Bevacizumab (Avastin) in combination with trastuzumab and chemotherapy for HER2-positive breast cancer – adjuvant therapy

April 2012

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The NIHR Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Bevacizumab (Avastin) in combination with trastuzumab and chemotherapy for HER2-positive breast cancer – adjuvant therapy

Target group
- Breast cancer: HER2-positive, node-positive or high risk node-negative – adjuvant therapy; in combination with trastuzumab and chemotherapy.

Technology description
Bevacizumab (Avastin; rhuMAb-VEGF) is a humanised anti-vascular endothelial growth factor (VEGF) monoclonal antibody that inhibits VEGF induced signalling and VEGF driven angiogenesis, thereby reducing vascularisation of tumours and inhibiting tumour growth. Bevacizumab is administered by intravenous (IV) infusion at 15mg/kg every 21 days in combination with trastuzumab and docetaxel or carboplatin chemotherapy.

Bevacizumab is licensed in the EU for cancers of the colon, rectum, breast (metastatic, in combination with chemotherapy), lung, kidney, ovary, fallopian tube and peritoneum.

Recognised adverse effects for bevacizumab (≥10%) include neutropenia and febrile neutropenia, leucopenia, thrombocytopenia, peripheral sensory neuropathy, hypertension, diarrhoea, nausea, vomiting, asthenia, fatigue, loss of appetite, dysgeusia, headache, eye disorders, increased lacrimation, dyspnoea, epistaxis, rhinitis, constipation, stomatitis, rectal haemorrhage, exfoliative dermatitis, dry skin, skin discolouration, arthralgia, proteinuria, pyrexia, pain and mucosal inflammation.

Bevacizumab is in phase III trials for:
- Breast cancer - metastatic (combination therapies)
- Carcinoid tumours
- Diffuse large B cell lymphoma
- Gastric cancer (combination therapy)
- Glioblastoma (combination therapy)
- Head and neck cancer (combination therapy)
- Non-small cell lung cancer (combination and adjuvant therapies)
- Ovarian cancer (combination therapy)

and in phase II trials for:
- Brain metastases (resulting from non-small cell lung cancer)
- Breast cancer (combination, adjuvant and neoadjuvant therapies)
- Cervical cancer (combination and neoadjuvant therapies)
- Chronic lymphocytic leukaemia
- Ewing’s sarcoma
- Glioblastoma (combination therapies; first line in adolescents and children)
- Haemangiosarcoma
- Liver cancer (combination therapy)
- Malignant melanoma
- Multiple myeloma (combination therapy)
- Neuroblastoma
- Neuroendocrine tumours (combination therapy)
- Non-Hodgkin’s lymphoma
- Non-small cell lung cancer (combination therapy, first line in the elderly)
- Rectal cancer (combination and neoadjuvant therapies)
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- Sarcoma
- Mesothelioma (combination therapy)

**Innovation and/or advantages**

If licensed, bevacizumab in combination with trastuzumab and chemotherapy may offer an alternative treatment option for this patient group.

**Developer**

Roche Products Ltd.

**Availability, launch or marketing dates, and licensing plans**

In phase III clinical trials.

**NHS or Government priority area**

This topic is relevant to Improving Outcomes: A Strategy for Cancer (2011).

**Relevant guidance**

**NICE Technology Appraisals**


**NICE Clinical Guidelines**


**NICE Cancer Service Guidance**


**Clinical need and burden of disease**

Breast cancer is the most common cancer in the UK, accounting for 31% of all cancers in women and affecting around 124 new women per 100,000 per year. In 2008, there were 42,612 new cases and 10,754 deaths registered (females and males) in England and Wales, equating to around 16% of all female cancer deaths in the UK. In England there were 177,801 admissions for malignant neoplasm of the breast (ICD C50), resulting in 148,334 bed days and 181,099 finished consultant episodes in 2010-11. Around 90-95% of patients present with localised (stage I – III) disease and would thus be eligible for surgery and adjuvant treatment. 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-risk groups such as women with a strong family history of the disease.
socioeconomic groups. Analysis of breast cancer survival by level of deprivation has consistently shown higher survival rates for more affluent women.

Nodal status is an important risk factor for disease relapse, with the risk being further defined by grade, tumour size, age and hormone receptor status. Node-positive breast cancer has an increased risk of recurrence while node-negative patients, where cancer cells in the lymph nodes are absent, will usually respond to localised treatments. However, around 30% of node-negative patients, categorised as high-risk node-negative, will require adjuvant therapy to reduce the risk of disease recurrence. Amplification of the HER2 gene and over-expression of the receptor occurs in 15-20% of breast cancers and is associated with a worse prognosis than HER2-negative tumours of similar stage and grade. As a result nearly all HER2-positive breast cancers require adjuvant treatment that incorporates trastuzumab.

The addition of adjuvant trastuzumab for 12 months to standard chemotherapy has significantly improved both disease-free and overall survival and become the standard of care. However many women with HER2-positive disease still develop recurrent or metastatic disease and will die of metastatic breast cancer. Such patients respond poorly to standard therapy with low response rates and short durations of response. Expert opinion suggests there is a need for more effective therapies in HER2-positive early breast cancer.

