Chemotherapy Protocol

Breast Cancer

NERATINIB

Regimen

- Breast Cancer – Neratinib

Indication

- Neratinib for extended adjuvant therapy for hormone receptor positive HER2-overexpressed early breast cancer after completion of adjuvant therapy with HER2 targeted monotherapy with trastuzumab where:

    - The patient has a histologically documented breast cancer which is both hormone receptor positive and HER2 over-expresssed (HER2 3+ by immunohistochemistry and/or has a ratio of greater than or equal to 2 by in situ hybridisation).
    - Patient has diagnosed with early breast cancer and this has been adequately excised.
    - The patient did not receive neoadjuvant therapy or the patient was treated with neoadjuvant therapy AND there was residual invasive carcinoma in the breast and/or the axilla.
    - The patient has received chemotherapy in the management of the early breast cancer either as neoadjuvant treatment pre-definitive surgery or as adjuvant therapy post-surgery.
    - The patient has completed adjuvant therapy with trastuzumab as HER2-targeted monotherapy and is within 1 year of completing such trastuzumab monotherapy (NICE has not recommended use of neratinib if the patient received any pertuzumab as part of adjuvant therapy. Patients treated with neoadjuvant chemotherapy in combination with pertuzumab and trastuzumab are only eligible for neratinib therapy if the pertuzumab was solely used as part of neoadjuvant treatment and no pertuzumab was used as part of adjuvant therapy.
    - The patient has an ECOG performance status of 0 or 1.
    - The patient has a left ventricular ejection fraction prior to commencing extended adjuvant therapy with neratinib is greater than or equal to 50%.
    - The patient will be counselled to initiate prophylactic treatment with anti-diarrhoeal medication with the first dose of neratinib and maintain regular dosing of the anti-diarrhoeal medication during the first 1-2 months of neratinib treatment, titrating the anti-diarrhoeal medication to a frequency of 1-2 bowel movements per day.
    - A formal medical review as to whether extended adjuvant treatment with neratinib should continue and at what dose will be scheduled to occur at least by the start of the 2nd month of treatment.
    - Treatment breaks of up to 3 weeks (as per SmPC recommendations) are allowed, but solely to allow toxicities to settle.

Drug	Adverse Effect
Neratinib	Diarrhoea, nausea, fatigue, vomiting, abdominal pain, rash, decreased appetite, stomatitis, muscle spasms.

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

Drugs

- FBC and U&Es prior to each cycle. LFTs should be monitored after the first week of therapy in cycle 1 and then prior to each cycle thereafter.

- Left ventricular dysfunction has been associated with HER2 inhibition. In patients with known cardiac risk factors cardiac monitoring should be completed including assessment of LVEF, as clinically indicated.

Dose Modifications

The dose modifications listed are for haematological, liver and renal function only. Dose adjustments may be necessary for other toxicities as well. In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing if appropriate. The approach may be different depending on the clinical circumstances. The following is a general guide only.

Dose modifications

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

Dose modifications for haematological toxicity in the table below are for general guidance only. Always refer to the responsible consultant as any dose reductions or delays will be dependent on clinical circumstances and treatment intent.

Consider blood transfusion or the use of erythropoietin according to NICE TA323 if patient symptomatic of anaemia or has haemoglobin of less than 8g/dL (80g/L)

Prior to prescribing cycle 1 the following criteria must be met.

Criteria	Eligible Level
Neutrophils	Equal to or more than $1x10^9$/L
Platelets	Equal to or more than $100x10^9$/L

Hepatic Impairment

Severity of hepatotoxicity	Dose modification/Action
Grade 3 ALT/AST (greater than 5-20xULN) OR Grade 3 bilirubin (greater than 3-10xULN)	• Stop Neratinib until recovery to grade 0-1. • Evaluated alternative causes. • Resume neratinib at the next lower dose level if recovery to grade 0-1 occurs within 3 weeks. If grade 3 ALT or bilirubin occurs again despite one dose reduction, permanently discontinue neratinib. • If grade 3 hepatotoxicity persists longer than 3 weeks, discontinue neratinib permanently
Grade 4 ALT (greater than 20xULN) OR Grade 4 bilirubin (greater than 10xULN)	• Permanently discontinue neratinib • Evaluate alternative causes

Renal Impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment. Neratinib has not been studied in patients with severe renal impairment including patients on dialysis. Treatment of patients with severe renal impairment or on dialysis is not recommended.

