

☐ Other: uncertain unit cost compared to IV formulation.

Other issues

☐ Clinical uncertainty or other research question identified:

☑ None identified

References

   http://www.medicines.org.uk/EMC/medicine/3567/SPC/Herceptin+150mg+Powder+for+concentrate+for+solutio
2. 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.
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.
   High dose fulvestrant for the treatment of locally advanced or metastatic breast cancer. Expected date of issue 
   to be confirmed.
   breast cancer (for use in women with previously treated advanced or metastatic breast cancer). Expected date 
   of issue to be confirmed.
   combination with non-taxane chemotherapy for the first line treatment of metastatic breast cancer. Expected 
   date of issue to be confirmed.
   breast cancer who have received two or more chemotherapy regimens for locally advanced or metastatic disease. Expected date of issue to be confirmed.
10. National Institute for Health and Clinical Excellence. Docetaxel for the adjuvant treatment of early node-
11. National Institute for Health and Clinical Excellence. Paclitaxel for the adjuvant treatment of early node-
13. National Institute for Health and Clinical Excellence. The clinical effectiveness and cost effectiveness of 
    London: NICE; October 2006.
    guidance CSGBC. London: NICE; August 2002.
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