Systemic Anti Cancer Therapy Protocol

Neratinib and Capecitabine Early Access Program (EAP) Metastatic Breast Cancer

Protocol Reference: MPHANECABR
(Version No: 1.1)

Approved for use in:

- HER2 positive metastatic breast cancer after ≥ 2 lines of HER2-directed treatment.
- Patient must be registered with Pierre Fabre for Neratinib (Nerlynx) EAP via the Caligor Coghlan Pharma Services (CCPS) Early Access Programs Portal.

Please NOTE: this is unlicensed use.

Please refer to the 'CCC Unlicensed Medicines Policy' for full details on consenting, prescribing, documentation and supply of unlicensed medicines. As per trust policy please provide the 'Unlicensed Medicines Information' to patients and carers as appropriate

Dosage:

Drug	Dose	Route	Frequency
Neratinib	**240mg**	orally	Once daily
Capecitabine	**750mg/m^2**	orally	Twice daily, at 12 hour interval For 14 days followed by 7 day break

The cycle is repeated every 21 days until progression or unacceptable toxicity

Neratinib is supplied as 40mg film coated tablets, this is from commercial stock

Capecitabine is available as 500mg and 150mg tablets.

Caution in patients with pre-existing coronary heart disease, angina pectoris, arrhythmias or those on high dose aspirin or anticoagulants with capecitabine.

Neratinib requires adequate LVEF at end of previous HER2 treatment

Administration:

Neratinib

- Should be taken with food, preferably in the morning.
- Tablets cannot be crushed or dissolved
- Loperamide, 4mg to be taken with the first dose of neratinib , followed by 2 mg every 4 hours for the first 3 days (maximum 8 tablets per day). Thereafter, loperamide 2 mg every 6-8 hours until the end of the first cycle, regardless of whether the patient experienced diarrhoea or not (maximum 8 tablets per day). Then as required for subsequent cycles. To be taken regularly during the first cycle with dose adjusted to ensure **no more than 2 bowel movements per day**
- Give advice to all patients on importance of maintaining fluid intake to avoid dehydration.
- Women of child-bearing potential must use highly effective contraceptive measures while taking neratinib and for 1 month after stopping treatment.
- **Note: significant drug interactions, please refer to interactions section below**.

Capecitabine

- Tablets should be taken 12 hours apart
- Swallow whole with water within 30 minutes of a meal
- Do not add doses missed due to toxicity onto the end of the cycle. Continue according to the treatment plan and stop taking on the originally scheduled day.
- Take missed doses if remembered within 2 hours of the normal scheduled time. Otherwise continue with the next scheduled dose. Do not double up on missed doses.
- In case of swallowing difficulties the tablets may be dissolved in 200ml warm water. Once dissolved stir the contents with a spoon and drink immediately. Wash well and reserve the glass and spoon for chemotherapy administration only

Emetogenic risk:

Low emetogenic risk. Diarrhoea is the main side effect for both treatments

Supportive treatments:

Loperamide, 4mg to be taken with the first dose of neratinib , followed by 2 mg every 4 hours for the first 3 days (maximum 8 tablets per day). Thereafter, loperamide 2 mg every 6-8 hours

until the end of the first cycle, regardless of whether the patient experienced diarrhoea or not (maximum 8 tablets per day). Then loperamide 4mg to be taken at the onset of loose stool and then 2mg after each loose stool (maximum of 8 tablets in 24 hours) for subsequent cycles.

To be taken regularly during the first cycle with dose adjusted to ensure **no more than 2 bowel movements per day** (see counselling section above). If bowels do not settle, please escalate loperamide dosing as per 'Dose Modifications and Toxicity Management' section below.

Domperidone 10mg tablets, three times daily as required

Extravasation risk:

Not applicable

Dosing in renal and hepatic impairment:

Renal

Neratinib
GFR ≥ 30ml/min: no dose adjustment is needed
GFR <30ml/min or haemodialysis: no need for dose adjustment is expected.

