Lancashire & South Cumbria Cancer Network
Systemic Anticancer Treatment Protocol

DRUG REGIMEN
Neratinib (Nerlynx)

Indication for use
Extended adjuvant treatment of hormone receptor positive early stage breast cancer in adults who completed adjuvant trastuzumab-based therapy less than 1 year ago only if:-

- trastuzumab is the only HER2 directed adjuvant treatment they have had, and
- if they had neoadjuvant chemotherapy-based regimens they still had residual invasive disease in the breast or axilla following the neoadjuvant treatment

Regimen
240mg (six 40mg tablets) taken orally once daily, 28 day cycle – taken continuously for 1 year

Anti-diarrhoea prophylaxis

Week 1-2 (Day 1-14)	Loperamide 4mg TDS
Week 3-8 (Day 15-56)	Loperamide 4mg BD
Week 9-52 (Day 57–365)	Loperamide 4mg PRN (Not to exceed 16mg per day)

Patients should be instructed to take loperamide regularly as prescribed for the first 8 weeks of treatment (see under "Cautions" below)

Investigation prior to initiating treatment
FBC, U&E, LFT, cardiac MUGA scan

Cautions
Diarrhoea – In the ExteNET trial (without loperamide prophylaxis) 37.5% of patients experienced grade 3 diarrhoea and 95% experienced at least 1 episode of diarrhoea.

Primary prophylactic treatment with loperamide should be initiated at the time of starting neratinib and continued for first 8 weeks (see above). Patients with pre-existing GI disorders were not included in the trial and should be monitored carefully.

Drug interactions are likely with strong CYP3A inducers (phenytoin, rifampicin, dexamethasone, carbamazepine) and inhibitors (ketoconazole, clarithromycin, grapefruit juice, fluconazole, diltiazem, verapamil, erythromycin) – coadministration should be avoided.

Hepatotoxicity can occur – LFTs should be monitored after 1 week, monthly for first 3 months, then 6 weekly thereafter

LV dysfunction is associated with HER2 inhibition. LVEF should be within normal range at start of treatment. In patients with known cardiac risk factors consider cardiac monitoring as clinically indicated

Absorption of neratinib is pH dependent. Co-administration with PPI or H2 receptor antagonist is not recommended. If antacid is taken separate the dosing by at least 3 hours

Investigations and consultations prior to each cycle
LFTs and U&E should be monitored after 1 week, then monthly prior to starting each cycle
Review in clinic fortnightly for first cycle, then 4 weekly for first three months, then 3 monthly

Acceptable levels for treatment to proceed (if outside these levels defer one week or contact consultant)
See dose modification criteria re liver toxicity

Side Effects
Diarrhoea, nausea, fatigue, vomiting, abdo pain, poor appetite, stomatitis, rash, nail disorders, hepatotoxicity

Dose Modification Criteria

Dose Level	Neratinib
Starting dose	240mg
First dose reduction	200mg
Second dose reduction	160mg
Third dose reduction	120mg

Toxicity	Grade	Neratinib dose
General	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
	4	Discontinue neratinib permanently
Hepatotoxicity	3 (ALT or bilirubin)	Stop neratinib until recover to <=grade 1. Assess 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
	4 (ALT or Bilirubin)	Permanently discontinue neratinib. Evaluate alternative causes
Diarrhoea		
	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 ~2 L should be maintained to avoid dehydration • Once event resolves to ≤ Grade 1 or baseline, consider restarting anti-diarrhoeal prophylaxis, if appropriate with each subsequent Nerlynx administration
	Any grade with complicated features† • Grade 2 diarrhoea lasting 5 days or longer‡ • Grade 3 diarrhoea lasting between 2 days and 3 weeks‡	Interrupt Nerlynx treatment • Diet modifications • Fluid intake of ~2 L should be maintained to avoid dehydration • If diarrhoea resolves to Grade 0-1 in one week or less, then resume Nerlynx treatment at the same dose. • If diarrhoea resolves to Grade 0-1 in longer than one week, then resume Nerlynx treatment at reduced dose • Once event resolves to ≤ Grade 1 or baseline, consider restarting anti-diarrhoeal prophylaxis, if appropriate with each subsequent Nerlynx administration. • If grade 3 diarrhoea persists longer than 3 weeks, discontinue Nerlynx permanently.
	Grade 4 diarrhoea [life-threatening consequences; urgent intervention	Permanently discontinue Nerlynx treatment

	indicated] or Diarrhoea recurs to Grade 2 or higher at 120 mg per day	

† Complicated features include dehydration, fever, hypotension, renal failure, or Grade 3 or 4 neutropenia

‡ Despite being treated with optimal medical therapy

THIS PROTOCOL HAS BEEN DIRECTED BY DR Eaton, CONSULTANT MEDICAL ONCOLOGIST

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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