Existing comparators and treatments
The choice of treatment for each patient depends upon many factors including stage and grade of cancer, previous treatment, site of tumour, receptor status of tumour cells, menopausal status, health and informed patient choice. Current treatment options for HER2-positive localised breast cancer include:

- Surgery – lumpectomy or mastectomy, with axillary lymph node dissection.
- Radiotherapy – to the remainder of the breast tissue, chest wall and nodal areas as indicated by histology.
- 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).
  - Docetaxel plus carboplatin (TCa).
- Hormonal therapy – ovarian suppression therapy, tamoxifen and aromatase inhibitors.
- Biological therapy - trastuzumab.

Efficacy and safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>BETH, NCT00625898, NSABP B-44-1, CIRG (TRIO) 011, Roche BO20906; adults; trastuzumab and chemotherapy with or without bevacizumab; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>National Surgical Adjuvant Breast and Bowel Project (NSABP).</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry.</td>
</tr>
</tbody>
</table>

* Expert opinion
<table>
<thead>
<tr>
<th>Location</th>
<th>EU (inc UK), USA, Canada and other countries.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Randomised, controlled, open label.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=3,509 (planned); adult females; breast cancer; HER2-positive; node positive or high risk node negative; resected.</td>
</tr>
<tr>
<td>and schedule</td>
<td>Randomised to:</td>
</tr>
<tr>
<td></td>
<td>Arm 1A: docetaxel, 75mg/m² IV, every 21 days for 6 cycles, plus carboplatin, 6mg/ml/min IV, every 21 days for 6 cycles, plus trastuzumab, 8mg/kg IV on day 1 of first cycle, followed by 6mg/kg IV, every 21 days for cycles 2-6. Following completion of chemotherapy, trastuzumab, 6mg/kg IV is continued every 21 days for 1 year following first trastuzumab dose.</td>
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<tr>
<td></td>
<td>Arm 1B: docetaxel, carboplatin and trastuzumab as arm 1A, plus bevacizumab, 15mg/kg IV, every 21 days for 6 cycles. Following completion of chemotherapy, bevacizumab, 15mg/kg IV is continued every 21 days for 1 year following first bevacizumab dose.</td>
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<td></td>
<td>Arm 2A: docetaxel, 100mg/m² IV, every 21 days for cycles 1-3, followed by 5FU, 600mg/m² IV, every 21 days for cycles 4-6, plus epirubicin, 90mg/m² IV, every 21 days for cycles 4-6, plus cyclophosphamide, 600mg/m² IV, every 21 days for cycles 4-6. In addition, trastuzumab, 8mg/kg IV, on day 1 of first cycle, followed by 6mg/kg IV, every 21 days for cycles 2-3. 21 days after last chemotherapy dose, trastuzumab, 8mg/kg IV, for one dose only followed by subsequent doses of 6mg/kg IV, every 21 days for 1 year following first trastuzumab dose.</td>
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<tr>
<td></td>
<td>Arm 2B: docetaxel, 5FU, epirubicin, cyclophosphamide and trastuzumab as arm 2A, plus bevacizumab, 15mg/kg IV, every 21 days for cycles 1-3. 21 days after last chemotherapy dose, bevacizumab, 15mg/kg IV, every 21 days for 1 year following first bevacizumab dose.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>1 year; 10 years follow-up.</td>
</tr>
<tr>
<td>Primary</td>
<td>Invasive disease-free survival.</td>
</tr>
<tr>
<td>outcome</td>
<td>Disease-free survival; overall survival; recurrence-free interval; distant recurrence-free survival; cardiac toxicity; non-cardiac toxicity; identification of biomarkers predictive for the level of benefit from the addition of bevacizumab.</td>
</tr>
<tr>
<td>secondary</td>
<td>Interim results expected in Q4 2013, with full publication in Q4 2014.</td>
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<td>outcomes</td>
<td>Estimated cost and cost impact</td>
</tr>
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<td></td>
<td>A single dose of bevacizumab at 15mg/kg costs approximately £2,773, with an annual cost of around £47,000. This will be in addition to the cost of current chemotherapy regimens and trastuzumab.</td>
</tr>
</tbody>
</table>

**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
- □ None identified

**Services**

- □ Increased use
- □ Service organisation
- □ Staff requirements
- □ Decreased use
- □ Other:
- ✔ None identified

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b Based on an average weight of 70.2kg.
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Costs

☐ Increased unit cost compared to alternative
☐ Increased costs: more patients coming for treatment
☐ Increased costs: capital investment needed
☐ New costs: additional treatment option
☐ Savings:
☐ Other:

Other issues

☐ Clinical uncertainty or other research question identified:
☐ None identified

References

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24 National Horizon Scanning Centre. Everolimus (Afinitor) in combination with trastuzumab (Herceptin) and vinorelbine (Navelbine) for Her2/neu positive, locally advanced or metastatic breast cancer. Birmingham: NHSC; February 2012.

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