Trastuzumab (Herceptin) in combination with aromatase inhibitors for stage IV - metastatic breast cancer

December 2006

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Trastuzumab (Herceptin) in combination with aromatase inhibitor for stage IV - metastatic breast cancer

Target group
- Postmenopausal women with metastatic breast cancers that are over-expressing HER2, and positive for either oestrogen or progesterone receptors, in combination with an aromatase inhibitor.

Technology description
Trastuzumab (Herceptin) is a recombinant humanised monoclonal antibody that specifically targets the epidermal growth factor receptor (HER2) protein. Trastuzumab is administered intravenously, with the dose and frequency for this new indication the same as for monotherapy treatment of metastatic breast cancer. i.e. an initial loading dose of 4mg/kg, then 2mg/kg weekly, until disease progression.

Trastuzumab is already licensed for patients with breast cancer whose tumours over-express HER2:
- As a monotherapy for patients with metastatic breast cancer who have received at least 2 chemotherapy regimes including, where appropriate, an anthracycline and a taxane. Women with oestrogen-receptor-positive breast cancer should also have received a hormonal therapy (e.g. aromatase inhibitors, tamoxifen).
- In combination with paclitaxel or docetaxel, for patients with metastatic breast cancer who have not received chemotherapy, and in whom anthracycline treatment is inappropriate.
- For the treatment of early breast cancer, which should be preceded by surgery, neoadjuvant or adjuvant chemotherapy, and radiotherapy (if appropriate).

Trastuzumab is also in development for ovarian, gastric, colorectal, pancreatic, prostate, non-small cell lung, and salivary gland cancer.

Innovation and/or advantages
HER2 positive cancers are associated with a worse prognosis than HER2 negative tumours. A published trial showed that the median progression free survival time was longer when anastrozole therapy was given in combination with trastuzumab, in women who were co-positive for HER2 and either oestrogen or progesterone receptors.

Developer
Roche (Genentech – co-developer)

Place of use
- Home care e.g. home dialysis
- Community or residential care e.g. district nurses, physio
- Primary care e.g. used by GPs or practice nurses
- 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
- General public e.g. over the counter
- Other:

NHS or Government priority area:
- Cancer
- Cardiovascular disease
- Children
- Diabetes
- Chronic conditions
- Mental health
- Diabetes
- Chronic conditions
- Mental health

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Relevant guidance

- NICE. Breast cancer service guideline, 2002¹.
- Published NICE guidance for advanced breast cancer includes: trastuzumab (2002²), capecitabine (2003³), taxanes (docetaxel and paclitaxel, 2001⁴), and vinorelbine (2002⁵).
- NICE guidance for early stage breast cancer includes: adjuvant hormonal therapies (2006⁶), a published appraisal for the use of trastuzumab for adjuvant treatment (2006⁷), and an appraisal in development for the use of trastuzumab for adjuvant treatment (no publication date indicated).

Clinical need and burden of disease

There were 38,909 women newly diagnosed with breast cancer in England and Wales during 2003⁹, and in 2004 there were 10,945 deaths¹⁰. Between 16% and 20% of women (an estimated 6,225 to 7,781 women) presenting with breast cancer have advanced disease with distant metastases⁵, and in 2002 NICE estimated that around 50% (an estimated 15,564 to 16,342 women) of those presenting with early or localised breast cancer will eventually develop metastatic breast cancer³.

It is estimated that approximately two thirds of women diagnosed with breast cancer have tumours that are hormone receptor positive for oestrogen or progesterone⁷. It is estimated that approximately 15-20% of women with metastatic breast cancer over-express HER2 at the 3+ level⁵. Although, hormone-receptor positive tumours tend to grow less aggressively, resulting in a generally better prognosis, over-expression of the HER2 protein is associated with a poorer prognosis.

Existing comparators and treatments

- For patients with hormone positive metastatic breast cancer several endocrine agents are available, including selective oestrogen agents (e.g. tamoxifen and toremifene), aromatase inhibitors (e.g. anastrozole, letrozole, and exemestane), and selective oestrogen receptor down regulators (e.g. fulvestrant).
- Aromatase inhibitors were traditionally reserved for second-line treatment, but there is evidence of their efficacy as a first-line therapy.

