Lapatinib (Tyverb) in combination with a taxane for HER2-positive metastatic breast cancer – first line

February 2012

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The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
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Target group
- Breast cancer: human epidermal growth factor receptor 2 (HER2) positive, metastatic – first line; in combination with a taxane.

Technology description
Lapatinib (Tyverb, GW-572016) is a small molecule, dual inhibitor of HER1 (ErbB1) and HER2 (ErbB2) receptor tyrosine kinases. Lapatinib binds to the intracellular kinase domain of these receptors, thus inhibiting receptor activation and signal transmission that stimulate cell proliferation and survival. Lapatinib in combination with a taxane is intended as an alternative to trastuzumab-based treatment. Lapatinib is administered orally at 1,250mg/day in combination a taxane via intravenous (IV) administration.

Lapatinib is licensed in the EU for the treatment of advanced or metastatic HER2-positive breast cancer in combination with capecitabine following therapy with an anthracycline, a taxane and trastuzumab, and in combination with an aromatase inhibitor in post-menopausal women¹. Recognised adverse effects (>10%) include: diarrhoea, rash, nausea, vomiting, gastrointestinal events, back pain, breathing difficulties, cough, dry skin, hair loss, headaches, hot flushes, itching, joint pain, nose bleed, pain in the extremities and weakness².

Lapatinib is in phase III trials for prevention of brain metastases (arising from breast cancer), gastric cancer (in combination with capecitabine and oxaliplatin), adjuvant treatment of high risk resected head and neck cancer (in combination with chemotherapy), and breast cancer (adjuvant), and in phase II trials for head and neck cancer (adjuvant and combination therapies), gastric cancer (in combination with capecitabine), colorectal cancer (in combination with capecitabine) and breast cancer (neoadjuvant therapy).

Innovation and/or advantages
If licensed, lapatinib in combination with a taxane may offer an alternative treatment option for this patient group.

Developer
GlaxoSmithKline.

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 technology appraisal in development. Lapatinib and trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone receptor positive breast cancer which over-expresses HER2. Expected June 2012⁴.


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. 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 rates for more affluent women.

Metastatic breast cancer is the presence of disease at distant sites; most commonly 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. Over-expression of the product of the HER2 oncogene occurs in about 20% of women with metastatic breast cancer, and is associated with a worse prognosis.

Existing comparators and treatments

For women with 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. Current treatment options for patients with HER2-positive metastatic breast cancer include.
• Surgery if appropriate.
• Radiotherapy - for local control and painful bone metastases.
• Biological therapies
  o Trastuzumab – alone or in combination with chemotherapy e.g. taxanes.
  o Bevacizumab – not recommended by NICE.
  o Lapatinib – currently being appraised by NICE.
• Chemotherapies
  o Anthracyclines – doxorubicin and epirubicin.
  o Taxanes – docetaxel and paclitaxel.
  o Alkylating agents – cyclophosphamide usually in combination with an anthracycline or taxane.
  o Platinum-based drugs, e.g. carboplatin.
  o Vinorelbine.
  o Gemcitabine – in combination with paclitaxel.
  o Capecitabine – as monotherapy or in combination with docetaxel.
  o Eribulin – currently being appraised by NICE.
• Hormonal therapies – oestrogen receptor positive (ER+) and/or progesterone receptor positive (PR+) disease
  o Anti-oestrogens, e.g. tamoxifen.
  o Oestrogen receptor down-regulator – fulvestrant (not recommended by NICE within licensed indication).
  o Aromatase inhibitors, e.g. anastrozole, letrozole, exemestane.
  o Ovarian ablation.
  o Progestogens, e.g. megestrol acetate, medroxyprogesterone acetate.
  o Pituitary down regulators, e.g. goserelin.
• Bisphosphonates – for patients with metastatic bone disease.

