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NHSC National Horizon Scanning Centre

Bevacizumab (Avastin) in combination with trastuzumab and docetaxel for metastatic HER2 positive breast cancer – first line

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Target group

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

Technology description

Bevacizumab (Avastin; anti-VEGF monoclonal antibody; R 435; RG435; rhuMAb-VEGF) is a humanised anti-vascular endothelial growth factor (VEGF) monoclonal antibody that inhibits VEGF induced signalling and VEGF driven angiogenesis. This reduces vascularisation of tumours, thereby inhibiting tumour growth. The combination of bevacizumab, trastuzumab (HER2 inhibitor) and docetaxel (mitosis inhibitor), is intended to be used for the treatment of breast cancer with over expression of human epidermal growth factor receptor 2 (HER2). Bevacizumab is administered by IV infusion at 15mg/kg every 3 weeks in combination with trastuzumab (8mg/kg loading dose, thereafter 6mg/kg every 3 weeks) and docetaxel (100mg/m^2 every 3 weeks) until disease progression.

Bevacizumab is currently licensed for:

- Metastatic breast cancer: first line treatment in combination with paclitaxel or docetaxel.
- Metastatic colorectal cancer: in combination with fluoropyrimidine based chemotherapy.
- Advanced non-small cell lung cancer (NSCLC): first line treatment in combination with platinum based therapy.
- Advanced and/or metastatic renal cell cancer: first line in combination with interferon alfa-2a.

Bevacizumab is in phase III clinical trials for the treatment of glioblastoma, carcinoid tumour, NSCLC, gastric, colon, fallopian tube, head and neck, ovarian, pancreatic, peritoneal and prostate cancers. It is also in phase II clinical trials for multiple myeloma, non-Hodgkin's lymphoma, brain and liver cancers.

The most serious adverse effects (AEs) of bevacizumab include gastro-intestinal perforation, haemorrhage, and arterial thromboembolism. The most frequently reported AEs are hypertension, diarrhoea, abdominal pain, fatigue, and asthenia[1].

Innovation and/or advantages

HER2 over expression in breast cancer is associated with VEGF over expression. The combined blockade of the HER2 receptor and VEGF has the potential to increase anti-tumour efficacy compared with either treatment alone.

Developer

Roche Products Ltd.

Availability, launch or marketing dates, and licensing plans

In phase III clinical trial.

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 for breast cancer (for use in women with previously treated advanced or metastatic breast cancer). Expected date of issue to be confirmed[2].
- 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[3].
- In development. Bevacizumab in combination with a taxane for the first line treatment of HER2 negative metastatic breast cancer. Expected date of issue to be confirmed[4].
- In development. Ixabepilone for locally advanced or metastatic breast cancer**.** Suspended April 2009[5].
- In development. Sunitinib in combination with capecitabine within its licensed indication for the treatment of advanced and/or metastatic breast cancer. Suspended March 2009[6].
- In development. Intensity modulated radiotherapy for breast cancer. Suspended March 2008[7].
- In development. Lapatinib for breast cancer (first line use in advanced or metastatic hormone-sensitive breast cancer). Suspended December 2007[8].
- The clinical effectiveness and cost effectiveness of trastuzumab for breast cancer. 2002[9].

NICE Clinical Guidelines

- Advanced breast cancer – diagnosis and treatment. 2009[10].
- Breast cancer (early & locally advanced): diagnosis and treatment. 2009[11.]
- Familial breast cancer: the classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care. 2006[12].

Other Guidelines

- SIGN. Management of breast cancer in women. 2005[13].
- Cancer Services Collaborative Improvement Partnership. Breast cancer service improvement guide. 2003[14].

Clinical need and burden of disease

Breast cancer is the most common cancer affecting women in the UK, accounting for about 30% of all cancers in women[15]. In England and Wales, around 40,800 new cases and 10,800 deaths are registered every year[16,17,18]. 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. Analysis of breast cancer survival by level of deprivation has consistently shown higher survival for more affluent women[19].

For breast cancer, the most common sites for metastases are the lymph nodes, bone, liver, lungs and brain[20]. It has been estimated that 5% of women with breast cancer have metastases at diagnosis and a further 35% will develop them over the following 10 years[10]. 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[21].

Existing comparators and treatments

The choice of treatment for each patient depends upon many factors including previous treatment, site of metastases, receptor status of tumour cells, menopausal status, health and informed patient choice.

