Product Information
NERLYNX® (neratinib) Tablets

Read the enclosed insert carefully before use
Keep out of reach of children
Prescription medicine only

1 NAME OF THE MEDICINE

RxNERLYNX (neratinib)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ACTIVE INGREDIENT: neratinib maleate, equivalent to 40 mg neratinib.

EXCIPIENTS:

Tablet core
Mannitol, Microcrystalline cellulose, Crospovidone, Povidone, Colloidal Silicon Dioxide, Magnesium stearate

Tablet coating
Polyvinyl alcohol, Titanium dioxide, Polyethylene Glycol, Talc, Iron oxide red

3 PHARMACEUTICAL FORM

Film-coated tablet.

Oval, red film-coated tablet with 'W104' debossed on one side and plain on the other side. Tablet dimensions are 10.5 mm x 4.3 mm with thickness of 3.1 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indication

Extended Adjuvant Treatment of Early-Stage Breast Cancer
NERLYNX as a single agent is indicated for the extended adjuvant treatment of adult patients with early-stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than one year ago.

Advanced or Metastatic Breast Cancer
NERLYNX in combination with capecitabine is indicated for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting.

4.2 Dose and method of administration

NERLYNX treatment should be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products.

Instruct patients to take NERLYNX at approximately the same time every day. The tablets should be swallowed whole, preferably with water, and should not be chewed, crushed, split or dissolved prior to swallowing. NERLYNX should be taken with food, preferably in the morning.

Extended Adjuvant Treatment of Early- Stage Breast Cancer
The recommended dose of NERLYNX is 240 mg (six tablets) given orally once daily, with food, continuously until disease recurrence or for up to one year.

Advanced or Metastatic Breast Cancer
The recommended dose of NERLYNX is 240 mg (six tablets) given orally once daily with food on Days 1–21 of a 21-day cycle plus capecitabine (750 mg/m^2 given orally twice daily) on Days 1–14 of a 21-day cycle until disease progression or unacceptable toxicities.

Management of Diarrhoea
The diarrhoea associated with NERLYNX can be managed with either loperamide prophylaxis starting with the first dose of NERLYNX or by the dose escalation of NERLYNX over the first 2 weeks.

Premedication for Diarrhoea
When not using dose escalation, administer anti-diarrhoeal prophylaxis during the first 56 days of treatment and initiate with the first dose of NERLYNX.

Instruct patients to take loperamide as directed in Table 1, titrating to 1-2 bowel movements per day.

Table 1. Loperamide Prophylaxis

Time on NERLYNX	**Loperamide Dose and Frequency**
Weeks 1-2 (days 1 - 14)	4 mg three times daily
Weeks 3-8 (days 15 - 56)	4 mg twice daily
Weeks 9– Discontinuation of NERLYNX	4 mg as needed, not to exceed 16 mg per day; titrate dosing to achieve 1–2 bowel movements per day

If diarrhoea occurs despite recommended prophylaxis, treat with additional anti-diarrhoeals, fluids and electrolytes as clinically indicated. NERLYNX dose interruptions and dose reductions may also be required to manage diarrhoea.

NERLYNX Dose Escalation
A two week dose escalation for NERLYNX may be considered instead of starting at the 240 mg daily dose for patients with early-stage breast cancer and metastatic breast cancer, as described in Table 2.

Table 2: NERLYNX Dose Escalation and Treatment Schedule

Time on Nerlynx	**NERLYNX Dose**
Week 1 (days 1–7)	120 mg daily (three 40 mg tablets)
Week 2 (days 8–14)	160 mg daily (four 40 mg tablets)
Week 3 and onwards	240 mg daily (six 40 mg tablets, recommended dose)

If diarrhoea occurs, treat with antidiarrhoeal medications, fluids, and electrolytes as clinically indicated. NERLYNX dose interruptions and dose reductions may also be required to manage diarrhoea.

Guidelines for adjusting doses of NERLYNX in the setting of diarrhoea are shown in Table 4 and Table 6. Diarrhoea management requires the correct use of an anti-diarrhoeal medicinal product, dietary changes, and appropriate dose modifications of NERLYNX.

Dose Modifications for Adverse Reactions
NERLYNX dose modification is recommended based on individual safety and tolerability. Management of some adverse reactions may require dose interruption and/or dose reduction as shown in Table 3 to Table 6.

Discontinue NERLYNX for patients:
- with treatment related adverse reactions that fail to recover to Grade 0 to 1 or baseline,
- with toxicities that result in a treatment delay > 3 weeks, or
- who are unable to tolerate 120 mg daily

Additional clinical situations may result in dose adjustments as clinically indicated (e.g. intolerable toxicities, persistent Grade 2 adverse reactions, etc.).

When NERLYNX is used in combination with capecitabine, refer to the capecitabine prescribing information for dose modifications of capecitabine.

Table 3: NERLYNX Monotherapy Dose Modifications for Adverse Reactions

Dose Level	**NERLYNX Dose**
Recommended starting dose	240 mg daily (six 40 mg tablets)
First dose reduction	200 mg daily (five 40 mg tablets)
Second dose reduction	160 mg daily (four 40 mg tablets)
Third dose reduction	120 mg daily (three 40 mg tablets)

Table 4: Recommended Dosage Modifications for Adverse Reactions with NERLYNX Monotherapy

Adverse Reaction	**Severity†**	**Action/Dose Modification**
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 antidiarrhoeal treatment • Diet modifications • Fluid intake of ~2 L/day should be maintained to avoid dehydration • Once event resolves to ≤Grade 1 or baseline, start loperamide 4 mg with each subsequent NERLYNX administration
	• Any grade with complicated features* • Grade 2 diarrhoea lasting longer than 5 days‡	• Interrupt NERLYNX treatment • Diet modifications