Capecitabine
Calculate CrCl using Cockroft and Gault formula at baseline and before each cycle and adjust dose according to table
Note: starting dose in this regimen for capecitabine is reduced, therefore table below applies to changes in creatinine clearance during treatment. Please speak to pharmacist for further advice.

CrCl (mL/min)	Capecitabine dose
> 50	Give 100% dose
30 to 50	Give 75% dose
Below 30	Omit

Hepatic

Neratinib

Child-Pugh A and B: no dose adjustment is needed
Child-Pugh C: recommended dose 80mg once daily

Parameters	1 point	2 points	3 points
Total bilirubin (µmol/L)	< 34	34–50	> 50

Serum albumin (g/L)	> 35	28–35	< 28
Prothrombin time, prolongation (s) *Or* INR	< 4 < 1.7	4–6 1.7-2.3	> 6 >2.3
Ascites	None	Mild to Moderate (diuretic responsive)	Severe (diuretic refractory)
Hepatic encephalopathy	None	Grade I–II (or suppressed with medication)	Grade III–IV (or refractory to medication)

INR: International Normalised Ratio.
Child-Pugh Class A = 5-6 points
Child-Pugh Class B = 7-9 points
Child-Pugh Class C = 10 or more points
Please note: assessment of Child-Pugh Class is to help guide clinical teams when prescribing and pharmacists when screening.

Capecitabine

No dose adjustment is needed

Interactions:

Refer to for each agent for full details on interactions. For any interaction queries please contact Cytopharmacy.

Neratinib

Primarily metabolized by CYP3A4 and is a P-gp substrate.

CYP3A4/P-gp inducers

Concomitant use of strong CYP3A4/P-gp inducers significantly decreased neratinib exposure, therefore concurrent use of neratinib with strong CYP3A4/P-gp inducers is contraindicated (**e.g. strong inducers: phenytoin, carbamazepine, rifampicin, or herbal preparations containing St John's Wort (Hypericum perforatum**)). Concurrent use of neratinib with moderate CYP3A4/P-gp inducers is not recommended as it may also lead to loss of efficacy (e.g. moderate inducers: bosentan, efavirenz, etravirine, phenobarbital, primidone, dexamethasone).

CYP3A4/P-gp inhibitors

Concomitant use of strong or moderate CYP3A4/P-gp inhibitors significantly increased neratinib systemic exposure, therefore, concomitant use of neratinib with strong and moderate CYP3A4/P-gp inhibitors is not recommended (e.g. strong inhibitors: atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, lopinavir, ketoconazole, itraconazole, clarithromycin, troleandomycin, voriconazole, and cobicistat; moderate inhibitors: ciprofloxacin, cyclosporin, diltiazem, fluconazole, erythromycin, fluvoxamine and verapamil). If the inhibitor cannot be avoided, reduce dose to:

- 40 mg taken once daily with a strong CYP3A4/P-gp inhibitor.
- 40 mg taken once daily with a moderate CYP3A4/P-gp inhibitor. If well tolerated, increase to 80 mg for at least 1 week, then to 120 mg for at least 1 week, and to 160 mg as a maximal daily dose. Patient should be monitored carefully, especially GI effects including diarrhoea and hepatotoxicity.

After discontinuation of a strong or moderate CYP3A4/P-gp inhibitor, resume previous dose of neratinib 240 mg.

Grapefruit/pomegranate or grapefruit/pomegranate juice may also increase neratinib plasma concentrations and should be avoided.

Proton pump inhibitors, H2-receptor antagonists and antacids

Co-administration with proton pump inhibitors (PPIs) is not recommended (e.g. omeprazole or lansoprazole). Neratinib should be taken at least 2 hours before or 10 hours after the intake of the H2-receptor antagonist.

Capecitabine:

Phenytoin – potentially toxic levels of phenytoin have been reported- monitor carefully
Warfarin and other coumarin anticoagulants – increased bleeding risk, monitor INR carefully, consider switch to LMWH.

