NERATINIB (Nerlynx)

INDICATION (ICD10) C50

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/) (NER1)

1. The extended adjuvant therapy for hormone receptor positive HER2-overexpressed (HER2 3+) early breast cancer, which has been adequately excised, after completion of adjuvant therapy with HER2 targeted monotherapy within the last year, who did not have complete remission after neoadjuvant treatment.PS 0 or 1. (TA612)

REGIMEN

NERATINIB 240mg tablet oral once daily continuously

CYCLE FREQUENCY AND NUMBER OF CYCLES

Every 28 days continuously for up to 1 year.
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.

ADMINISTRATION

Available as 40mg tablets
Take with food and must be swallowed intact, preferably in the morning

ANTI-EMETICS

Low risk all days

CONCURRENT MEDICATION REQUIRED

Neratinib	Loperamide 2mg after each loose stool, to maximum of 8 doses in 24 hours. Taken regularly during the first 2 months with dose adjusted to ensure no more than 2 bowel movements per day. Budesonide 3mg tds cycle 1

EXTRAVASATION AND TYPE OF LINE / FILTERS

Not applicable

INVESTIGATIONS

Blood results required before SACT administration
FBC, U&E and LFTs every cycle
Neutrophils x 10^9/L ≥1.0
Platelets x 10^9/L ≥100
Serum creatinine - GFR each cycle
The left ventricular ejection fraction ≥50% prior to commencing extended adjuvant neratinib.

MAIN TOXICITES AND ADVERSE REACTIONS

Neratinib	Diarrhoea is the most common side effect, generally occurring during the first month of treatment. Affects 93.6% of patients. Increased LFTs Mucositis Increased creatinine Rash

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS
(not exhaustive list check SPC/BNF/Stockleys)

Neratinib	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/P-gp inhibitors. If inhibitor cannot be avoided, reduce neratinib dose to 40mg once daily. Avoid strong CYP3A4/P-gp inducers as neratinib exposure is significantly decreased.

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

Discontinue neratinib for patients who:
• Fail to recover to grade 0 to 1 from treatment-related toxicity,
• For toxicities that result in a treatment delay >3 weeks, or
• For patients that are unable to tolerate 120mg daily
Additional clinical situations may result in dose adjustments as clinically indicated (e.g. intolerable toxicities, persistent grade 2 adverse reactions, etc.).

Haematological
Neratinib
Proceed if Neutrophils x 10^9/L ≥1.0 and platelets x 10^9/L≥100
Delay for one week if counts are below this.

Non-haematological

Neratinib

Grade 1 diarrhoea [increase of <4 stools per day over baseline] Grade 2 diarrhoea [increase of 4-6 stools per day over baseline] lasting <5 days Grade 3 diarrhoea [increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; limiting self-care activities of daily living] lasting ≤2 days	• Adjust anti-diarrhoeal treatment • Diet modifications • Fluid intake of ~2L should be maintained to avoid dehydration • Once event resolves to ≤grade 1 or baseline, consider restarting anti-diarrhoeal prophylaxis, if appropriate with each subsequent neratinib administration
Any grade with complicated features (include dehydration, fever, hypotension, renal failure, or Grade 3 or 4 neutropenia) Grade 2 diarrhoea lasting 5 days or longer Grade 3 diarrhoea lasting between 2 days and 3 weeks	• Interrupt neratinib treatment • Diet modifications • 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 treatment 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 1 or baseline, consider restarting anti-diarrhoeal prophylaxis, if appropriate with each subsequent neratinib administration. • If grade 3 diarrhoea persists 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

General toxicities grade 3	Stop neratinib until recovery to grade ≤ 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
General toxicities grade 4	Permanently discontinue neratinib treatment

Hepatotoxicity grade 3 ALT (>5-20xULN) or grade 3 bilirubin (>3-10xULN)	• Stop neratinib until recovery to ≤grade 1 • Evaluate alternative causes • Resume neratinib at the next lower dose level if recovery to ≤grade 1 occurs within 3 weeks. If grade 3 ALT or bilirubin occurs again despite one dose reduction, permanently discontinue neratinib.
Hepatotoxicity grade 4 ALT (>20xULN) or grade 4 bilirubin (>10xULN)	• Permanently discontinue neratinib • Evaluate alternative causes

Hepatic impairment
Neratinib
Child-Pugh scores are based on ascites, encephalopathy, INR, albumin, total bilirubin
No dose adjustments in patients with Child Pugh A or B liver impairment
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.

Renal impairment
Neratinib
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.

REFERENCES
1. SPC December 2019
2. Lancet Oncology, 2017 18: 1688-1700. ExteNET clinical trial. Martin et al