Adverse Reaction	Severity†	Action/Dose Modification
	• Grade 3 diarrhoea lasting longer than 2 days‡	• Fluid intake of ~2 L/day should be maintained to avoid dehydration • If diarrhoea resolves to ≤Grade 1 in one week or less, then resume NERLYNX treatment at the same dose • If diarrhoea resolves to ≤Grade 1 in longer than one week, then resume NERLYNX treatment at reduced dose (see Table 3) • Once event resolves to ≤Grade 1 or baseline, start loperamide 4 mg with each subsequent NERLYNX administration
	• Grade 4 diarrhoea [life-threatening consequences; urgent intervention indicated]	• Permanently discontinue NERLYNX treatment
	• Diarrhoea recurs to Grade 2 or higher at 120 mg per day	• Permanently discontinue NERLYNX treatment
Hepatotoxicity	• Grade 3 ALT or AST (>5–20× ULN) OR • Grade 3 bilirubin (>3–10× ULN)	• Hold NERLYNX until recovery to ≤Grade 1 • Evaluate alternative causes • Resume NERLYNX at the next lower dose level if recovery to ≤Grade 1 occurs within 3 weeks. If Grade 3 ALT or AST, or bilirubin occurs again despite one dose reduction, permanently discontinue NERLYNX.
	• Grade 4 ALT or AST (>20× ULN) OR • Grade 4 bilirubin (>10× ULN)	• Permanently discontinue NERLYNX • Evaluate alternative causes
Other	• Grade 3	• Hold NERLYNX until recovery to Grade ≤1 or baseline within 3 weeks of stopping treatment. Then resume NERLYNX at the next lower dose level.
	• Grade 4	• Discontinue NERLYNX permanently

ALT=Alanine Aminotransferase; AST=Aspartate Aminotransferase; ULN=Upper Limit Normal
† Per CTCAE v4.0
* Complicated features include dehydration, fever, hypotension, renal failure, or Grade 3 or 4 neutropenia
‡ Despite being treated with optimal medical therapy

Table 5: NERLYNX in Combination with Capecitabine Dose Modifications for Adverse Reactions

Dose Level	NERLYNX Dose
Recommended starting dose	240 mg daily (six 40 mg tablets)
First dose reduction	160 mg daily (four 40 mg tablets)
Second dose reduction	120 mg daily (three 40 mg tablets)

Table 6: Recommended Dosage Modifications for Adverse Reactions with NERLYNX in Combination with Capecitabine

Adverse Reaction	Severity[†]	Action/Dose Modification
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 and activities of daily living] lasting ≤2 days	• Adjust antidiarrhoeal treatment • Continue NERLYNX and capecitabine at full doses • Diet modifications • Fluid intake of ~2 L/day should be maintained to avoid dehydration • Once the event resolves to Grade ≤1 or baseline, start loperamide 4 mg with each subsequent NERLYNX administration
	• Persisting and intolerable Grade 2 Diarrhoea: lasting >5 days • Grade 3 Diarrhoea lasting >2 days • Grade 4 Diarrhoea [Life-threatening consequences; urgent intervention indicated]	• Adjust antidiarrhoeal treatment • Hold NERLYNX and capecitabine until recovery to Grade ≤1 or baseline • Diet modifications • Fluid intake of ~2 L/day should be maintained intravenously, if needed • If recovery occurs: o ≤1 week after withholding treatment, resume same doses of NERLYNX and capecitabine o Within 1–3 weeks after withholding treatment, reduce NERLYNX dose to 160 mg and maintain the same dose of capecitabine • If event occurs a second time and the NERLYNX dose has not already been decreased, reduce NERLYNX dose to 160 mg (maintain the same dose of

Adverse Reaction	Severity†	Action/Dose Modification
		capecitabine). If NERLYNX dose has already been reduced, then reduce the dose of capecitabine to 550 mg/m^2 given twice daily[a] (maintain the same dose of NERLYNX). • If subsequent events occur, reduce the dose of NERLYNX or capecitabine to the next lower dose level in an alternate fashion (i.e., reduce capecitabine to 375 mg/m^2 given twice daily [a] if NERLYNX was previously reduced, or reduce NERLYNX to 120 mg if capecitabine was previously reduced) • Once the event resolves to Grade ≤1 or baseline, start loperamide 4 mg with each subsequent NERLYNX administration
Hepatotoxicity	• Grade 3 ALT or AST (>5–20× ULN) OR • Grade 3 bilirubin (>3–10× ULN)	• Hold NERLYNX until recovery to ≤Grade 1 • Evaluate alternative causes • Resume NERLYNX at the next lower dose level if recovery to ≤Grade 1 occurs within 3 weeks. If Grade 3 ALT or AST, or bilirubin occurs again despite one dose reduction, permanently discontinue NERLYNX.
	• Grade 4 ALT or AST (>20× ULN) OR • Grade 4 bilirubin (>10× ULN)	• Permanently discontinue NERLYNX • Evaluate alternative causes
Other	• Grade 3	• Hold NERLYNX until recovery to Grade ≤1 or baseline within 3 weeks of stopping treatment. Then resume NERLYNX at the next lower dose level.
	• Grade 4	• Discontinue NERLYNX permanently

ALT=Alanine Aminotransferase; AST=Aspartate Aminotransferase; ULN=Upper Limit Normal

† Per CTCAE v4.0

[a] Since capecitabine is provided as 150 mg or 500 mg tablets, it is recommended that the capecitabine dose reduction(s) is(are) rounded down to the nearest 500 mg or multiple of 150 mg for the twice daily dose. If the patient's body surface area is >2.0, the standard of care for the study center can be utilized for capecitabine mg/m^2 dosing.

Missed dose
Missed doses should not be replaced and treatment should resume with the next scheduled daily dose.

Use of Gastric Acid- Reducing Agents
Proton pump inhibitors (PPI): Avoid concomitant use with NERLYNX (*see* ***Section 4.5 Interactions with other medicines and other forms of interactions***).

H2-receptor antagonists: NERLYNX must be taken at least 2 hours before the next dose of the H2-receptor antagonist or 10 hours after the H2-receptor antagonist (*see* ***Section 4.5 Interactions with other medicines and other forms of interactions***).

Antacids*:* Separate dosing of NERLYNX and antacids by 3 hours after antacids (*see* ***Section 4.5 Interactions with other medicines and other forms of interactions)***.

Use of CYP3A4 inhibitors
If the inhibitor cannot be avoided, reduce NERLYNX dose to 40 mg (one 40 mg tablet) taken once daily with a strong CYP3A4 inhibitor or 200 mg (five 40 mg tablets) taken once daily with a moderate CYP3A4 inhibitor. After discontinuation of a strong or moderate CYP3A4 inhibitor, resume previous dose of NERLYNX 240 mg (see ***Section 4.3 Contraindications and Section 4.5 Interactions with other medicines and other forms of interactions***).

Use of CYP3A4 inducers
If a potent or moderate CYP3A4 inducer cannot be avoided, increase NERLYNX dose to 320 mg (eight 40 mg tablets) taken once daily. After discontinuation of a CYP3A4 inducer, resume previous dose of NERLYNX 240 mg. The daily dose of NERLYNX should not exceed 320 mg (see ***Section 4.3 Contraindications and Section 4.5 Interactions with other medicines and other forms of interactions***).

