Neratinib with capecitabine for advanced or metastatic HER2-positive breast cancer – third line

SUMMARY
NIHR HSRIC ID: 4084

Neratinib (in combination with capecitabine) is intended to be used as a third line therapy for the treatment of advanced or metastatic HER2-positive breast cancer. If licensed it would offer an additional oral treatment option for patients with this disease who have already received at least two prior HER2-directed therapies. Neratinib is a potent irreversible pan-erythroblastic leukaemia viral oncogene homolog (erbB) tyrosine kinase inhibitor 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 the UK, accounting for 30% of all cancers in women. In England, there were 42,773 recorded cases of breast cancer in 2012 with an incidence of 130 per 100,000 population in women. An estimated 5% of patients present with metastatic breast cancer, and approximately 30% of people who present with localised breast cancer later develop metastatic disease. An estimated 20% of women with breast cancer will have HER2-positive tumours which are associated with a worse prognosis than HER2-negative tumours of similar stage and grade.

The aim of treatment for advanced or metastatic breast cancer is to control disease-related symptoms, slow disease progression, minimise treatment-related toxicity, and reduce the intrusion of the disease and treatment on a patient’s life. Treatment options for metastatic 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, in combination with capecitabine, is currently in one phase III clinical trial comparing its effect on progression free survival against treatment with lapatinib in combination with capecitabine. The trial is expected to complete in May 2017.
TARGET GROUP

- Breast cancer: advanced or metastatic; HER2-positive; – third line; in combination with capecitabine.

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 once daily on days 1-21 of a 21 day cycle with capecitabine 1,500mg/m² orally once daily on days 1-14.

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 early breast cancer, 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 (in combination with capecitabine) will offer an additional oral treatment option for patients with advanced or metastatic HER2-positive breast cancer who have already received at least two prior HER2-directed therapies.

DEVELOPER

Puma Biotechnology.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

Breast cancer arises from the tissues of the breast duct or the lobules of the breast; metastatic disease represents spread to distant sites of the body. The most common sites for metastases include the lymph nodes, bone, liver, lungs and brain. Once breast cancer becomes metastatic it is rarely, if ever, curable.

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to:

CLINICAL NEED and BURDEN OF DISEASE

Breast cancer is the most common cancer in the UK, accounting for 30% of all cancers in women. In England, there were 42,773 recorded cases of breast cancer in 2012 with an incidence of 130 per 100,000 population in women (ICD-10 C50). In 2013, 10,230 deaths from breast cancer were registered in England and Wales (ICD-10 C50). In 2013-14, there were 188,103 admissions for breast cancer (ICD-10 C50) in England, resulting in 106,988 bed-days and 191,337 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.

An estimated 5% of patients present with metastatic breast cancer, and approximately 30% of people who present with localised breast cancer will later develop metastatic disease. 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. The population likely to be eligible to receive neratinib could not be estimated from available published sources.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

- NICE technology appraisal in development. Breast cancer (HER2-positive, metastatic) - pertuzumab (with trastuzumab and docetaxel) [ID523]. Expected publication date: TBC.
- NICE technology appraisal in development. Breast cancer (HER2-positive, unresectable) - trastuzumab emtansine (after trastuzumab & taxane) [ID603]. Expected publication date: TBC.
- NICE technology appraisal. Lapatinib or trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone receptor positive breast cancer which over-expresses HER2 (TA257). June 2012.


European Society for Medical Oncology. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). 2014.


European Society for Medical Oncology. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2013.

European Society for Medical Oncology. Locally recurrent or metastatic breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2012.


CURRENT TREATMENT OPTIONS

The aims of treatment for patients with metastatic breast cancer are to improve quality of life and prolong survival, without necessarily offering a realistic hope of cure. The central tenets of treatment are therefore to control disease-related symptoms, slow disease progression, minimise treatment-related toxicity, and reduce the intrusion of the disease and treatment on a patient’s life. Whenever possible, isolated loco-regional recurrence should be treated with a curative intent; if feasible, complete excision of recurrent tumour is recommended. At the time of recurrence, patients will have typically received a taxane and an anthracycline as adjuvant treatment, therefore very few pharmaceutical anti-cancer treatment options remain available for metastatic breast cancer.

