Neratinib for HER2-positive early breast cancer

SUMMARY

Neratinib is intended to be used as a second line therapy for the treatment of HER2-positive early breast cancer. If licenced, neratinib will offer an extended adjuvant treatment option for patients with early HER2-positive disease. Neratinib is an irreversible pan-erythroblastic leukemia viral oncogene homolog (erbB) tyrosine kinase inhibitor (TKI) that blocks signal transduction through three epidermal growth factor receptors, erbB1, erbB2/HER2, and erbB4, resulting in sustained inhibition of these growth-promoting pathways. Neratinib does not currently have Marketing Authorisation in the EU for any indication.

Breast cancer is the most common cancer in UK, accounting for 30% of all cancers in women. In England, there were 41,826 new cases of breast cancer in both men and women in 2011, and 41,523 cases in women alone (representing 124.8 cases per 100,000 population). Approximately 90% of breast cancer is diagnosed in the early stages of the disease, before the tumour has spread significantly within the breast or to other organs of the body. It is estimated that 20% of women with breast cancer will have HER2-positive tumours. In 2012, there were 10,373 deaths from breast cancer registered in England and Wales.

Treatment for patients with HER2-positive early breast cancer may include: surgery (lumpectomy or mastectomy), radiotherapy, biological therapy (adjuvant or neoadjuvant trastuzumab), chemotherapy (adjuvant or neoadjuvant), and hormone therapy (adjuvant and neoadjuvant), as well as bisphosphonates for the management of treatment-induced bone loss. Neratinib is currently in one phase III clinical trial comparing its effect on disease-free survival against treatment with placebo. This trial was expected to complete in November 2013.
TARGET GROUP

- Breast cancer: early; HER2-positive – second line; following adjuvant trastuzumab therapy.

TECHNOLOGY

DESCRIPTION

Neratinib (HKI-272; PB-272) is a potent irreversible pan-erythroblastic leukemia viral oncogene homolog (erbB) tyrosine kinase inhibitor (TKI) that blocks signal transduction through three epidermal growth factor receptors, erbB1, erbB2/HER2, and erbB4, resulting in sustained inhibition of these growth-promoting pathways. In the phase III clinical trial neratinib is administered orally at 240mg daily for one year.

Neratinib does not currently have Marketing Authorisation in the EU for any indication. Neratinib is currently also in phase III clinical trials for HER2-positive metastatic breast cancer (combination therapy) and in phase II clinical trials for metastatic colorectal cancer (combination therapy), locally advanced HER2-positive breast cancer (neoadjuvant combination therapy), breast cancer with brain metastases, and solid tumours with activating HER2, HER3 or EGFR mutations.

INNOVATION and/or ADVANTAGES

If licensed, neratinib will offer an extended adjuvant treatment option for patients with early HER2-positive breast cancer.

DEVELOPER

Puma Biotechnology.

AVAILABILITY, LAUNCH OR MARKETING

Neratinib is currently in phase III clinical trials.

PATIENT GROUP

BACKGROUND

Breast cancer arises from the tissues of the breast duct or the lobules of the breast; early breast cancer (stage I-II) describes cancer that has not spread beyond the breast or axillary lymph nodes on the same side of the body\(^1,2\). Breast cancer is further classified according to over-expression of the human epidermal growth factor receptor 2 on tumour cells (known as HER2-positive). Patients with HER2-positive disease typically have a worse prognosis\(^3\).

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to:
Breast cancer is the most common cancer in the UK, accounting for 30% of all cancers in women. In England, there were 41,826 new cases of breast cancer in both men and women in 2011, and 41,523 cases in women alone (representing 124.8 cases per 100,000 population). In 2012, there were 10,373 deaths from breast cancer registered in England and Wales (ICD C50), as well as 177,514 admissions for malignant neoplasm of the breast (ICD C50) in England, which resulted in 109,365 bed days and 180,595 finished consultant episodes.

Breast cancer risk is strongly related to age, with 81% of cases occurring in women aged over 50 years, and while the incidence of breast cancer is highest in those from higher socioeconomic groups, survival is lowest in those from lower socioeconomic groups. This pattern persists even after allowing for the higher overall premature all-cause mortality observed in lower socioeconomic groups compared to higher socioeconomic groups. Approximately 90% of breast cancer is diagnosed in the early stages of the disease, before the tumour has spread significantly within the breast or to other organs of the body.

