

# **Horizon Scanning Technology Briefing**

*National  
Horizon  
Scanning  
Centre*

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

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**UNIVERSITY OF  
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This technology summary is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes.

## 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

- |  |   |  |
|--|---|--|
| <input type="checkbox"/> Home care e.g. home dialysis                                    | <input type="checkbox"/> Community or residential care e.g. district nurses, physio           | <input type="checkbox"/> Primary care e.g. used by GPs or practice nurses    |
| <input checked="" type="checkbox"/> Secondary care e.g. general, non-specialist hospital | <input checked="" type="checkbox"/> Tertiary care e.g. highly specialist services or hospital | <input type="checkbox"/> Emergency care e.g. paramedic services, trauma care |
| <input type="checkbox"/> General public e.g. over the counter                            | <input type="checkbox"/> Other:   |  |

### NHS or Government priority area:

- |  |   |  |
|--|---|--|
| <input checked="" type="checkbox"/> Cancer | <input type="checkbox"/> Cardiovascular disease | <input type="checkbox"/> Children      |
| <input type="checkbox"/> Diabetes          | <input type="checkbox"/> Chronic conditions     | <input type="checkbox"/> Mental health |

- |   |  |  |
|---|--|--|
| <input type="checkbox"/> Older people   | <input type="checkbox"/> Public health   | <input type="checkbox"/> Renal disease |
| <input type="checkbox"/> Women's health | <input type="checkbox"/> None identified | <input type="checkbox"/> Other:        |

### Relevant guidance

- NICE clinical guideline. The diagnosis and treatment of breast cancer. In progress (due July 2008).
- NICE. Breast cancer service guideline, 2002<sup>1</sup>.
- Published NICE guidance for advanced breast cancer includes: trastuzumab (2002<sup>2</sup>), capecitabine (2003<sup>3</sup>), taxanes (docetaxel and paclitaxel, 2001<sup>4</sup>), and vinorelbine (2002<sup>5</sup>).
- Appraisal in progress for advanced breast cancer: gemcitabine (due January 2007).
- NICE guidance for early stage breast cancer includes: adjuvant hormonal therapies (2006<sup>6</sup>), a published appraisal for the use of trastuzumab for adjuvant treatment (2006<sup>7</sup>), and an appraisal in development for the use of trastuzumab for adjuvant treatment (no publication date indicated).
- SIGN clinical guideline. Management of breast cancer in women, 2005<sup>8</sup>.

### Clinical need and burden of disease

There were 38,909 women newly diagnosed with breast cancer in England and Wales during 2003<sup>9</sup>, and in 2004 there were 10,945 deaths<sup>10</sup>. Between 16% and 20% of women (an estimated 6,225 to 7,781 women) presenting with breast cancer have advanced disease with distant metastases<sup>3</sup>, 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 cancer<sup>3</sup>.

It is estimated that approximately two thirds of women diagnosed with breast cancer have tumours that are hormone receptor positive for oestrogen or progesterone<sup>7</sup>. It is estimated that approximately 15-20% of women with metastatic breast cancer over-express HER2 at the 3+ level<sup>3</sup>. 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

Trial name or code	TAnDEM study Anastrozole & Trastuzumab	Efficacy trial Letrozole & Trastuzumab	NCT00171847 <sup>11</sup> Letrozole & Trastuzumab
Sponsor	Roche	Genentech Novartis	Novartis Roche <sup>a</sup>
Status	Abstract <sup>12,13</sup>	Abstract & slides <sup>14</sup>	Ongoing

<sup>a</sup> 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.

Location	Multicentre	Multicentre, US	Germany
Design	Phase III, randomised, open label, active control.	Phase II, non-randomised, open-label	Phase IV, randomised, open label, active control.
Participants in trial	n=208, women with co-positive HER2 and hormone receptor breast cancers. <b>Arm1:</b> (n=103) trastuzumab, 2mg/kg/week after initial loading dose of 4 mg/kg, plus anastrozole, 1 mg daily. <b>Arm2:</b> (n=104) anastrozole, 1 mg daily. Patients treated until disease progression.	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.	n=370 (expected)
Follow-up	Unknown	3 and 6 months	Every 3 months.
Primary outcome	Progression-free survival.	Response rate confirmed by CT scan.	Time to disease progression (clinical palpation and radiologic imaging).
Secondary outcomes	Response; time to progression; survival. Safety – haematology; serum chemistry; clinical safety assessments; cardiac monitoring.	Duration of response time; time to progression; safety profile.	Objective response rate; clinical benefit rate; time to treatment failure; duration of response/ clinical benefit; overall survival.
Key results	<ul style="list-style-type: none"> <li>• Median progression free survival – combination therapy 4.8 months; anastrozole 2.4 months, (p=0.0016).</li> <li>• Time-to-progression - combination therapy 4.8 months; anastrozole 2.4 months, (p=0.0007).</li> <li>• Response to treatment – Partial response: combination therapy (n=17/74); anastrozole (n=7/73), (p=0.018). Overall response rate:</li> </ul>	<p>Results for n=30</p> <ul style="list-style-type: none"> <li>• Complete response (n=2); partial response (n=6); stable disease (n=8); progressive disease (n=14).</li> <li>• Clinical benefit rate (complete or partial response or stable disease at 24 weeks) 53%.</li> <li>• Median duration of response 72 weeks (8 patients, range 204 to 202 weeks).</li> </ul>	

	<p>combination therapy (n=74) 20.3%; anastrozole (n=73) 6.8%, (p=0.018).</p> <p>• Overall survival – combination therapy 28.5 months; anastrozole 23.9 months, (p=0.325).</p>	<p>• Median time to progression 35.4 weeks (30 patients, range 5.9 to 202 weeks).</p> <p>• 1 year progression-free survival 46%.</p>	
Expected reporting date	Unknown		Unknown
Major adverse effects	No new or unexpected adverse events (as experienced in other trastuzumab trials).	Toxicities were mainly grade 1 to 2. The only serious complication was cardiomyopathy in a patient with prior doxorubicin and left chest wall irradiation.	