Patients with hepatic impairment
No dose adjustment is required in patients with Child Pugh A or B (mild to moderate) hepatic impairment. Treatment of patients with Child Pugh C hepatic impairment is not recommended (see ***Section 4.4 Special warnings and precautions for use and 4.3 Contraindications***).

Dose modifications for hepatotoxicity
Guidelines for dose adjustment of NERLYNX in the event of liver toxicity are shown in Table 7. Patients who experience ≥ Grade 3 diarrhoea requiring IV fluid treatment or any signs or symptoms of hepatotoxicity, such as worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia, should be evaluated for changes in liver function tests. Fractionated bilirubin and prothrombin time should also be collected during hepatotoxicity evaluation (see ***Section 4.4 Special warnings and precautions for use***).

Table 7: Dose Modifications for Hepatotoxicity

Severity of Hepatotoxicity*	**Action**
• Grade 3 ALT or AST (>5-20 x ULN) OR • Grade 3 bilirubin (>3-10 x ULN)	• Stop NERLYNX until recovery to ≤ Grade 1 • Evaluate alternative causes • Resume NERLYNX at the next lower dose level if recovery to ≤ Grade 1 occurs within 3 weeks. If Grade 3 ALT or AST, or bilirubin occurs again despite one dose reduction, permanently discontinue NERLYNX
• Grade 4 ALT or AST (>20 x ULN)	• Permanently discontinue NERLYNX

Severity of Hepatotoxicity*	Action
OR • Grade 4 bilirubin (>10 x ULN)	• Evaluate alternative causes

ULN=Upper Limit Normal; ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase
* PER CTCAE V4.0

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients contained in NERLYNX.

Co-administration with the following medical products that are strong inducers of the CYP3A4/P-gp isoform of cytochrome P450:

- carbamazepine, phenobarbital, phenytoin (antiepileptics)
- St John's wort (*Hypericum perforatum*) (herbal product)
- rifampin (antimycobacterial)

Co-administration with moderate CYP3A4/P-gp inhibitors:

- fluconazole (antifungal)
- diltiazem, verapamil (calcium-channel blockers)
- erythromycin (antibiotic)

Severe hepatic impairment (Child-Pugh C).

4.4 Special warnings and precautions for use

Diarrhoea

Diarrhoea has been reported during treatment with NERLYNX. The diarrhoea may be severe and associated with dehydration. Diarrhoea generally occurs early during the first or second week of treatment with NERLYNX and may be recurrent. (see ***Section 4.2 Dose and method of administration and Section 4.8 Adverse effects [Undesirable effects]).***

The diarrhoea associated with NERLYNX can be managed proactively with either loperamide prophylaxis with the first dose of NERLYNX or by the dose escalation of NERLYNX over the first 2 weeks.

Loperamide Prophylaxis

Patients should be instructed to initiate prophylactic treatment with an anti-diarrhoeal medicinal product (e.g., loperamide) with the first dose of NERLYNX, and maintain regular dosing of the anti-diarrhoeal medicinal product during the first 2 cycles of NERLYNX treatment, titrating to 1-2 bowel movements per day, and continue prophylactic anti-diarrhoeal medicinal product (e.g., loperamide) for subsequent months as needed. Do not exceed 16 mg loperamide per day. Proactive management of diarrhoea including adequate hydration combined with anti-diarrhoeal medicinal product, especially within the first 2 cycles of NERLYNX treatment, should start at the first signs of diarrhoea. As necessary, the dose of anti-diarrhoeal medicinal product should be escalated to the highest recommended approved dose; they should be readily available to patients and continued until loose bowel movements cease for 12 hours.

NERLYNX Dose Escalation

Alternatively, a weekly NERLYNX dose escalation approach for the first 2 weeks prior to initiation of the recommended treatment regimen with NERLYNX can also be considered for diarrhoea management (see ***Section 4.2 Dose and method of administration***). Grade 3 diarrhoea was observed in 13% of patients who used NERLYNX dose escalation. The median time to first

onset of Grade ≥3 diarrhoea was 45 days (range, 15–132) and the median cumulative duration of Grade ≥3 diarrhoea was 2.5 days (range, 1–6) *(see **4.8 Adverse effects [Undesirable effects]).***

SEVERE DIARRHOEA OCCURRENCES, DESPITE PROPHYLAXIS TREATMENT, SHOULD BE AGGRESSIVELY MANAGED WITH ADDITIONAL ANTIDIARRHOEAL AGENTS, ELECTROLYTES AND FLUIDS REPLACEMENT, AND/OR INTERRUPTION, REDUCTION, OR DISCONTINUATION OF THERAPY WITH NERLYNX.

Patients with a significant chronic gastrointestinal disorder
Patients with a significant chronic gastrointestinal disorder with diarrhoea as a major symptom were not included in the pivotal study and should be carefully monitored.

Left ventricular function
Left ventricular dysfunction has been associated with HER2 inhibition. NERLYNX has not been studied in patients with less than lower limit of normal left ventricular ejection fraction (LVEF) or with significant cardiac history. In patients with known cardiac risk factors, conduct cardiac monitoring, including assessment of LVEF, as clinically indicated.

Skin and subcutaneous tissue disorders
NERLYNX is associated with skin and subcutaneous tissue disorders. Patients with symptomatic skin and subcutaneous tissue disorders should be carefully monitored.

Use in hepatic impairment
In patients with severe hepatic impairment (Child-Pugh C) there is a 2.8-fold increase of exposure to neratinib (see ***Section 5.2 Pharmacokinetic properties***).

Hepatotoxicity has been reported in patients treated with NERLYNX. Liver function tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin should be monitored at 1 week, then monthly for the first 3 months and every 6 weeks thereafter while on treatment or as clinically indicated (see ***Section 4.2 Dose and method of administration***).

Use in renal impairment
Patients with renal impairment are at a higher risk of complications of dehydration if they develop diarrhoea, and these patients should be carefully monitored (see ***Section 4.2 Dose and method of administration***).

NERLYNX 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 (see ***Section 5.2 Pharmacokinetic properties***).

Use in the elderly
Elderly patients (≥65 years of age) are at a higher risk of renal insufficiency and dehydration which may be a complication of diarrhoea and these patients should be carefully monitored.

