Neratinib

Indication

Extended adjuvant treatment of hormone receptor positive, human epidermal growth factor receptor 2 (HER2) positive early stage breast cancer for patients who have completed trastuzumab based treatment less than one year ago. Patients must have only had trastuzumab as HER2 directed adjuvant treatment and if they received neoadjuvant treatment they must have still had residual invasive disease in the breast or axilla following neoadjuvant treatment.

(NICE TA612)

ICD-10 codes

Codes with a prefix C50.

Regimen details

Day	Drug	Dose	Route
1-28	Neratinib	240mg OD	PO

Treatment should be initiated within 1 year of completing trastuzumab.

Cycle frequency

Taken continuously for one year.

Number of cycles

As above.

Administration

Neratinib is available as 40mg tablets. Tablets should be swallowed whole with water. The doses should be taken with food, preferably in the morning.

Patients should be advised to avoid grapefruit and grapefruit juice whilst taking neratinib.

If a patient misses a dose it should be omitted and the next scheduled dose taken as planned.

Pre-medication

No pre-medication required.

Emetogenicity

Neratinib has mild emetic potential.

Additional supportive medication

Loperamide should be supplied. Patients should be instructed to initiate prophylactic treatment with loperamide with the first dose of neratinib and to take regularly during the first 1-2 months of treatment, titrating the dose to 1-2 bowel movements per day.

See below for management of diarrhoea.

Extravasation

N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+Es (including creatinine)	14 days
LFTs	14 days
Magnesium	14 days
Blood pressure	Baseline

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	7 days
U+Es (including creatinine)	7 days
LFTs	7 days
Magnesium	7 days
Blood pressure	As clinically indicated

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 100 x 10^9/L
Creatinine clearance	≥ 30mL/min
Bilirubin	< 3 x ULN
AST/ALT	< 5 x ULN

Dose modifications

Dose level	Neratinib dose
Full dose	240mg
First dose reduction	200mg
Second dose reduction	160mg
Third dose reduction	120mg

- **Haematological toxicity**

If neutrophils < 1.0 x 10^9/L and/or platelets <100 x 10^9/L delay for one week and repeat blood tests.

- **Renal impairment**

No modifications required for mild-moderate renal impairment. Neratinib has not been studied and so is not recommended in patients with severe renal impairment or on dialysis.

- **Hepatic impairment**

No modifications required for patients with Child Pugh A or B (mild to moderate) hepatic impairment. Neratinib is not recommended in patients with Child Pugh C hepatic impairment.

See below for management of hepatotoxicity.

- **Other toxicities**

For any grade 3 toxicity:

- Withhold neratinib until recover to ≤ grade 1.
- Resume with one dose level reduction.
- If recovery does not occur within 3 weeks, discontinue treatment.

For any grade 4 toxicity discontinue neratinib.
Neratinib should be discontinued if:

- Patient fails to recover to Grade 0 to 1 from treatment-related toxicity
- Toxicities cause in a treatment delay > 3 weeks
- Patients are unable to tolerate 120 mg daily

Diarrhoea

Patients should be given supplies of loperamide (as above) and advised to maintain good oral fluid intake to avoid dehydration.

Grade of diarrhoea	Description	Action
Grade 1	Increase < 4 stools per day over baseline	• Adjust anti-diarrhoeal treatment. • Diet modifications. • Fluid intake of approximately 2L should be maintained to avoid dehydration. • Once event resolves to ≤ Grade 1 or baseline, consider restarting anti-diarrhoeal prophylaxis, if appropriate.
Grade 2	Increase 4-6 stools per day over baseline for < 5 days	
Grade 3	Increase ≥7 stools per day over baseline, incontinence, hospitalisation, limiting activities of daily living	
Any grade with complicated features	Dehydration, fever, hypotension, renal failure, grade 3-4 neutropenia	• Withhold treatment. • Diet modifications. • Fluid intake of approximately 2L should be maintained to avoid dehydration. • If diarrhoea resolves to Grade 0-1 in one week or less, then resume treatment at the same dose. • If diarrhoea resolves to Grade 0-1 in longer than one week, then resume treatment at reduced dose. • Once event resolves to ≤ Grade 1 or baseline, consider restarting anti-diarrhoeal prophylaxis, if appropriate. • If grade 3 diarrhoea persists longer than 3 weeks, discontinue permanently.
Grade 2	For ≥ 5 days	
Grade 3	For 2 days - 3 weeks	
Grade 4	Life threatening	Permanently discontinue
Recurrent ≥ grade 2 diarrhoea at 120mg dose		Permanently discontinue

Hepatotoxicity

Description of hepatotoxicity	Action
Grade 3 increased ALT (>5-20 x ULN) or Grade 3 increased bilirubin (>3-10 x ULN)	• Withhold neratinib until recovery to ≤ Grade 1 • Consider alternative causes • Resume 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 treatment.
Grade 3 increased ALT (>20 x ULN) or Grade 3 increased bilirubin (>10 x ULN)	• Consider alternative causes • Permanently discontinue treatment.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Diarrhoea
Renal failure

- **Frequently occurring side effects**

Diarrhoea
Nausea and vomiting
UTIs
Deranged liver function tests
Reduced appetite
Fatigue
Rash
Mucositis

- **Other side effects**

Muscle spasms

Significant drug interactions – for full details consult product literature/ reference texts

Concomitant use of **strong CYP3A4/P-gp inhibitors** (e.g. atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, ketoconazole, itraconazole, clarithromycin, telithromycin, and voriconazole) should be avoided.

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

Concomitant treatment with substances that increase gastric pH should be avoided, as neratinib solubility and absorption may decrease. Co-administration with proton pump inhibitors (PPIs) and H2-receptor antagonists is not recommended. Separate dosing of neratinib and antacids by at least 3 hours.

Concurrent use of neratinib with **potent CYP3A4/P-gp inducers** (e.g. phenytoin, carbamazepine, rifampicin, phenobarbital or herbal preparations containing St John's Wort/Hypericum perforatum) should be avoided.

It is currently unknown whether neratinib reduces the effectiveness of systemically acting **hormonal contraceptives** so barrier contraception is required.

Patients who are treated with **BCRP inhibitors** (e.g., rosuvastatin and sulfasalazine) should be monitored carefully as they may be inhibited by neratinib.

Patients who are treated concomitantly with **therapeutic agents whose metabolism involves P-gp substrates** in the gastrointestinal tract window (e.g. dabigatran, digoxin, and fexofenadine) should be monitored carefully.

Additional comments

References

- NICE Technology Appraisal Guidance 612. Accessed 9 July 2020 via www.nice.org.uk
- Summary of Product Characteristic - Neratinib accessed 9 July 2020 via www.medicines.org
- Martin, M., et al. Neratinib after Trastuzumab based Adjuvant Therapy in HER2 positive breast cancer. (ExteNET). Lancet Oncology, 2017 18: 1688-1700.

Written/reviewed by: Dr J Braybrooke (Consultant Oncologist, UHBristol NHS Trust)

Checked by: Sarah Murdoch (Senior Oncology Pharmacist, SW Clinical Network)

Authorised by: Dr J Braybrooke (Consultant Oncologist, UHBristol NHS Trust, SW Clinical Network)

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