### Estimated cost and cost impact

The cost of a 150mg vial of trastuzumab is £407.40<sup>15</sup>. 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<sup>15</sup>. 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

- |   |   |  |
|---|---|--|
| <input checked="" type="checkbox"/> Reduced morbidity       | <input checked="" type="checkbox"/> Reduced mortality or increased survival | <input type="checkbox"/> Improved quality of life for patients and/or carers |
| <input type="checkbox"/> Quicker or more accurate diagnosis | <input type="checkbox"/> Earlier identification of disease                  | <input type="checkbox"/> Other:  |

#### Services

- |   |  |   |
|---|--|---|
| <input checked="" type="checkbox"/> Increased use                                     | <input type="checkbox"/> Service reorganisation required | <input type="checkbox"/> Staff or training required |
| <input type="checkbox"/> Decreased use e.g. shorter length of stay, reduced referrals | <input type="checkbox"/> Other:                          |   |

#### Costs

- |   |  |   |
|---|--|---|
| <input checked="" type="checkbox"/> Increased unit cost compared to alternative in the short term | <input type="checkbox"/> Increased costs: more patients coming for treatment | <input type="checkbox"/> Increased costs: capital investment needed |
| <input type="checkbox"/> New costs:   | <input type="checkbox"/> Savings:  | <input type="checkbox"/> Other:                                     |

## References

- <sup>1</sup> Improving outcomes in breast cancer, Cancer service Guidance, National Institute for Health and Clinical Excellence, August 2002.
- <sup>2</sup> National Institute for Health and Clinical Excellence. Guidance on the use of trastuzumab for advanced breast cancer: The clinical effectiveness and cost effectiveness of trastuzumab for breast cancer, March 2002; Technology Appraisal Guidance number 34.
- <sup>3</sup> National Institute for Health and Clinical Excellence. Guidance on the use of capecitabine for advanced breast cancer: The clinical effectiveness and cost effectiveness of capecitabine for breast cancer, May 2003; Technology Appraisal Guidance number 62.
- <sup>4</sup> National Institute for Health and Clinical Excellence. Guidance on the use of taxanes for advanced breast cancer: Taxanes for the treatment of breast cancer, September 2001; Technology Appraisal Guidance number 30.
- <sup>5</sup> National Institute for Health and Clinical Excellence. Guidance on the use of vinorelbine for advanced breast cancer: The clinical effectiveness and cost effectiveness of vinorelbine for breast cancer, December 2002; Technology Appraisal Guidance number 54.
- <sup>6</sup> National Institute for Health and Clinical Excellence. Guidance on the use of hormonal treatments for early stage breast cancer: Hormonal therapies for the adjuvant treatment of early oestrogen-receptor-positive breast cancer, November 2006, Technology Appraisal Guidance number 112.
- <sup>7</sup> National Institute for Health and Clinical Excellence. Guidance on the use of trastuzumab for early-stage breast cancer: Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer, August 2006; Technology Appraisal Guidance number 107.
- <sup>8</sup> Scottish Intercollegiate Guideline Network. Management of breast cancer in women. Guideline 84, December 2005.
- <sup>9</sup> Cancer Research UK. UK Breast Cancer incidence statistics. Available at: <http://info.cancerresearchuk.org/cancerstats/types/breast/incidence> (accessed 14/12/06).
- <sup>10</sup> Cancer Research UK. UK Breast Cancer mortality statistics. Available at: <http://info.cancerresearchuk.org/cancerstats/types/breast/mortality> (accessed 14/12/06).
- <sup>11</sup> Clinicaltrials.gov. Study of the efficacy and safety of letrozole combined with trastuzumab in patients with metastatic breast cancer. Study ID – NCT00171847. Available at: <http://www.clinicaltrials.gov/ct/show/NCT00171847> (accessed 12/12/06).
- <sup>12</sup> Baselga J. Trastuzumab + anastrozole in postmenopausal women with HER2-positive HR-positive MBC: the TAnDEM study. Conference slides for presentation at the 31<sup>st</sup> European Society for Medical Oncology Symposium. Istanbul. 29-30 September 2006.
- <sup>13</sup> Mackey J, Kaufman B, Clemes M, *et al.* Trastuzumab prolongs progression-free survival in hormone-dependent and HER2-positive metastatic breast cancer. Abstract for presentation at the San Antonio Breast Cancer Symposium. 14-17 December 2006.
- <sup>14</sup> Marcom P, Isaacs C, Harris L, *et al.* A phase II trial of letrozole and trastuzumab for ER and/or PgR and HER2 positive metastatic breast cancer: final results. Abstract and slides for 2005 American Society of Clinical Oncology (ASCO) Annual Meeting Proceedings. Journal of Clinical Oncology, 2005; 23 (16S), Part I of II: 596. Slides available at: <http://media.asco.org/media/VM2005/Poster/Lectures/2249/PPT/1.jpg> (accessed 19/12/06).
- <sup>15</sup> British National Formulary, September 2006: 52.

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