Current management options for HER2 positive breast cancer include[10,22]:

- Biological therapy:
  - Trastuzumab (Herceptin) alone or in combination with chemotherapy e.g. taxanes.
  - Lapatinib (Tyverb) - licensed for the treatment of advanced or metastatic HER2 positive breast cancer. (Not part of current routine clinical practice and not recommended by NICE).
  - Bevacizumab (Avastin) - licensed for the treatment of advanced or metastatic breast cancer. (Not part of current routine clinical practice and 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) in combination with paclitaxel.
  - Capecitabine (Xeloda) - monotherapy or in combination with docetaxel, or following docetaxel at progression.
- Bisphosphonates - for patients with symptomatic bone metastases.
- Radiotherapy - for local control.
- Surgical excision (rarely indicated).

Efficacy and safety

Trial	BO20231, NCT00391092; trastuzumab and docetaxel with or without bevacizumab; phase III.	OSU-06027, NCT00428922; bevacizumab, trastuzumab and docetaxel; phase II.
Sponsor	Hoffmann-La Roche.	Hoffmann-La Roche.
Status	Ongoing.	Ongoing.
Source of information	Trial registry[23].	Trial registry[24].
Location	EU (inc UK), Canada and other countries.	USA.
Design	Randomised, active-controlled.	Single arm, uncontrolled.
Participants and schedule	n=410 (planned); adults; HER2 positive breast cancer; locally recurrent or metastatic; no prior chemotherapy; left ventricular ejection fraction ≥50%. Randomised to 3 weekly cycle of trastuzumab (8mg/kg loading dose, thereafter 6mg/kg) and docetaxel (100mg/m^2) with or without bevacizumab at 15mg/kg until disease progression.	n=39 (planned); adults; HER2 positive breast cancer; metastatic; no prior chemotherapy; no prior trastuzumab except in adjuvant or neoadjuvant setting. Randomised to 3 weekly cycle of bevacizumab (15mg/kg), trastuzumab (8mg/kg loading dose, thereafter 6mg/kg) and docetaxel (100mg/m^2), for a minimum of 6 cycles.
Follow-up	Active treatment until disease progression.	Minimum active treatment period of 18 weeks, unless disease progression or intolerable toxicity.
Primary outcomes	Progression free survival (PFS).	PFS, safety.
Secondary outcomes	Overall survival, best overall response, duration of response, time to treatment failure, quality of life, AEs.	Circulating endothelial cells (CTCs), circulating tumour cell (CECs), clinical benefit.
Expected	Study expected to complete December	Not available.

reporting date	2011.	

Estimated cost[25] and cost impact

A single dose of bevacizumab at 15mg/kg costs £2,457[a], with annual treatment costs limited to £23,500[b]. The cost of treatment with trastuzumab is £1,467 for the loading dose and £1,100 for subsequent doses[b]. Docetaxel costs £1,383 per dose[c].

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: longer to deliver each chemo cycle, potentially increasing nursing and pharmacy time.
- ☐ 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 element to treatment regimen.
- ☐ Savings:
- ☐ Other:

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[3] 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.

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[5] National Institute for Health and Clinical Excellence. Technology appraisal in development. Ixabepilone for locally advanced or metastatic breast cancer. Suspended April 2009.

[6] National Institute for Health and Clinical Excellence. Technology appraisal in development. Sunitinib in combination with capecitabine within its licensed indication for the treatment of advanced and/or metastatic breast cancer. Suspended March 2009.

[a] Based on average weight 67.5kg.

[b] Information from the company: achieved through capping the drug acquisition cost per patient to the value associated with a cumulative annual dose (CAD), of 10,000mg. Any patient whose CAD exceeds 10,000mg will be entitled to bevacizumab free of charge, provided as a quarterly rebate to the organisation that is financially accountable for the bevacizumab (through direct purchase or subsequent billing). The programme is open to all eligible patients within the UK. For patients to be eligible their treatment will need to be registered with Roche. All data will be held confidentially within the Roche medical department.

[c] Based on average surface area 1.7m^2.

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The National Horizon Scanning Centre,
Department of Public Health and Epidemiology
University of Birmingham, 90 Vincent Drive, Edgbaston, Birmingham, B15 2SP, England
Tel: +44 (0)121 414 7831 Fax +44 (0)121 414 2269
www.haps.bham.ac.uk/publichealth/horizon