**Systemic Anti Cancer Therapy Protocol**

# Neratinib Adjuvant Treatment Breast Cancer

**PROTOCOL REF: MPHANERBR**
**(Version No: 1.1)**

**The protocol has been temporarily amended – please see the Oral SACT Operational Changes During Covid-19. Amendments may include less frequent blood monitoring, telephone SACT assessments and longer durations of treatment being dispensed.**

## Approved for use in:

- Extended adjuvant treatment of hormone receptor positive, HER2 positive early breast cancer, when 12 months of adjuvant trastuzumab has been completed less than a year ago
- And patient can only have had trastuzumab as their adjuvant HER2 therapy (i.e. not eligible if had combination with adjuvant pertuzumab)
- If they had neoadjuvant treatment and had residual invasive disease in the breast or axilla following the neoadjuvant treatment. Patients who received pertuzumab and trastuzumab combination only in the neoadjuvant setting (i.e. node negative) are eligible.

**Blueteq registration required: see blueteq for full eligibility criteria**

## Dosage:

| Drug | Dose | Route | Frequency |
|---|---|---|---|
| **Neratinib** | **240mg** | orally | Once daily, for 12 months<br>Treatment will be supplied every 28 days |

Available as 40mg film coated tablets

## Administration and Counselling Points:

Neratinib should be taken with food, preferably in the morning.

Tablets cannot be crushed or dissolved

Regular loperamide should be taken for the first 2 months, with dose adjusted to ensure no more than 2 bowel movements per day.

Patients should be taking effective contraception if relevant.

## Emetogenic risk (if applicable)

Low emetogenic risk. Diarrhoea is the main side effect

## Supportive treatments:

Loperamide 2mg after each loose stool, to maximum of 8 doses in 24 hours. Taken regularly during the first 2 months (see counselling section above)

## Extravasation risk (if applicable)

Not applicable

## Dosing in renal and hepatic impairment

| | |
|---|---|
| **Renal** | No dose adjustments necessary for mild to moderate renal impairment. No data available for patients with severe impairment or on dialysis therefore should not be used. |

| | |
|---|---|
| **Hepatic** | No dose adjustments in patients with Child Pugh A or B liver impairment<br><br>Neratinib should be paused if ALT is greater than 5 times upper limit of normal, and/or bilirubin greater than 3 times upper limit of normal. |

## Interactions:

Proton pump inhibitors and ranitidine should be avoided, if antacid is required then the dosing should be separated by at least 3 hours

Avoid strong CYP3A4 inhibitors

## Treatment schedule:

| Drug | Dose | Route | Frequency |
|---|---|---|---|
| **Neratinib** | **240mg** | orally | Once daily, for 12 months<br>Treatment will be supplied every 28 days |

## Main toxicities:

Diarrhoea is the most common side effect, generally occurring during the first month of treatment.

Increased liver function test results, decreased appetite, fatigue, rash, mucositis, muscle spasms, increased creatinine, nausea and vomiting and UTI's are other common side effects. https://www.ema.europa.eu/en/medicines/human/EPAR/nerlynx

## Investigations and treatment plan:

| | Pre | Cycle 1 | Cycle 1 D8 | Cycle 2 | Cycle 3 | Cycle 4 | Ongoing |
|---|---|---|---|---|---|---|---|
| Informed Consent | x | | | | | | |
| Clinical Assessment | x | | | x | | | Then every 3 months |
| SACT Assessment (to include PS and toxicities) | x | x | x | x | x | x | Every cycle |
| FBC | x | x | x | x | x | x | Every cycle |
| U&E & LFTs & Magnesium | x | x | x | x | x | x | Every cycle |
| CrCl (Cockcroft and Gault) | x | x | x | x | x | x | Every cycle |
| Blood pressure measurement | x | | | | | | Repeat if clinically indicated |
| Height recorded | x | | | | | | |
| Weight recorded | x | x | | x | x | x | Every cycle |

See guidance in non-haematological toxicity section for action to take if day 8 blood test results are abnormal.

If neratinib is discontinued due to raised LFTs then repeat weekly until recovered.

## Dose Modifications and Toxicity Management:

| Dose level | Neratinib dose |
|---|---|
| Recommended starting dose | 240mg daily |
| First dose reduction | 200mg daily |
| Second dose reduction | 160mg daily |
| Third dose reduction | 120mg daily |

## Haematological toxicity (if required):

Proceed on day 1 if-

| | |
|---|---|
| ANC ≥ 1.0 x $10^9$/L | Plt ≥ 100 x $10^9$/L |

Delay 1 week on day 1 if-

| | |
|---|---|
| ANC ≤ 0.9 x $10^9$/L | Plt ≤ 99 x $10^9$/L |

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

## Non- Haematological toxicity (if required):

**Diarrhoea**

Give advice to all patients on importance of maintaining fluid intake to avoid dehydration.

| Severity/Grade | Action |
|---|---|
| Grade 2 (increase of 4 to 6 stools per day) | Ensure appropriate anti-diarrhoeal treatment.<br>If diarrhoea persists for 5 days then withhold neratinib until resolves to grade 1.<br>If diarrhea takes more than 7 days to resolve resume at reduced dose. |
| Grade 3 (increase of 7 stools or more per day, incontinence, hospitalization required) | Interrupt neratinib if this continues beyond 24 hours.<br>Ensure appropriate anti-diarrhoeal treatment.<br>Resume treatment at next dose reduction once diarrhea has resolved to grade 1.<br>If it continues beyond 3 weeks then treatment should be discontinued. |
| Grade 4 | Discontinue treatment |

**Hepatotoxicity**

| Severity | Action |
|---|---|
| Grade 3 ALT (> 5 to 20 x ULN)<br>Or<br>Grade 3 bilirubin (> 3 to 10 x ULN) | Stop neratinib until recovery to grade 1<br>Resume at the next lower dose if recovered within 3 weeks. |
| Grade 4 ALT (> 20 x ULN)<br>Or<br>Grade 4 bilirubin (> 10 x ULN) | Permanently discontinue |

## References:


1. https://www.ema.europa.eu/en
2. Lancet Oncology, 2017 18: 1688-1700. ExteNET clinical trial. Martin et al
3. NICE guidance (awaiting TA publication)