Other

Diarrhoea

Treatment with antidiarrheal agents, dietary changes and appropriate dose modification may be necessary.

Diarrhoea	**Management Recommendations**
• Grade 1 diarrhoea (increase <4 stools per day over baseline). • Grade 2 diarrhoea (increase 4-6 stools per day over baseline) lasting <5 days. • Grade 3 diarrhoea (increase of ≥7 stools per day over baseline, incontinence, hospitalisation indicated: limiting self-care activities of daily living) lasting <2 days	• Adjust anti-diarrhoeal treatment • Diet modification • Fluid intake of ~2L should be maintained to avoid dehydration. • Once event resolves to grade 0-1 or baseline, consider restarting anti-diarrhoeal prophylaxis, if appropriate with each subsequent neratinib administration.
• Any grade with complicated features.	• Interrupt neratinib treatment. • Diet modification

• Grade 2 diarrhoea lasting 5 days or longer (despite being treated with optimal medical therapy). • Grade 3 diarrhoea lasting between 2 days and 3 weeks (despite being treated with optimal medical therapy).	• Fluid intake of ~2L should be maintained to avoid dehydration. • If diarrhoea resolves to grade 0-1 in one week or less, then resume neratinib at the same dose. • If diarrhoea resolves to Grade 0-1 in longer than one week, then resume neratinib treatment at reduced dose. • Once event resolves to grade 0-1 or baseline, consider restarting anti-diarrhoeal prophylaxis, if appropriate with each subsequent neratinib administration. • If grade 3 diarrhoea persists for longer than 3 weeks, discontinue neratinib permanently.
• Grade 4 diarrhoea (life threatening consequences; urgent intervention indicated)	• Permanently discontinue neratinib treatment.
• Diarrhoea recurs to grade 2 or higher at 120mg per day.	• Permanently discontinue neratinib treatment.

Complicated features include dehydration, fever, hypotension, renal failure, or grade 3 or 4 neutropenia.

Other toxicities should be managed as follows;

Toxicity (not haematology or diarrhoea or liver)	Management Recommendations
Grade 3	Stop neratinib until recovery to grade 0-1 or baseline within 3 weeks of stopping treatment. Then resume neratinib at the next lower dose level. If grade 3 toxicity does not recover within 3 weeks, discontinue neratinib permanently.
Grade 4	Discontinue neratinib permanently.

Regimen

28 day (twelve cycles will be set in ARIA)

Drug	Dose	Days	Route
Neratinib	240mg once a day	Days 1-28 inclusive	Oral

Dose Information

- Neratinib is available as 40mg film coated tablets.

Administration Information

- If a patient misses a dose of neratinib it should not be replaced, and treatment should resume with the next scheduled daily dose.

- Neratinib tablets should be swallowed whole preferably with water and should not be crushed or dissolved.

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

Supportive Treatments

- Loperamide 4mg three times a day for 2 weeks, then 4mg twice a day for 6 weeks, then 2-4mg prn (max 16mg daily) titrated to 1 – 2 bowel movements per day.

Additional Information

- The National Patient Safety Alert on oral chemotherapy (NPSA/2008/RRR001) must be followed in relation to neratinib

- It must be made clear to all staff, including those in the community, that neratinib should only be prescribed under the supervision of a consultant oncologist

- Neratinib interacts with many other agents. Always check for drug interactions.

References

1. Pierre Fabre Limited (2022). Nerlynx summary of product characteristics. Available from: www.medicines.org.uk (accessed 05/08/2022)
2. Martin M et al (2017). Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncology. 12: 1688-1700.

REGIMEN SUMMARY

Neratinib

Cycle One Day One

1. Neratinib 240mg every morning for 28 days oral.
   Administration Instructions
   Oral SACT
   Swallow whole with water. Take with or after food.

2. Loperamide as directed
   Administration Instructions
   For the first six weeks of treatment only take 4mg three times a day for 2 weeks, then 4mg twice a day for 6 weeks. There after take 2-4mg when required (titrated to 1-2 bowel movements per day). Maximum 16mg/24 hours. Please supply 4x30x2mg capsules on cycle one only then 30x2mg capsules on each cycle after cycle one (or nearest equivalent pack size to 30 capsules)

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	August 2022	None	Alexandra Pritchard Pharmacist	Dr Marcus Remer Consultant

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that

originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.