Sorivudine and analogues – Potentially fatal interaction – avoid completely
Allopurinol – reduced efficacy of capecitabine – avoid.

Treatment schedule:

Drug	Dose	Route	Frequency
Neratinib	**240mg**	orally	Once daily continuously
Capecitabine	**750mg/m^2**	orally	Twice daily, at 12 hour intervals For 14 days of a 21 day cycle

Main toxicities:

This list is not exhaustive, please refer to SmPC for each agent for full list of toxicities

Neratinib

Diarrhoea is the most common side effect, generally occurring during the first month of treatment. **As per clinical trial Grade 3 diarrhoea occurs in ~25% of cases and predominantly in the first month.**

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.

Capecitabine

Haematological	Neutropenia, anaemia, thrombocytopenia,
Cardiac and Vascular disorders	Angina
Gastrointestinal	Nausea, vomiting, diarrhoea, constipation, mucositis
Hepatobiliary	Elevation of liver transaminases, alkaline phosphatase and bilirubin.
Skin and subcutaneous tissue disorders	Palmar Plantar Erythema (PPE or hand- foot syndrome),
General	Fatigue, taste changes Infertility, early menopause
DPD deficiency (encoded by DPYD gene)	Leads to severe early 5FU toxicity, affects approximately 3-6% of population, may be life threatening in up to 1% of cases.

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 6 weeks
SACT Assessment (to include PS and toxicities)	x	x	x	x	x	x	Every cycle
Dihydropyrimidine dehydrogenase (DPD) deficiency test**	X						This test is normally only required if a patient has not had capecitabine, or fluorouracil in the past. However a consultant may still request this test if capecitabine or fluorouracil was not tolerated previously. The result must be available before administration of chemotherapy unless clear documentation from the consultant is available to the contrary. Treatment with capecitabine and fluorouracil is contraindicated in patients with known complete DPD deficiency.
FBC	x	x		x	x	x	Every cycle
U&E & LFTs (including ALT, AST and bilirubin) & Magnesium	x	x	x	x	x	x	Every cycle
CrCl (Cockcroft and Gault)	x	x	x	x	x	x	Every cycle

Monitor LVEF (via echocardiogram or multigated acquisition (MUGA) scan	x				x		At baseline then the start of cycles 3 and 6, and every 6 cycles thereafter
Blood pressure measurement	x						Repeat if clinically indicated
Weight recorded	x	x		x	x	x	Every cycle
Height	x						

*DPD deficiency is encoded by the DPYD gene therefore the test is **otherwise referred to as the DPYD test**.

Dose Modifications and Toxicity Management:

Haematological toxicity:

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.

Proceed on day 1 if-

ANC ≥ 1.0 x 10^9/L	Plt ≥ 100 x 10^9/L

And

Baseline LVEF prior to commencing extended adjuvant therapy with neratinib is ≥ 50%.

Delay 1 week on day 1 if-

ANC ≤ 0.9 x 10^9/L	Plt ≤ 99 x 10^9/L

Day 8 Monitoring-

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

Neratinib-induced hepatotoxicity (LFTs)

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

Diarrhoea and potential associated effects on electrolyte imbalances (U&Es) and/or renal function (CrCl).

Refer to Dose 'Modifications and Toxicity Management' section for grading and management.
Electrolyte imbalances are to be corrected with appropriate supplementation.
For declines in renal function please refer to 'Dosing in renal and hepatic impairment' section and discuss with clinical teams as appropriate.

