Sorafenib in combination with capecitabine for HER2-negative locally advanced or metastatic breast cancer

August 2011

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.
Sorafenib in combination with capecitabine for HER2-negative locally advanced or metastatic breast cancer

Target group
- Breast cancer: locally advanced or metastatic (not amenable to resection with curative intent – stage IIIb or IIIc), HER2-negative – second line; in combination with capecitabine.

Technology description
Sorafenib (Nexavar; BAY 43-9006) is a raf signalling pathway inhibitor with raf kinase inhibitor activity. It has a dual action that targets serine/threonine and receptor tyrosine kinases, inhibiting (1) the raf cascade to prevent the downstream mediation of cell growth and proliferation, and (2) the VEGFR-2/3, PDGFR-β signalling cascade to inhibit the activation of angiogenesis, thus acting on both tumour cell growth and tumour vasculature. Sorafenib in combination with capecitabine is intended to treat locally advanced or metastatic HER2-negative breast cancer in patients who have received no more than one prior chemotherapy regimen. Sorafenib is administered orally at 600mg daily, 200mg in the morning and 400mg at night, with capecitabine administered at 1,000mg/m², twice daily on days 1-14 of a 21 day cycle.

Sorafenib is licensed and has received orphan designation in the EU for the treatment of advanced renal cell carcinoma and hepatocellular carcinoma. It is currently in phase III clinical trials for liver cancer, non-small cell lung cancer, renal cancer and thyroid cancer. Sorafenib is also in phase II clinical trials for a variety of cancers, including acute myeloid leukaemia, head and neck, colorectal, gastric, ovarian, germ cell and embryonal neoplasms.

Recognised adverse effects (≥10%) include: abnormal laboratory test results, gastrointestinal, respiratory and brain haemorrhage, lymphopenia, diarrhoea, hair loss, hand-foot syndrome, itching, hypophosphataemia, nausea, pain, hypertension, skin rashes, tiredness and vomiting1.

Innovation and/or advantages
If licensed, sorafenib in combination with capecitabine may offer an additional treatment option for this patient group.

Developer
Bayer.

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 (2000) and Improving Outcomes: A Strategy for Cancer (2011).

Relevant guidance
NICE Technology Appraisals

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1 VEGFR: vascular endothelial growth factor receptor; PDGFR: platelet-derived growth factor receptor.
In development. Lapatinib for breast cancer (for use in women with previously treated advanced or metastatic breast cancer). Suspended October 2010.

In development. Eribulin monotherapy for the treatment of people with breast cancer who have received two or more chemotherapy regimens for locally advanced or metastatic disease. Expected December 2011.


**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 per 100,000 women. In England and Wales, 42,612 new cases (male and female) were diagnosed in 2008 and in 2009, 10,374 deaths occurred, equating to 4.1% of all female deaths. There were 173,653 hospital admissions due to breast cancer in England in 2009-10, accounting for 176,962 finished consultant episodes and 173,653 bed days (ICD10: C50). 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 socioeconomic groups. Analysis of breast cancer survival by level of deprivation has consistently shown higher survival for more affluent women.

Locally advanced breast cancer refers to the stage where the tumour has spread to locally adjacent tissues and/lymph nodes. Metastatic breast cancer is the presence of disease at distant sites. The most common sites for metastases are the lymph nodes, bone, liver, lungs and brain. An estimated 5% of women have metastases at diagnosis and a further 35% will develop them over the following 10 years. Estimates of the number of people living with advanced breast cancer vary, and population level data for describing the epidemiology of advanced breast cancer is relatively sparse. Between 75% and 85% of breast cancers in women are HER2-negative and estimates suggest this figure is higher in men.

**Existing comparators and treatments**

For women with locally advanced or metastatic disease, the aim of treatment is to ameliorate symptoms, maintain quality of life and prolong survival. 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.
Treatment options for locally advanced or metastatic, HER2-negative breast cancer exclude currently available biological therapies (e.g. trastuzumab). Current management options include:

- Surgery if appropriate.
- Radiotherapy - for local control and painful bone metastases.
- Standard chemotherapy regimens – adjuvant or neoadjuvant
  - Doxorubicin and cyclophosphamide (AC).
  - 5-Fluorouracil, epirubicin and cyclophosphamide (FEC).
  - Cyclophosphamide, methotrexate and 5-fluorouracil (CMF).
  - Docetaxel (Taxotere) or paclitaxel.
  - Vinorelbine.
  - Gemcitabine in combination with paclitaxel.
  - Capecitabine – monotherapy, in combination with docetaxel, or following docetaxel at progression.
- Hormonal therapy e.g. tamoxifen and aromatase inhibitors (for oestrogen receptor positive breast cancer).
- Bisphosphonates - for patients with symptomatic bone metastases.