Paediatric use
The safety and efficacy of NERLYNX in the paediatric population has not been studied in breast cancer.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

Effects of other substances on neratinib

CYP3A4 inhibitors
Co-administration of a single oral dose of 240 mg of neratinib in the presence of ketoconazole (400 mg once daily for 5 days), a strong CYP3A4 inhibitor, increased neratinib systemic exposure. The C_{max} of neratinib increased by 3.2-fold and AUC increased by 4.8-fold when co-administered with ketoconazole, compared with neratinib administered alone. Simulations using physiologically-based pharmacokinetic (PBPK) models suggested that a moderate CYP3A4 inhibitor (fluconazole) may increase the C_{max} and AUC of neratinib by 6% and 19%, respectively.

Concomitant use of strong CYP3A4 inhibitors (e.g. atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, ketoconazole, itraconazole, clarithromycin, telithromycin, and voriconazole) should be avoided. Grapefruit, grapefruit juice, grapefruit hybrids, pomelos, star-fruit, and Seville oranges may also increase neratinib plasma concentrations and should be avoided.

Proton pump inhibitors, H2-receptor antagonists and antacids
Neratinib solubility decreases with increasing pH. Drugs that alter the pH of the upper GI tract may alter the solubility of neratinib and hence its bioavailability. When a proton pump inhibitor (lansoprazole) was co-administered with NERLYNX the neratinib C_{max} and AUC decreased by 71% and 65%, respectively. When NERLYNX was administered 2 hours following a 300 mg dose of an H-2 receptor antagonist (ranitidine), the neratinib C_{max} and AUC were reduced by 55% and 47%, respectively. When NERLYNX was administered 2 hours prior to ranitidine 150 mg twice daily (administered in the morning and evening, approximately 12 hours apart), the neratinib C_{max} and AUC were reduced by 40% and 30%, respectively. Increasing the dose of NERLYNX when co-administered with gastric acid reducing agents is not likely to compensate for this loss of exposure (see ***Section 4.2 Dose and method of administration***).

CYP3A4 inducers
Following concomitant administration with repeated doses of 600 mg rifampin, a strong CYP3A4 inducer, neratinib exposures were significantly decreased with mean values that were 24% and 13% of reference values (neratinib administered alone) for C_{max} and AUC, respectively.

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

Simulations using PBPK models suggested that a moderate CYP3A4 inducer (efavirenz) may decrease the C_{max} and AUC of neratinib by 12% and 32%, respectively.

Effects of neratinib on other substances

Hormonal contraceptives
It is currently unknown whether NERLYNX reduces the effectiveness of systemically acting hormonal contraceptives. Therefore, women using systemically acting hormonal contraceptives should add a barrier method (see ***Section 4.6 Fertility, pregnancy and lactation***).

Breast cancer resistance protein inhibitors
Neratinib may inhibit breast cancer resistance protein (BCRP) moderately as suggested by *in vitro* studies. Clinical studies with BCRP substrates have not been conducted. Patients who are treated with BCRP substrates (e.g., rosuvastatin and sulfasalazine) should be monitored carefully.

P-glycoprotein transporters
In *in-vitro* studies, neratinib is an inhibitor of P-glycoprotein (P-gp) substrates. In healthy subjects, digoxin increased C_{max} by 54% and AUC increased by 32% when co-administered with multiple oral doses of neratinib 240 mg compared with exposures of digoxin alone. The clearance values of digoxin were equivalent following digoxin and digoxin plus neratinib. It appeared that the inhibitory effect of neratinib was primarily on P-gp activity in the gastrointestinal tract as a result of pre-systemic inhibition. This pre-systemic interaction of neratinib with digoxin might be clinically relevant for P-gp substrates with a narrow therapeutic window (e.g. dabigatran, digoxin, and fexofenadine). Patients who are treated concomitantly with therapeutic agents whose metabolism involves P-gp substrates in the gastrointestinal tract should be monitored carefully.

Other transporters
In *in vitro* studies, neratinib had no clinically-relevant inhibitory activity on BSEP, OATP1B1, OATP1B3, OAT1, OAT3 and OCT2.

CYP3A4 substrates
In vitro studies indicate neratinib may alter the pharmacokinetics of orally-administered CYP3A4 substrates.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females and males
Based on findings in animals, neratinib may cause foetal harm when administered to pregnant women. Women should avoid becoming pregnant while taking NERLYNX and for up to 1 month after ending treatment. Therefore, women of child-bearing potential must use highly effective contraceptive measures while taking NERLYNX and for 1 month after stopping treatment.

It is currently unknown whether neratinib may reduce the effectiveness of systemically acting hormonal contraceptives, and therefore women using systemically acting hormonal contraceptives should add a barrier method.

Men should use a barrier method of contraception during treatment and for 3 months after stopping treatment.

Effects on fertility
No fertility studies in women or men have been conducted. No significant changes in fertility parameters in male and female rats were detected following oral dosing up to 12 mg/kg/day resulting in estimated exposures 22 times the clinical AUC.

Use in pregnancy - **Category D**
There are no data from the use of NERLYNX in pregnant women. Studies in animals have shown embryo-fetal lethality and fetal morphological anomalies. In rabbits, an increased incidence of fetal skeletal variations/ abnormalities ((fetal gross external (domed head), soft tissue (dilation of the brain ventricles and a ventricular septal defect), skeletal (misshapen anterior fontanelles and enlarged anterior and/or posterior fontanelles) abnormalities, ventricular septum defect of heart) were observed at an oral dose of ≥ 6 mg/kg/day, with exposures below (based on AUC) the clinical exposure.

The potential risk for humans is unknown. NERLYNX is not recommended during pregnancy and in women of childbearing potential not using contraception.

If neratinib is used during pregnancy, or if the patient becomes pregnant while taking NERLYNX, the patient should be informed of the potential hazard to the fetus.

Use in lactation

It is not known whether neratinib is excreted in human milk. A risk to the breast-fed infant cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue NERLYNX, taking into account the importance of NERLYNX to the mother and the benefit of breast-feeding to the child.

4.7 Effects on ability to drive and use machines

NERLYNX has minor or moderate influence on the ability to drive and use machines. Fatigue, dizziness, dehydration, and syncope have been reported as adverse reactions with neratinib. The clinical status of the patient should be considered when assessing the patient's ability to perform tasks that require judgment, motor, or cognitive skills.