Efficacy and safety

<table>
<thead>
<tr>
<th>Trial name or code</th>
<th>TAnDEM study</th>
<th>Efficacy trial</th>
<th>NCT00171847⁹¹¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anastrozole &amp; Trastuzumab</td>
<td>Letrozole &amp; Trastuzumab</td>
<td>Letrozole &amp; Trastuzumab</td>
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<tr>
<td>Sponsor</td>
<td>Roche</td>
<td>Genentech</td>
<td>Novartis Roche¹</td>
</tr>
<tr>
<td>Status</td>
<td>Abstract¹²¹⁴</td>
<td>Abstract &amp; slides¹⁴</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

¹ Roche is supplying trastuzumab for the Novartis-Roche trial of letrozole and trastuzumab. They report that they have no further information as this trial is not recruiting patients in the UK.
<table>
<thead>
<tr>
<th>Location</th>
<th>Design</th>
<th>Participants in trial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Phase III, randomised, open label, active control.</td>
<td>n=208, women with co-positive HER2 and hormone receptor breast cancers. Arm1: (n=103) trastuzumab, 2mg/kg/week after initial loading dose of 4 mg/kg, plus anastrozole, 1 mg daily. Arm2: (n=104) anastrozole, 1 mg daily. Patients treated until disease progression.</td>
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<td></td>
<td>Phase II, non-randomised, open-label</td>
<td>n=33 metastatic breast cancer co-positive for HER2 and oestrogen/progesterone receptors; tamoxifen-resistant or endocrine-therapy naïve. Letrozole (2.5mg/day) plus trastuzumab (4mg/kg loading dose plus 2mg/kg weekly). A protocol amendment (December 2001) allowed trastuzumab to be administered at a 8mg/kg loading dose followed by a 6mg/kg every 3 weeks. 27 patients had received prior tamoxifen, 5 were endocrine-therapy naïve, 1 was premenopausal but had received an aromatase inhibitor.</td>
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<tr>
<td></td>
<td>Phase IV, randomised, open label, active control.</td>
<td>n=370 (expected)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Unknown</th>
<th>3 and 6 months</th>
<th>Every 3 months.</th>
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</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>Progression-free survival.</td>
<td>Response rate confirmed by CT scan.</td>
<td>Time to disease progression (clinical palpation and radiologic imaging).</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Response; time to progression; survival.</td>
<td>Duration of response time; time to progression; safety profile.</td>
<td>Objective response rate; clinical benefit rate; time to treatment failure; duration of response/clinical benefit; overall survival.</td>
</tr>
<tr>
<td></td>
<td>Safety – haematology; serum chemistry; clinical safety assessments; cardiac monitoring.</td>
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<td></td>
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<tr>
<td></td>
<td>Results for n=30</td>
<td>• Median progression free survival – combination therapy 4.8 months; anastrozole 2.4 months, (p=0.0016).</td>
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<tr>
<td></td>
<td></td>
<td>• Time-to-progression - combination therapy 4.8 months; anastrozole 2.4 months, (p=0.0007).</td>
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<td>• Response to treatment – Partial response: combination therapy (n=17/74); anastrozole (n=7/73), (p=0.018). Overall response rate:</td>
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<td>• Complete response (n=2); partial response (n=6); stable disease (n=8); progressive disease (n=14).</td>
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<td>• Clinical benefit rate (complete or partial response or stable disease at 24 weeks) 53%.</td>
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<td>• Median duration of response 72 weeks (8 patients, range 204 to 202 weeks).</td>
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combination therapy (n=74) 20.3%; anastrozole (n=73) 6.8%, (p=0.018).
• Overall survival – combination therapy 28.5 months; anastrozole 23.9 months, (p=0.325).
• Median time to progression 35.4 weeks (30 patients, range 5.9 to 202 weeks).
• 1 year progression-free survival 46%.

<table>
<thead>
<tr>
<th>Expected reporting date</th>
<th>Unknown</th>
<th>Unknown</th>
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<tbody>
<tr>
<td>Major adverse effects</td>
<td>No new or unexpected adverse events (as experienced in other trastuzumab trials).</td>
<td>Toxicities were mainly grade 1 to 2. The only serious complication was cardiomyopathy in a patient with prior doxorubicin and left chest wall irradiation.</td>
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</tbody>
</table>

**Estimated cost and cost impact**

The cost of a 150mg vial of trastuzumab is £407.40\(^{15}\). A 20 week course for a 65kg woman would cost £8,555.40 (allowing for wastage).

The cost of a 28 pack of 1mg anastrozole tablets is £68.56\(^{15}\). From trial results it can be estimated that women treated with trastuzumab in combination with anastrozole are likely to remain on anastrozole therapy for longer than anastrozole alone. If a patient remains progression free for 10 additional weeks, this would cost an extra £171.40.

**Potential or intended impact – speculative**

Patients

- ✔ Reduced morbidity
- ✔ Reduced mortality or increased survival
- ✔ Improved quality of life for patients and/or carers
- □ Quicker or more accurate diagnosis
- □ Earlier identification of disease
- □ Other:

Services

- ✔ Increased use
- □ Service reorganisation required
- □ Staff or training required
- □ Decreased use e.g. shorter length of stay, reduced referrals
- □ Other:

Costs

- ✔ Increased unit cost compared to alternative in the short term
- □ Increased costs: more patients coming for treatment
- □ Increased costs: capital investment needed
- □ New costs:
- □ Savings:
- □ Other:
References

1 Improving outcomes in breast cancer, Cancer service Guidance, National Institute for Health and Clinical Excellence, August 2002.

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