Non- Haematological toxicity:

Capecitabine

Toxicity grades / Haematological parameter	Dose changes within a treatment cycle	Dose adjustment for next cycle/dose (% of starting dose)
• *Grade 1*	Maintain dose level	Maintain dose level
• *Grade 2*		
-1st appearance	Interrupt until resolved to grade 0-1	100%
-2nd appearance		75%
-3rd appearance		50%
-4th appearance	Discontinue treatment permanently	Not applicable
• *Grade 3*		
-1st appearance	Interrupt until resolved to grade 0-1	75%
-2nd appearance		50%
-3rd appearance	Discontinue treatment permanently	Not applicable
• *Grade 4*		
-1st appearance	Discontinue permanently *Or* If physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1	50%
-2nd appearance	Discontinue permanently	Not applicable

Renal Impairment	
CrCl (mL/min)	**Capecitabine dose**
> 50	Give 100% dose
30 to 50	Give 75% dose
Below 30	Omit

Neratinib

Patients who experience ≥ Grade 3 diarrhoea requiring IV fluid treatment or any signs or symptoms of hepatotoxicity, such as worsening of fatigue, nausea, vomiting, jaundice, right upper quadrant pain or tenderness, fever, rash, or eosinophilia, should be evaluated for changes in LFTs. Fractionated bilirubin and prothrombin time should also be collected during hepatotoxicity evaluation.

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

Diarrhoea

Severity/Grade	Action
Uncomplicated (without dehydration, fever, hypotension, renal failure, and/or Grade 3 or 4 neutropenia): Grade 1 Diarrhoea (Increase of < 4 stools per day over baseline) OR Grade 2 (increase of 4 to 6 stools per day over baseline) lasting < 5 days	Continue neratinib at full dose. **Dietetic measures** • Stop all lactose-containing products. • Drink 8 to 10 large glasses of clear liquids per day (~2000 mL). • Eat frequent small meals. • Recommend low fat regimen enriched with bananas, rice, applesauce and toast until resolution of diarrhoea. **Treatment** Administer loperamide: initial dose of 4 mg with the first bout of diarrhoea followed by 2 mg every 4 hours or after every unformed stool (maximum 16 mg a day) and continue loperamide at this frequency until diarrhoea free for 12 hours. Once event resolves to ≤ Grade 1 or baseline, start loperamide anti-diarrhoeal prophylaxis, if appropriate with each subsequent neratinib administration.
Any grade diarrhoea with complicated features (dehydration, fever, hypotension, renal failure, or Grade 3 or 4 neutropenia) OR	Interrupt neratinib and capecitabine treatment until resolves to grade 1 Diet modification and treatment as above. Resume neratinib at same dose level unless diarrhoea takes more than 7 days to resolve then reduce dose by 1 dose level.

Grade 2 Diarrhoea lasting >5 days despite being treated with optimal medical therapy	
Grade 3 Diarrhoea (Increase of ≥7 stools per day over baseline incontinence, hospitalization required)	Interrupt neratinib and capecitabine if this continues beyond 24 hours. Diet modification and treatment as above. Resume treatment at next dose reduction once diarrhoea has resolved to grade 1. If it continues beyond 3 weeks then treatment should be discontinued.
Grade 4 diarrhoea OR Diarrhoea recurs to Grade 2 or higher at 120 mg of neratinib per day	Discontinue treatment

Hepatotoxicity

Severity	**Action**
Grade 3 ALT (> 5 to 20 x ULN) Or Grade 3 bilirubin (> 3 to 10 x ULN)	Stop neratinib until recovery to grade 1. 1st occurrence- resume at the next lower dose **if recovered within 3 weeks**(if persists longer than 3 weeks, permanently discontinue neratinib). 2nd occurrence- permanently discontinue neratinib.
Grade 4 ALT (> 20 x ULN) Or Grade 4 bilirubin (> 10 x ULN)	Permanently discontinue

References:

1. https://ema.europa.eu

2. NALA trial, Saura C et al, JCO 2020 38:3138-3149 Lancet Oncology, 2017 18: 1688-1700. ExteNET clinical trial. Martin et al

3. Neratinib SmPC (last updated 26th October 2020)

4. Nerlynx Early Access Program Treatment Plan V1.0 (21st January 2020)

5. NICE TA62 2003, now updated in CB81 August 2017

6. O'Shaughnessy JA et al, Annals of Oncology 2001 12:1247-1254

7. Blum JL et al, JCO 1999 17(2):485

8. Supplement to: Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20: e201–08.