It is estimated that 20% of women with breast cancer will have HER2-positive tumours. Amplification of the HER2 gene and over-expression of the receptor is associated with a worse prognosis than HER2-negative tumours of similar stage and grade. As a result nearly all patients with HER2-positive breast cancers are offered 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 approximately 15% of patients relapse after therapy, indicating the presence of de novo or acquired trastuzumab resistance. As a result many women with HER2-positive disease develop recurrent or metastatic disease and will die of breast cancer. Such patients respond poorly to standard therapy with low response rates and short durations of response.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**

- NICE technology appraisal in development. Breast cancer (HER2 positive, unresectable) - trastuzumab emtansine (after trastuzumab & taxane) [ID603]. Expected August 2014.
The choice of treatment for patients with HER2-positive early breast cancer depends upon factors such as the precise stage and grade of cancer, previous treatment, site of tumour, hormone 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.
- Biological therapy – adjuvant or neoadjuvant:
  - trastuzumab (in combination with taxane-based chemotherapy, 1 year regimen).
- Standard chemotherapy regimens – adjuvant or neoadjuvant:
  - 5-fluorouracil (5FU), epirubicin and cyclophosphamide (FEC).
  - FEC followed by docetaxel (also called Taxotere) (FEC-D).
  - Docetaxel, doxorubicin (also called adriamycin) and cyclophosphamide (TAC).
  - doxorubicin and cyclophosphamide (AC).
  - cyclophosphamide, methotrexate and 5FU (CMF).
  - epirubicin and CMF (E-CMF).
  - docetaxel plus carboplatin (TCa).
- Hormone therapy – adjuvant and neoadjuvant:
• tamoxifen – oestrogen receptor (ER)-positive early breast cancer.
• ovarian ablation through the use of luteinising hormone releasing hormone agonists (e.g. goserelin), oophorectomy (surgical removal of the ovaries), or radiotherapy - ER-positive early breast cancer in premenopausal women.
• aromatase inhibitors e.g. anastrozole, letrozole, exemestane – ER-positive early breast cancer in postmenopausal women.

• Bisphosphonates are indicated for the management of treatment-induced bone loss.

### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>ExteNET, NCT00878709, neratinib vs placebo; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Puma Biotechnology.</td>
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<tr>
<td>Status</td>
<td>Complete but unpublished.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Abstract[^35], trial registry[^37], manufacturer.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (incl UK), USA, Canada and other countries.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
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<tr>
<td>Participants</td>
<td>n=2,842; 18 years and older; females; breast cancer; HER-2/erbB-2-positive; stage II through IIIC; node positive disease; treated for early breast cancer with standard of care duration of trastuzumab; may have been treated neoadjuvantly but did not reach pathological complete response (pCR).</td>
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<tr>
<td>Schedule</td>
<td>Randomised to neratinib 240mg oral daily or placebo oral daily, both for one year.</td>
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<td>Follow-up</td>
<td>Active treatment for one year, follow-up four years.</td>
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<tr>
<td>Primary outcome/s</td>
<td>Disease-free survival (DFS).</td>
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<tr>
<td>Secondary outcome/s</td>
<td>Time to distant recurrence (TTDR) or death from breast cancer; disease-free survival including ductal carcinoma in situ (DFS-DCIS); distant disease free survival (DDFS), incidence of central nervous system recurrence; overall survival (OS).</td>
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<tr>
<td>Expected reporting date</td>
<td>Previously reported as November 2013.</td>
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### ESTIMATED COST and IMPACT

**COST**

The cost of neratinib is not yet known.

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**
- ☑ Reduced mortality/increased length of survival
- ☐ Other:
- ☐ Reduced symptoms or disability
- ☐ No impact identified

**Impact on Health and Social Care Services**
- ☑ Increased use of existing services
- ☐ Re-organisation of existing services
- ☐ Other:
- ☐ Decreased use of existing services
- ☐ Need for new services
- ☐ None identified
Impact on Costs and Other Resource Use

☑ Increased drug treatment costs  ☐ Reduced drug treatment costs
☐ Other increase in costs:  ☐ Other reduction in costs:
☐ Other:  ☐ None identified

Other Issues

☐ Clinical uncertainty or other research question identified  ☑ None identified

REFERENCES

5 Cancer Research UK. Data Table: Cancer cases and rates by country in the UK 2011.
12 National Institute for Health and Care Excellence. Breast cancer (HER2 positive, metastatic) - pertuzumab (with trastuzumab and docetaxel) - final scope ID523.
19 NIHR Horizon Scanning Centre. Everolimus (Afinitor) in combination with trastuzumab (Herceptin) and vinorelbine (Navelbine) for Her2/neu positive, locally advanced or metastatic breast cancer. Birmingham: NIHR-HSC; February 2012.