Systemic treatment options for metastatic breast cancer include:

- First line chemotherapy: this generally includes repeated anthracycline and/or taxanes, possibly combined with cyclophosphamide. In patients without directly life-threatening or severely symptomatic disease, single-agent chemotherapy is the preferred option.
- Second line chemotherapy: this may include 5-fluorouracil, gemcitabine, or vinorelbine.
- Bone-directed agents: such as bisphosphonates, denosumab.
- Targeted biological agents for HER2-positive disease: such as trastuzumab and lapatinib.
Palliative radiotherapy: the most common indications for palliative radiotherapy include; bone metastases which are painful or carry a risk of fracture and/or neurological complications, and brain metastases\textsuperscript{23}.

### Efficacy and Safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>NALA, NCT01808573; neratinib vs lapatinib, both in combination with capecitabine; phase III.</th>
<th>NCT00741260; neratinib and capecitabine; phase I/II.</th>
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</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Puma Biotechnology, Inc.</td>
<td>Puma Biotechnology, Inc.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Published.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry\textsuperscript{1}, manufacturer.</td>
<td>Publication\textsuperscript{27}, trial registry\textsuperscript{28}, manufacturer.</td>
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<tr>
<td>Location</td>
<td>EU (incl UK), USA, Canada and other countries.</td>
<td>EU (not UK), USA, and other countries.</td>
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<tr>
<td>Design</td>
<td>Randomised, active-controlled.</td>
<td>Uncontrolled, single arm.</td>
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<tr>
<td>Participants</td>
<td>n=600 (planned); aged ≥18 years; histologically confirmed stage IV metastatic breast cancer (MBC); documented HER2 overexpression or gene-amplified tumour; prior treatment with ≥2 HER2-directed regimens for MBC; no previous therapy with capecitabine, neratinib, lapatinib, or any other HER2-directed tyrosine kinase inhibitor.</td>
<td>For part 2 of NCT00741260: n=80; aged ≥18 years; female; confirmed metastatic or locally advanced breast cancer; erbB-2 (HER2) amplified tumour; disease progression on/following ≥1 prior trastuzumab containing regimen(s) for metastatic or locally advanced disease (prior adjuvant trastuzumab is allowed but not required); prior treatment with a taxane in the neoadjuvant, adjuvant, locally advanced, and/or metastatic disease treatment setting; ≥1 measurable lesion as defined by RECIST criteria; normal left ventricular ejection fraction; no prior treatment with capecitabine, lapatinib\textsuperscript{a} or any other HER2 targeted agents except trastuzumab; no prior treatment with anthracyclines with a cumulative dose of doxorubicin of greater than 400mg/m\textsuperscript{2}, epirubicin dose of greater than 800mg/m\textsuperscript{2}, or the equivalent dose for other anthracyclines; no subjects with bone as the only site of metastatic disease; no active uncontrolled or symptomatic central nervous system (CNS) metastases\textsuperscript{b}; no other significant co-morbid condition.</td>
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<td>Schedule</td>
<td>Randomised to neratinib 240mg orally, once daily on days 1-21 of a 21 day cycle with capecitabine 1,500mg/m\textsuperscript{2} orally daily on days 1-14; or lapatinib 1,250mg orally, once daily on days 1-21 of a 21 day cycle with capecitabine 2,000mg/m\textsuperscript{2} orally, daily on days 1-14.</td>
<td>Neratinib 240mg orally, once daily on days 1-21 of a 21 day cycle with capecitabine 1,500mg/m\textsuperscript{2} orally, daily on days 1-14.</td>
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</tbody>
</table>

\textsuperscript{a} 20 subjects with prior lapatinib exposure will be enrolled.

\textsuperscript{b} As indicated by clinical symptoms, cerebral oedema, and/or progressive growth. Subjects with a history of CNS metastases or cord compression are allowable if definitively treated, and off anticonvulsants and steroids for ≥4 weeks.
### Follow-up
- Active treatment until death, disease progression, unacceptable toxicity, or other specified withdrawal criterion; follow-up until patient death or withdrawal of consent.