4.8 Adverse effects (Undesirable effects)

Description of selected adverse reactions

Diarrhoea

Severe diarrhoea and sequelae, such as dehydration, hypotension, and renal failure occurred during treatment with NERLYNX. Diarrhoea was reported in 95% of NERLYNX-treated patients in ExteNET, a randomized placebo-controlled trial in the extended adjuvant setting who were not required to receive antidiarrhoeal prophylaxis. In the NERLYNX arm, Grade 3 diarrhoea occurred in 40% and Grade 4 diarrhoea occurred in 0.1% of patients. The majority of patients (93%) had diarrhoea in the first month of treatment, the median time to first onset of Grade ≥3 diarrhoea was 8 days (range, 1–350), and the median cumulative duration of Grade ≥3 diarrhoea was 5 days (range, 1–139).

Diarrhoea was reported in 83% of NERLYNX plus capecitabine treated patients in NALA, a randomized placebo-controlled trial in the metastatic breast cancer setting who were required to receive anti-diarrhoeal prophylaxis in the first 21-day cycle. The majority of patients (70%) had diarrhoea in the first 21-day of treatment, the median time to first onset of Grade ≥3 diarrhoea was 11 days (range, 2–728) and the median cumulative duration of Grade ≥3 diarrhoea was 3 days (range, 1–21). In the NERLYNX plus capecitabine arm, Grade 3 diarrhoea occurred in 24% of patients.

Antidiarrhoeal prophylaxis has been shown to lower the incidence and severity of diarrhoea. Instruct patients to initiate antidiarrhoeal prophylaxis with loperamide along with the first dose of NERLYNX and continue during the first 56 days of treatment; after day 56, titrate dose to achieve 1–2 bowel movements per day and not to exceed 16 mg loperamide per day (see ***Section 4.2 Dose and method of administration)***. Consider adding other agents to loperamide as clinically indicated.

Alternatively, a 2 weeks NERLYNX dose escalation approach prior to initiation of the recommended treatment regimen with NERLYNX can also be considered for diarrhoea management day (see ***Section 4.2 Dose and method of administration)***. For patients who used NERLYNX dose escalation, the median time to first onset of Grade ≥3 diarrhoea was 45 days (range, 15–132) and the median cumulative duration of Grade ≥3 diarrhoea was 2.5 days (range, 1–6). Grade 3 diarrhoea occurred in 13% of patients who used NERLYNX dose escalation..

Monitor patients for diarrhoea and treat with additional antidiarrhoeals as needed. When severe diarrhoea with dehydration occurs, administer fluid and electrolytes as needed, interrupt NERLYNX, and reduce subsequent doses day (see ***Section 4.2 Dose and method of administration)***. Perform stool cultures as clinically indicated to exclude infectious causes of Grade 3 or 4 diarrhoea or diarrhoea of any grade with complicating features (dehydration, fever, neutropenia).

4.8.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Extended Adjuvant Treatment of Early-Stage Breast Cancer

ExteNET

The data described below reflect the safety data of NERLYNX as a single agent in ExteNET, a multicenter, randomized, double-blind, placebo-controlled study of NERLYNX within 2 years after completion of adjuvant treatment with trastuzumab-based therapy in women with HER2-positive early-stage breast cancer. Patients who received NERLYNX in this trial were not required to receive any prophylaxis with antidiarrhoeal agents to prevent the NERLYNX-related diarrhoea. Patients were treated with 240 mg of NERLYNX given orally once daily with food, continuously until disease recurrence or for up to one year. The median duration of treatment was 11.6 months in the NERLYNX arm and 11.8 months in the placebo arm. The median age was 52 years (60% were ≥50 years old, 12% were ≥65 years old); 81% were Caucasian, 3% Black or African American, 14% Asian, and 3% other. A total of 1408 patients were treated with NERLYNX.

NERLYNX dose reduction due to an adverse reaction of any grade occurred in 31% of patients receiving NERLYNX compared to 2.6% of patients receiving placebo. Permanent discontinuation due to any adverse reaction was reported in 28% of NERLYNX-treated patients. The most common adverse reaction leading to discontinuation was diarrhoea, accounting for 17% of NERLYNX-treated patients.

The most common adverse reactions (≥5%) were diarrhoea, nausea, abdominal pain, fatigue, vomiting, rash, stomatitis, decreased appetite, muscle spasms, dyspepsia, AST or ALT increased, nail disorder, dry skin, abdominal distention, epistaxis, weight decreased, and urinary tract infection. The most frequently reported Grade 3 or 4 adverse reactions were diarrhoea, vomiting, nausea, and abdominal pain.

Serious adverse reactions in the NERLYNX arm included diarrhoea (1.6%), vomiting (0.9%), dehydration (0.6%), cellulitis (0.4%), renal failure (0.4%), erysipelas (0.4%), ALT (0.3%), AST increased (0.3%), nausea (0.3%), fatigue (0.2%), and abdominal pain (0.2%).

Table 8 summarizes the adverse reactions in ExteNET.

Table 8: Adverse Reactions Reported in ≥2% of NERLYNX-Treated Patients in ExteNET

System Organ Class (Preferred Term)	NERLYNX n=1408			Placebo n=1408		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Gastrointestinal Disorders						
Diarrhoea	95	40	0.1	35	2	0
Nausea	43	2	0	22	0.1	0
Abdominal pain*	36	2	0	15	0.4	0
Vomiting	26	3	0	8	0.4	0
Stomatitis†	14	0.6	0	6	0.1	0
Dyspepsia	10	0.4	0	4	0	0
Abdominal distension	5	0.3	0	3	0	0

System Organ Class (Preferred Term)	NERLYNX n=1408			Placebo n=1408		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Dry mouth	3	0.1	0	2	0	0
General Disorders and Administration Site Conditions						
Fatigue	27	2	0	20	0.4	0
Hepatobiliary Disorders						
Alanine aminotransferase increased	9	1	0.2	3	0.2	0
Aspartate aminotransferase increased	7	0.5	0.2	3	0.3	0
Infections and Infestations						
Urinary tract infection	5	0.1	0	2	0	0
Investigations						
Weight decreased	5	0.1	0	0.5	0	0
Metabolism and Nutrition Disorders						
Decreased appetite	12	0.2	0	3	0	0
Dehydration	4	0.9	0.1	0.4	0.1	0
Musculoskeletal and Connective Tissue Disorders						
Muscle spasms	11	0.1	0	3	0.1	0
Respiratory, Thoracic and Mediastinal Disorders						
Epistaxis	5	0	0	1	0.1	0
Skin and Subcutaneous Tissue Disorders						
Rash‡	18	0.6	0	9	0	0
Dry skin	6	0	0	2	0	0
Nail Disorder§	8	0.3	0	2	0	0
Skin fissures	2	0.1	0	0.1	0	0

* Includes abdominal pain, abdominal pain upper, and abdominal pain lower

† Includes stomatitis, aphthous stomatitis, mouth ulceration, oral mucosal blistering, mucosal inflammation, oropharyngeal pain, oral pain, glossodynia, glossitis, and cheilitis

‡ Includes rash, rash erythematous, rash follicular, rash generalized, rash pruritic, rash pustular, rash maculo-papular, rash papular, dermatitis, dermatitis acneiform, and toxic skin eruption

§ Includes nail disorder, paronychia, onychoclasis, nail discoloration, nail toxicity, nail growth abnormal, and nail dystrophy

Advanced or Metastatic Breast Cancer

NALA

The data described below reflect the safety data of NERLYNX plus capecitabine in NALA, a randomized, multicenter, multinational, open-label, active-controlled study of HER2+ metastatic breast cancer in patients, with or without brain metastases, who have received two or more prior anti HER2-based regimens in the metastatic setting.