### Efficacy and safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Status</th>
<th>Source of information</th>
<th>Location</th>
<th>Participants and schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00667251, MA31, CAN-NCIC-MA31, GSK-EGF108919, EUDRACT-2007-004568-27, CDR0000594764; Lapatinib with a taxane vs trastuzumab with a taxane; phase III.</td>
<td>GlaxoSmithKline.</td>
<td>Ongoing.</td>
<td>Trial registry25.</td>
<td>USA, Canada, EU (inc UK) and other countries.</td>
<td>n=600 (planned); adult females; breast cancer; HER2-positive; metastatic (stage IV) at primary diagnosis or at relapse</td>
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<td>NCT00281658, EGF104535; paclitaxel with lapatinib vs paclitaxel with placebo; phase III.</td>
<td>GlaxoSmithKline.</td>
<td>Complete and published in abstract.</td>
<td>Poster26; trial registry27.</td>
<td>The Americas, Europe (EU and non-EU), South-East Asia, Western Pacific, and Eastern Mediterranean regions.</td>
<td>n=444; adults; breast cancer; HER2-positive; metastatic (stage IV). Randomised to lapatinib, 1,500mg once daily, with</td>
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<tr>
<td>NCT00356811, EGF105764; lapatinib with paclitaxel; phase II.</td>
<td>GlaxoSmithKline.</td>
<td>Published.</td>
<td>Publication28, trial registry29.</td>
<td>Latvia, Poland, Romania and Russian Federation.</td>
<td>n=57; adult females; breast cancer; HER2-positive; metastatic (stage IV) with no prior therapy for metastatic disease.</td>
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<td>Following prior treatment with chemotherapeutic or HER2/neu targeted agents in neo-/adjuvant setting</td>
<td>paclitaxel, 80mg/m² IV on days 1, 8 and 15 of a 28 day cycle, or placebo with paclitaxel, 80mg/m² IV on days 1, 8 and 15 of a 28 day cycle. Patients on paclitaxel offered lapatinib monotherapy on disease progression. Paclitaxel administered for at least 6 cycles.</td>
<td>Lapatinib, 1,500mg daily with paclitaxel 80mg/m² IV weekly for 3 weeks of a 4 week cycle. Paclitaxel administered for at least 6 cycles.</td>
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<td>Randomised to: Arm 1: lapatinib, 1,250mg oral, once daily, with docetaxel, 75mg/m² IV on day 1 of a 3 week cycle for 8 cycles, or paclitaxel, 80mg/m² IV on days 1, 8 and 15 of a 4 week cycle for 6 cycles. Arm 2: trastuzumab, 4mg/kg IV on days 1, 8, 15 and 22, with paclitaxel, 80mg/m² IV on days 1, 8, and 15 of a 4 week cycle for 6 cycles, or trastuzumab, 6mg/kg IV with docetaxel, 75mg/m² IV on day 1 of a 3 week cycle for 8 cycles. Following completion of taxane therapy, all patients receive trastuzumab alone once every 3 weeks. Both arms: patients on docetaxel also receive filgrastim (G-CSF) according to institutional standard.</td>
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<td>Follow-up</td>
<td>After completion of treatment, follow up at 4 weeks and every 12 weeks thereafter.</td>
<td>Follow-up until death.</td>
<td>Treatment continued until disease progression or withdrawal.</td>
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<td>Primary outcome</td>
<td>Progression-free survival (PFS).</td>
<td>Overall survival (OS).</td>
<td>Overall response (OR).</td>
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<td>Secondary outcomes</td>
<td>OS; occurrence and time to CNS metastases; overall objective response rate, time to response; duration of response (DoR); clinical benefit; EORTC QLQ-C30° and Trial Specific Checklist; biomarker changes; economic evaluation including EQ-5Db.</td>
<td>PFS; OR; clinical benefit; DoR; complete or partial response.</td>
<td>DoR; time to response (TTR); time to progression (TTP), PFS, OS.</td>
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<td>Key results</td>
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<td>For lapatinib with paclitaxel, and placebo with paclitaxel, respectively: median OS</td>
<td>IRC° and investigator assessed, respectively (%): OR, 50.9 (95% CI 37.3-64.4), 77.2 (95% CI 64.2-</td>
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° EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of cancer patients.

* EQ-5D is a standardised instrument for use as a measure of health outcome.

° Independent Review Committee.
(mths), 27.8 (95% CI 23.2-32.2), 20.5 (95% CI 17.9-24.3), Hazard Ratio (HR) 0.74 (95% CI 0.58-0.94); median PFS (mths), 9.7 (95% CI 9.2-11.1), 6.5 (95% CI 5.5-7.3), HR 0.52 (95% CI 0.42-0.64); response rates by RECIST criteria, (%), complete response (CR), 7, 3; partial response (PR), 62, 46; stable disease (SD), 23, 33; SD ≥ 24 weeks, 5, 6; progressive disease 4, 13; OR, 69, 50 (odds ratio 2.30, 95% CI 1.54-3.47); clinical benefit response rate 87.3); median DoR (weeks), 39.7 (95% CI 26.9-50.0), 42.3 (95% CI 37.7-64.1); median PFS (weeks), 47.9 (95% CI 40.0 to NA), 50.9 (95% CI 47.0-64.3); median TTP (weeks) 47.9 (95% CI 40.0-NA), 50.9 (95% CI 47.0-64.3); median TTR (weeks), 8.4 (95% CI 7.9-11.1), 8.0 (95% CI 7.9-8.1).

Adverse effects (AEs) - For lapatinib with paclitaxel, and placebo with paclitaxel, respectively: AEs ≥20%, diarrhoea, 77, 29; neutropenia, 77, 46; alopecia, 46, 52; leukopenia, 53, 34; rash 59, 24; decreased appetite, 32, 19; nausea, 30, 18; fatigue 22, 17; vomiting, 22, 11; anaemia 23, 9. AEs >10% (%): diarrhoea 56; neutropenia 44; rash 40; fatigue 25; peripheral sensory neuropathy 25; elevated ALT 18; leukopenia 18; upper abdominal pain 16; alopecia 16; anaemia 16; nausea 14; peripheral neuropathy 14; nail disorders 12; arthralgia 11; peripheral oedema 11; upper respiratory tract infection 11; vomiting 11.

Expected reporting date - Estimated primary completion date June 2013.

Estimated cost and cost impact
The cost of lapatinib at 1,250mg once daily for 28 days is £1,608.6030.

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

☐ Other:

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+ CR+PR+SD≥24 weeks
^ Upper limit not available due to censoring of the longest PFS.
Services

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

Costs

- Increased unit cost compared to alternative
- New costs:
- Increased costs: more patients coming for treatment
- Increased costs: capital investment needed
- Savings:
- Other: likely to be similar direct drug cost to trastuzumab
- None identified

Other issues

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

References


The National Institute for Health Research National Horizon Scanning Centre Research Programme is funded by the Department of Health.
The views expressed in this publication are not necessarily those of the NHS, the NIHR or the Department of Health

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