### Primary outcome/s
- Progression free survival (PFS) and overall survival (OS).
- Assess safety and tolerability; define and confirm maximum tolerated dose (MTD).

### Secondary outcome/s
- Objective response rate (ORR); clinical benefit rate (CBR); duration of response (DOR); time to intervention for symptomatic metastatic CNS disease; adverse events (AEs); serious adverse events (SAEs); quality of life as assessed using EORTC QLQ-C30\(^d\), EORTC QLQ-BR23\(^e\), and EQ-5D-5L\(^f\).  
- ORR; CBR; PFS; duration of response; pharmacokinetics. No quality of life measurement included in trial outcomes.

### Key results

<table>
<thead>
<tr>
<th>Result</th>
<th>Lapatinib naïve</th>
<th>Lapatinib patients, respectively:</th>
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<tbody>
<tr>
<td>ORR, 64% (95% CI 51-76%)</td>
<td>64% (95% CI 51-76%)</td>
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<tr>
<td>CR, 12% (95% CI 18-90%)</td>
<td>12% (95% CI 18-90%)</td>
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<tr>
<td>PR, 53% (95% CI 43-93%)</td>
<td>53% (95% CI 43-93%)</td>
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<tr>
<td>DOR, 46.3 weeks, 48.3 weeks</td>
<td>46.3 weeks, 48.3 weeks</td>
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<tr>
<td>CBR 72% (95% CI 59-83%)</td>
<td>72% (95% CI 59-83%)</td>
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### Adverse effects (AEs)
- Very common (>10%) treatment-related grade 3-4 AEs for lapatinib naïve and prior lapatinib patients, respectively: diarrhoea, 26%, 29%; palmar-plantar erythrodysesthesia syndrome (PPE), 29%, 0%.
- Very common (>10%) treatment-related grade 3-4 AEs for all participants combined: diarrhoea, 26%; PPE, 14%.

### Expected reporting date
- Primary completion date reported as May 2017.

### 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
- Reduced symptoms or disability
- No impact identified
- Other: Results for the phase II study\(^g\) indicate that 90% of patients receiving the neratinib/capecitabine combination had diarrhoea\(^g\).

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\(^c\) CBR is defined as complete response (CR), partial response (PR) or stable disease (SD) for ≥24 weeks.

\(^d\) European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30).

\(^e\) EORTC QLQ-BR23 subscale (EORTC QLQ-BR23).

\(^f\) EuroQoL 5-dimension 5-level instrument (EQ-5D-5L).

\(^g\) Expert personal communication.
Impact on Health and Social Care Services

- Increased use of existing services
- Re-organisation of existing services
- Other: None identified
- 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: increased length of treatment.
- Other reduction in costs: None identified
- Other: uncertain unit cost compared to existing treatments
- None identified

Other Issues

- Clinical uncertainty or other research question identified: The interesting point about this molecule is that it appears non-cross-resistant in some patients and therefore, in an analogous manner to endocrine therapy, this means that sequential anti-HER2 therapy can be given with good effect. It is therefore possible that patients can be given a sequence of lapatinib then neratinib, assuming that they have already received trastuzumab in the adjuvant setting. Unfortunately, in order to compete with lapatinib, the strategy has been to compare cap/lap with cap/neratinib. This may encourage physicians to choose between the two regimens rather than extend the patient’s life by sequencing the drugsh.
- None identified

REFERENCES

1 ClinicalTrials.gov. A study of neratinib plus capecitabine versus lapatinib plus capecitabine in patients with HER2+ metastatic breast cancer who have received two or more prior HER2 directed regimens in the metastatic setting (NALA). https://clinicaltrials.gov/ct2/show/study/NCT01808573 Accessed 24 April 2015.

h Expert personal communication.
14 National Institute for Health and Care Excellence. Breast cancer (HER2 positive, metastatic) - pertuzumab (with trastuzumab and docetaxel) - final scope ID523.