Patients were treated with NERLNX 240 mg orally once daily Days 1–21 of a 21-day cycle in combination with capecitabine (750 mg/m^2 given orally twice daily) Days 1–14 of a 21-day cycle, or lapatinib 1250 mg orally once daily Days 1–21 of a 21-day cycle in combination with capecitabine (1000 mg/m^2 given orally twice daily) Days 1–14 of a 21-day cycle until disease progression. The median duration of treatment was 5.7 months in the NERLYNX plus capecitabine arm and 4.4 months in the lapatinib plus capecitabine arm.

NERLYNX dose reduction due to an adverse reaction of any grade occurred in 10% of patients receiving NERLYNX plus capecitabine. Permanent discontinuation due to any adverse reaction was reported in 14% of NERLYNX plus capecitabine treated patients. The most common adverse reactions leading to discontinuation were vomiting (3.6%), diarrhoea (2.6%), nausea (2.6%), and palmar-plantar erythrodysaesthesia syndrome (2.3%) of NERLYNX plus capecitabine-treated patients.

The most common adverse reactions of any grade (≥5%) in the NERLYNX plus capecitabine arm were diarrhoea, nausea, vomiting, decreased appetite, constipation, fatigue/asthenia, weight decreased, dizziness, back pain, arthralgia, urinary tract infection, upper respiratory tract infection, abdominal distention, renal impairment, and muscle spasms. The most frequently reported Grade 3 or 4 adverse reactions were diarrhoea, nausea, vomiting, fatigue, and decreased appetite.

Serious adverse reactions ≥2% in the NERLYNX plus capecitabine arm included diarrhoea (7%), vomiting (3%), nausea (2.3%), and acute kidney injury (2.3%).

Table 9 summarizes the adverse reactions in NALA.

Table 9: Adverse Reactions Reported in ≥2% of NERLYNX-Treated Patients in Combination with Capecitabine in NALA

System Organ Class (Preferred Term)	NERLYNX + capecitabine n=303			Lapatinib + capecitabine n=311		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Gastrointestinal Disorders						
Diarrhoea	83	25	0	66	13	0
Nausea	53	4.3	0	42	2.9	0
Vomiting	46	4	0	31	1.9	0
Constipation	31	1	0	13	0	0
Abdominal distension	8	0.3	0	3.2	0.6	0
General Disorders and Administration Site Conditions						
Fatigue/asthenia	45	6	0	40	4.5	0
Malaise	4.3	0	0	2.3	0.3	0
Influenza like illness	4	0	0	1.3	0	0
Infections and Infestations						
Urinary tract infection	9	0.7	0	4.2	0.6	0
Upper respiratory tract infection	8	0.3	0	4.5	0.3	0
Investigations						
Weight decreased	20	0.3	0	13	0.6	0
Metabolism and Nutrition Disorders						
Decreased appetite	35	2.6	0	22	2.3	0
Musculoskeletal and Connective Tissue Disorders						
Back Pain	10	0.3	0	8	0.3	0
Arthralgia	10	0	0	6	1	0
Muscle spasms	5	0	0	1.9	0	0
Nervous System Disorder						
Dizziness	14	0.3	0	10	0.6	0
Renal and urinary disorders						
Renal impairment*	7	2	0.3	1	0	0.3
Dysuria	4.6	0	0	1.9	0	0

* Renal impairment includes acute kidney injury, blood creatinine increased, renal failure, and renal impairment

Management of Diarrhoea

CONTROL Study

The CONTROL (NCT02400476) study was a multicenter, open-label, multi-cohort trial evaluating patients with early-stage HER2-positive breast cancer treated with NERLYNX 240 mg daily for up to one year receiving loperamide prophylaxis with additional anti-diarrhoeal treatment as needed or NERLYNX dose escalation with loperamide as needed. All patients in the prophylaxis cohort received loperamide 4 mg loading dose, followed by 4 mg three times a day from days 1-14, followed by 4 mg twice a day on days 15-56, followed by loperamide as needed through 1 year of treatment with NERLYNX day (see ***Section 4.2 Dose and method of administration)***. All patients in the dose escalation cohort received NERLYNX 120 mg for Week 1, followed by NERLYNX 160 mg for Week 2, followed by NERLYNX 240 mg for Week 3 and thereafter day (see ***Section 4.2 Dose and method of administration)***.

Table 10 summarizes the diarrhoea adverse reactions for NERLYNX with loperamide prophylaxis and NERLYNX dose escalation.

Table 10: Diarrhoea in Patients Treated with NERLYNX with Antidiarrhoeal Prophylaxis or Dose Escalation

	Loperamide Prophylaxis n=109	**NERLYNX Dose Escalation n=60**
Duration of Treatment, months		
Median	11.8	12.0
Range	0.1, 12.8	0.2, 12.4
Dose Intensity, mg per day		
Median	234	230
Range	46, 240	32, 236
Incidence of Diarrhoea, %		
Any Grade	78	98
Grade 2	25	45
Grade 3	32	13
Action Taken, %		
Discontinuation due to diarrhoea	18	3.3

Rash
In the NERLYNX monotherapy group, 16.7% of patients experienced rash. The incidence of Grade 1 and Grade 2 was 13.3% and 2.9% respectively; 0.4% of NERLYNX-treated patients experienced Grade 3 rash.

Nail disorders
In the NERLYNX monotherapy group, 7.8% patients experience nail disorders. The incidence of Grade 1 and Grade 2 was 6.2% and 1.4% respectively. There were 0.2% of NERLYNX treated patients who experienced Grade 3 nail disorder.

