Trastuzumab (Herceptin) for advanced gastric cancer

September 2007

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The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Trastuzumab (Herceptin) for advanced gastric cancer

Target group
- HER2-positive advanced gastric cancer.

Technology description
Trastuzumab (Herceptin) is a recombinant, humanized monoclonal antibody, which specifically targets the human epidermal growth factor receptor 2 (HER2) protein expressed on the cell-surface, inhibiting cell proliferation. The over-expression of the HER2 protein by tumour cells is associated with poor prognosis.

Trastuzumab is currently in phase III trials as an adjunct to the standard treatment (platinum and fluoropyrimidine-based cytotoxic therapy) for patients with HER2 positive advanced gastric cancer. It is anticipated that the dosing schedule for advanced gastric cancer will be an intravenous (iv) infusion with an initial loading dose of 8mg/kg followed by 6mg/kg every three weeks, until disease progression or unacceptable toxicity.

Trastuzumab is currently licensed for:
- HER2 positive metastatic breast cancer either as monotherapy or in combination with paclitaxel;
- In combination with docetaxel for metastatic breast cancer;
- As adjuvant therapy in HER2 positive early breast cancer.

Trastuzumab is in phase II clinical trials for colorectal, ovarian, pancreatic, prostate and salivary gland cancers.

Innovation and/or advantages
The addition of trastuzumab to current chemotherapy options in patients with HER2 positive tumours will provide the first treatment targeted at a specific tumour cell abnormality.

Developer
Roche (Genentech is co-developer).

Place of use
- Secondary care e.g. general, non-specialist hospital
- Tertiary care e.g. highly specialist services or hospital
- Emergency care e.g. paramedic services, trauma care

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.

Relevant guidance
Clinical need and burden of disease

Gastric cancer accounts for around 4% of cancers in men and 2% of cancers in women and is the 7\textsuperscript{th} most common cancer in the UK\textsuperscript{3}. In 2004 8,432 people in England and Wales were diagnosed with gastric cancer and in 2005 there were 4,927 deaths\textsuperscript{4}. The 5-year survival for gastric cancer is approximately 20\%\textsuperscript{5}.

The proportion of gastric cancers that over-express HER2 is estimated between 7-16%\textsuperscript{6,7,8,9,10}. Assuming all patients with HER2 positive advanced gastric cancer receive combination chemotherapy with trastuzumab there will be around 590-1,349 eligible patients each year.

Existing comparators and treatments

- Surgery - subtotal or total gastrectomy
- Cytotoxic chemotherapy regimens:
  - Cisplatin and 5-fluorouracil (5-FU);
  - Epirubicin, cisplatin and 5-FU (ECF);
  - Mitomycin, cisplatin and 5-FU (MCF);
  - Epirubicin, cisplatin and capecitabine [Xeloda\textsuperscript{®}] (ECX).

### Efficacy and safety

<table>
<thead>
<tr>
<th>Trial name or code</th>
<th>Sponsor</th>
<th>Status</th>
<th>Location</th>
<th>Design</th>
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<tbody>
<tr>
<td>TrialTrove 052574\textsuperscript{4} Phase II</td>
<td>Roche ML17263\textsuperscript{7} Phase II</td>
<td>Roche BO18255 (ToGA) Phase III</td>
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<tr>
<td>May be partly funded by Roche Spain.</td>
<td>Roche &amp; Germany</td>
<td>International including 6 UK centres.</td>
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<tr>
<td>Abstract</td>
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<td>Ongoing</td>
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<td>Spain</td>
<td>Open-label pilot; non-randomised; uncontrolled.</td>
<td>Randomised; placebo; controlled.</td>
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Participants

- n=126; HER2 positive gastric adenocarcinoma, previously untreated for advanced disease.
- n=100 (prior to screening); 18-75 years. HER2 positive metastatic or advanced gastric cancer after platinum or 5-FU-based chemotherapy. Patients received trastuzumab (loading dose 4 mg/kg, then 2 mg/kg weekly).
- Planned n=374. HER2 positive, inoperable, locally advanced or recurrent and/or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction. No prior treatment. Cisplatin with either capecitabine or 5-FU; and randomised to trastuzumab (8mg/kg loading dose plus 6 mg/kg every 21 days until disease progression) or placebo.

Primary outcome

- Efficacy and tolerability.
- Tumour response
- Overall survival

Secondary outcomes

- Interim: 13.5\% HER2 positive.
- Clinical benefit, time to progression, duration of response, survival and safety.
- Progression-free survival, overall response, clinical benefit, duration of response, safety and tolerability.

Key results

- Not known.
- Interim results n=3 (33 screened) HER2 positive. 1 partial response to monotherapy sustained for Not known.
Adverse effects | Cardiotoxicity associated with concomitant use with anthracyclines and infusion-related reactions | Not known. | -
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**Estimated cost and cost impact**

A loading dose of trastuzumab 8mg/kg costs £1,630 for an average adult, and £1,222 for each subsequent 6mg/kg dose. The median time to disease progression for advanced gastric cancer in a recent phase III study of cisplatin and capecitabine was approximately 5 months (equating to 7 x 3 week cycles). Trastuzumab over this time period would cost approximately £10,813 per patient. This is in addition to current chemotherapy costs. Other costs include:

- Preliminary assessment of HER2 levels in all patients (immunohistochemistry approximately £40, and fluorescence in situ hybridisation approximately £70);
- Regular measurement of left-ventricular ejection fraction by echocardiogram (ECG) before and during treatment (approximately every three months);
- Treatment of patients developing trastuzumab-related cardiotoxicity.

**Potential or intended impact — speculative**

Patients

- ☐ Increased use
- ☑ Service reorganisation required
- ☐ Staff or training required
- ☑ Non identified

Costs

- ☑ Increased unit cost compared to alternative
- ☐ New costs:

**References**


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4. BNF No. 53. March 2007. Average weight = 67.5kg
12 Kang YK, Kang WK, Shin DB et al. Randomized phase III trial of capecitabine/cisplatin (XP) vs. continuous infusion of 5-FU/cisplatin (FP) as first-line therapy in patients (pts) with advanced gastric cancer (AGC): efficacy and safety results. Abstract LBA4018 (and associated on-line presentation).