### Efficacy and safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01234337, 12444; adults; sorafenib with capecitabine vs placebo with capecitabine; phase III.</th>
<th>SOLTI-0701, 2007-00290-32; adults; sorafenib with capecitabine vs placebo; phase IIb.</th>
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</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Bayer.</td>
<td>Bayer.</td>
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<tr>
<td>Source of information</td>
<td>Trial registry.</td>
<td>Abstract, publication, trial registry, manufacturer.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (inc UK), USA and other countries.</td>
<td>EU and Brazil.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
<td>Randomised, placebo-controlled.</td>
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<tr>
<td>Participants and schedule</td>
<td>n=519 (planned); adults; HER2-negative locally advanced or metastatic breast cancer; resistant to, or failed prior taxane and anthracycline therapy, no more than one prior chemotherapy treatment. Randomised to sorafenib 600mg daily, (1 morning dose and 2 evening doses) for 21 days, plus capecitabine 1,000mg/m², twice daily for 14 days, or placebo (1 morning dose, 2 evening doses) for 21 days, plus capecitabine 1000mg/m², twice daily for 14 days.</td>
<td>n=220; women aged ≥18 years; locally advanced or metastatic HER2-negative breast cancer, &lt;2 prior chemotherapy regimens. Randomised to sorafenib 400mg, twice daily continuously plus capecitabine 1,000mg/m², twice daily for 14 of every 21 days, or placebo, twice daily continuously, plus capecitabine 1,000mg/m², twice daily for 14 of every 21 days.</td>
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<tr>
<td>Follow-up</td>
<td>Until disease progression.</td>
<td>Information not available.</td>
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<tr>
<td>Primary outcome</td>
<td>Progression-free survival (PFS).</td>
<td>PFS.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Overall survival (OS); time to progression (TTP); overall response rate; duration of response; patient reported outcomes.</td>
<td>Objective response rate (ORR); duration of response; TTP; OS.</td>
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<tr>
<td>Key results</td>
<td>-</td>
<td>For sorafenib and placebo respectively, median PFS (months), 6.4, 4.1 (HR 0.576, 95% CI: 0.410 to 0.809,</td>
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</table>
p=0.0006; first-line subgroup: PFS (mths), 7.6, 4.1 (HR 0.498, p=0.0022); second-line subgroup: PFS (mths), 5.7, 4.1 (HR 0.652, p=0.0339); TTP (mths) 6.8, 4.2 (HR 0.562, p=0.0005); ORR (%), 38, 31, p=0.122).

<table>
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<th>Expected reporting date</th>
<th>Not reported.</th>
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<td>Adverse effects (AEs)</td>
<td>-</td>
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</table>

AEs >3% for sorafenib and placebo respectively: hand-foot skin reaction, 45%, 13%; diarrhoea, 5%, 5%; dyspnoea, 5%, 4%, neutropaenia, 5%, 3%; mucositis, 1%, 4%.

**Estimated cost and cost impact**

The cost of sorafenib has not yet been determined for this indication. The cost of sorafenib for advanced renal cell carcinoma is £2,980.47 for a 200mg x 112 tablet pack. The cost of capecitabine for one cycle of 2,000mg/m² daily for 14 days is approximately £133.00\(^b\).

**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
- □ Quickier, earlier or more accurate diagnosis or identification of disease
- □ None identified

**Services**

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

**Costs**

- □ Increased unit cost compared to alternative
- ✔ New costs: add-on therapy
- □ Increased costs: more patients coming for treatment
- □ Increased costs: capital investment needed
- □ Savings:
- □ Other:

**Other issues**

- □ Clinical uncertainty or other research question identified:
- ✔ None identified

**References**


\(^b\) Costing based on average surface area of 1.7m².
3 National Institute for Health and Clinical Excellence. Eribulin monotherapy for the treatment of people with breast cancer who have received two or more chemotherapy regimens for locally advanced or metastatic disease. Technology appraisal in development. Expected December 2011.