Both rash and nail disorders led to treatment discontinuation in 0.6% of NERLYNX-treated

patients.

Hepatotoxicity
NERLYNX has been associated with hepatotoxicity characterized by increased liver enzymes. In ExteNET, 10% of patients experienced an alanine aminotransferase (ALT) increase ≥2× ULN, 5% of patients experienced an aspartate aminotransferase (AST) increase ≥2× ULN, and 1.7% of patients experienced an AST or ALT elevation >5× ULN (≥Grade 3). Hepatotoxicity or increases in liver transaminases led to drug discontinuation in 1.7% of NERLYNX-treated patients.

In the NALA study, in NERLYNX and capecitabine-treated patients, 7% experienced an ALT or AST >3× ULN, 2% experienced ALT or AST >5× ULN, 7% experienced a bilirubin >1.5× ULN, and 1.3% experienced a bilirubin >3× ULN. Hepatotoxicity or increases in liver transaminases led to drug discontinuation in 0.3% of NERLYNX and capecitabine-treated patients.

Total bilirubin, AST, ALT, and alkaline phosphatase should be measured prior to starting treatment with NERLYNX monthly for the first 3 months of treatment, then every 3 months while on treatment and as clinically indicated. These tests should also be performed in patients experiencing Grade 3 diarrhoea or any signs or symptoms of hepatotoxicity, such as worsening of fatigue, nausea, vomiting, right upper quadrant tenderness, fever, rash, or eosinophilia day (see ***Section 4.2 Dose and method of administration)***.

Other special populations

Elderly
In the ExteNET trial, in the NERLYNX arm; 1236 patients were <65 years, 172 patients were ≥65 years, of whom 25 patients were 75 years or older. There was a higher frequency of treatment discontinuations due to adverse reactions in the ≥65 years age group than in the <65 years age group; in the NERLYNX arm, the percentages were 45% compared with 25%, respectively, and in the placebo arm 6% and 5%, respectively. The incidence of serious adverse reactions in the NERLYNX arm vs placebo arm was 7% vs 6% (<65 years old) and 10% vs 8% (≥65 years old). The serious adverse reactions most frequently reported in the ≥65 years old group were vomiting (2.3%), diarrhoea (1.7%), renal failure (1.7%), and dehydration (1.2%).

In the NALA trial, in the NERLYNX plus capecitabine arm; 242 patients were <65 years, 61 patients were ≥65 years, of whom 12 patients were 75 years or older. The incidence of serious adverse reactions in the NERLYNX plus capecitabine arm in the ≥65 years age group was 36% and in the <65 years age group was 34%. The serious adverse reactions most frequently reported in the ≥65 years-old group were diarrhoea (16%), acute kidney injury (8%), and dehydration (7%). No overall differences in effectiveness were observed between patients ≥65 years old and patients <65 years old.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to: drugsafety-STA@stbiopharma.com.

4.9 Overdose

There is no specific antidote, and the benefit of haemodialysis in the treatment of NERLYNX overdose is unknown. In the event of an overdose, administration should be withheld and general supportive measures undertaken.

In the clinical trial setting, a limited number of patients reported adverse reactions associated with

overdose. The adverse reactions most commonly reported were diarrhoea, with or without nausea, vomiting and dehydration.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agent, other antineoplastic agents, protein kinase inhibitor, ATC code: L01EH02.

Mechanism of action

Neratinib is an irreversible inhibitor of 3 epidermal growth factor receptors (EGFRs): EGFR (encoded by ERBB1), HER2 (encoded by ERBB2), and HER4 (encoded by ERBB4). Neratinib binds to the HER2 receptor, reduces EGFR and HER2 autophosphorylation, downstream MAPK and AKT signalling pathways, and inhibits tumour cell proliferation *in vitro. In vivo,* oral administration of neratinib inhibited tumour growth in mouse xenograft models with tumour cell lines expressing HER2 and EGFR.

Clinical trials

Extended Adjuvant Treatment of Early-stage Breast Cancer

In the multicentre, randomised, double-blind, placebo-controlled, pivotal phase III study, ExteNET (3004), 2,840 women with early-stage HER2-positive breast cancer (as confirmed locally by assay) who had completed adjuvant treatment with trastuzumab were randomised 1:1 to receive either NERLYNX or placebo daily for one year. The median age in the intention-to-treat (ITT) population was 52.3 years (59.9% was ≥50 years old, 12.3% was ≥65 years old); 81.0% were Caucasian, 2.6% black or African American, 13.6% Asian and 2.9% other. At baseline, 57.4% had hormone receptor positive disease (defined as ER-positive and/or PgR-positive), 23.6% were node negative, 46.8% had one to three positive nodes and 29.6% had four or more positive nodes. Approximately 10% of patients had Stage I tumours, approximately 40% had Stage II tumours and approximately 30% had Stage III tumours. Median time from the last adjuvant trastuzumab treatment to randomisation was 4.5 months.

The primary endpoint of the study was invasive disease-free survival (iDFS). Secondary endpoints of the study included disease-free survival (DFS) including ductal carcinoma in situ (DFS-DCIS), time to distant recurrence (TTDR), distant disease-free survival (DDFS), cumulative incidence of central nervous system recurrence and overall survival (OS).

The primary analysis of the study 2 years post-randomisation demonstrated that NERLYNX significantly reduced the risk of invasive disease recurrence or death by 34% (HR=0.66 with 95% CI (0.49, 0.90), two-sided p = 0.008).

The results for the primary and secondary endpoints are shown in Table 11.

Table 11. Primary efficacy analyses – ITT population

Variable	Estimated 2 year event free rates[1] (%)		Stratified[2] hazard ratio (95 percent confidence interval)[3]	Stratified log rank test two sided p value[4]
	NERLYNX (n = 1420)	Placebo (n = 1420)		
Invasive disease-free survival	94.2	91.9	0.66 (0.49, 0.90)	0.008
Disease-free survival including ductal carcinoma *in situ*	94.2	91.3	0.61 (0.45, 0.83)	0.001
Distant disease-free survival	95.3	94.0	0.74 (0.52, 1.05)	0.094
Time to distant recurrence	95.5	94.2	0.73 (0.51, 1.04)	0.087
CNS recurrence	0.92	1.16	–	0.548

CNS = central nervous system.
1 Event-free rates for all endpoints, except for CNS recurrence for which cumulative incidence is reported.
2 Stratified by prior trastuzumab (concurrent vs. sequential), nodal status (0-3 positive nodes vs. ≥4 positive nodes), and ER/PR status (positive vs. negative)
3 Stratified Cox proportional hazards model
4 Stratified 2-sided log-rank test for all endpoints, except for CNS recurrence for which Gray's method was used.

Figure 1 shows the Kaplan-Meier plots for iDFS for the ITT population of study ExteNET (3004).

Figure 1 Kaplan-Meier plots for iDFS for the ITT population of study ExteNET (3004)

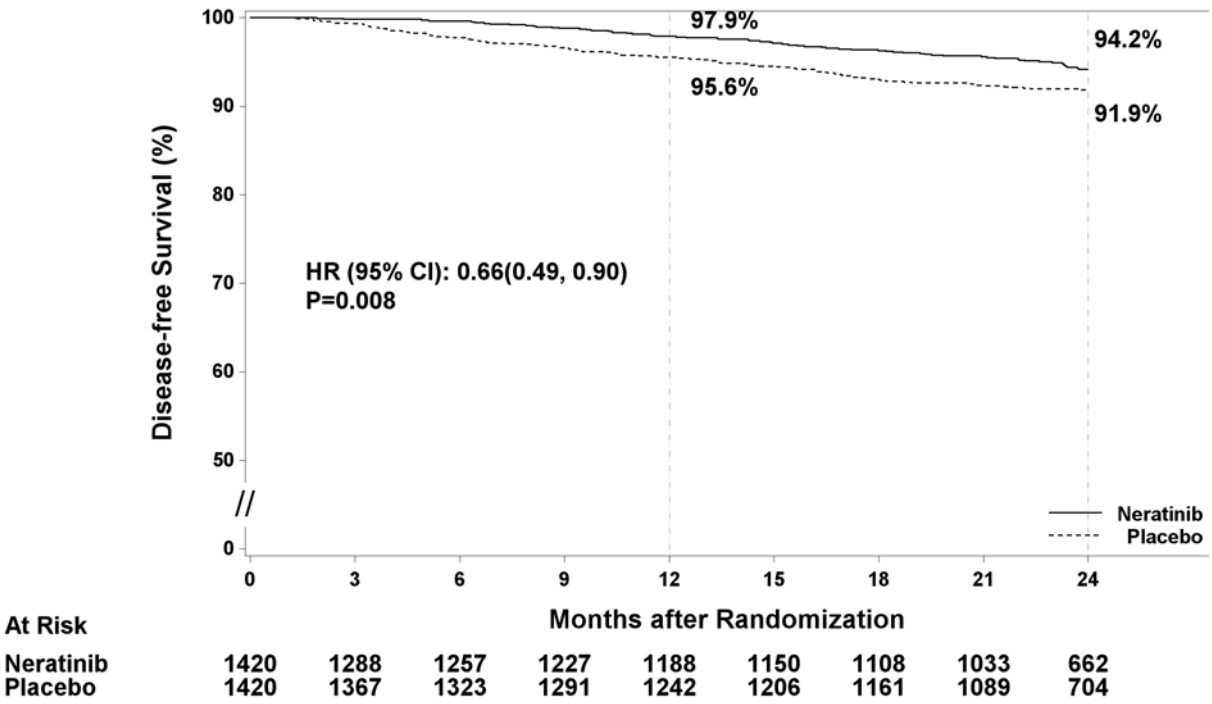
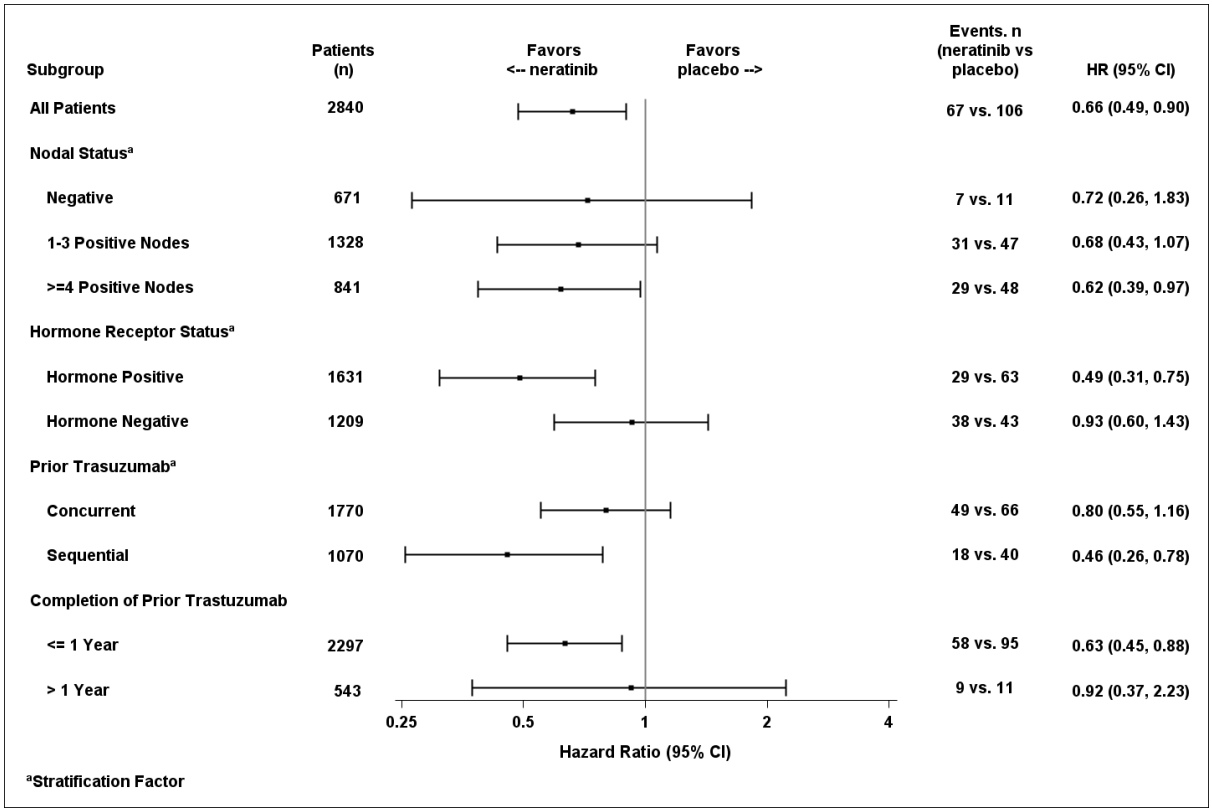


Figure 2 shows the Forrest Plot for iDFS by pre-specified patient subgroup.

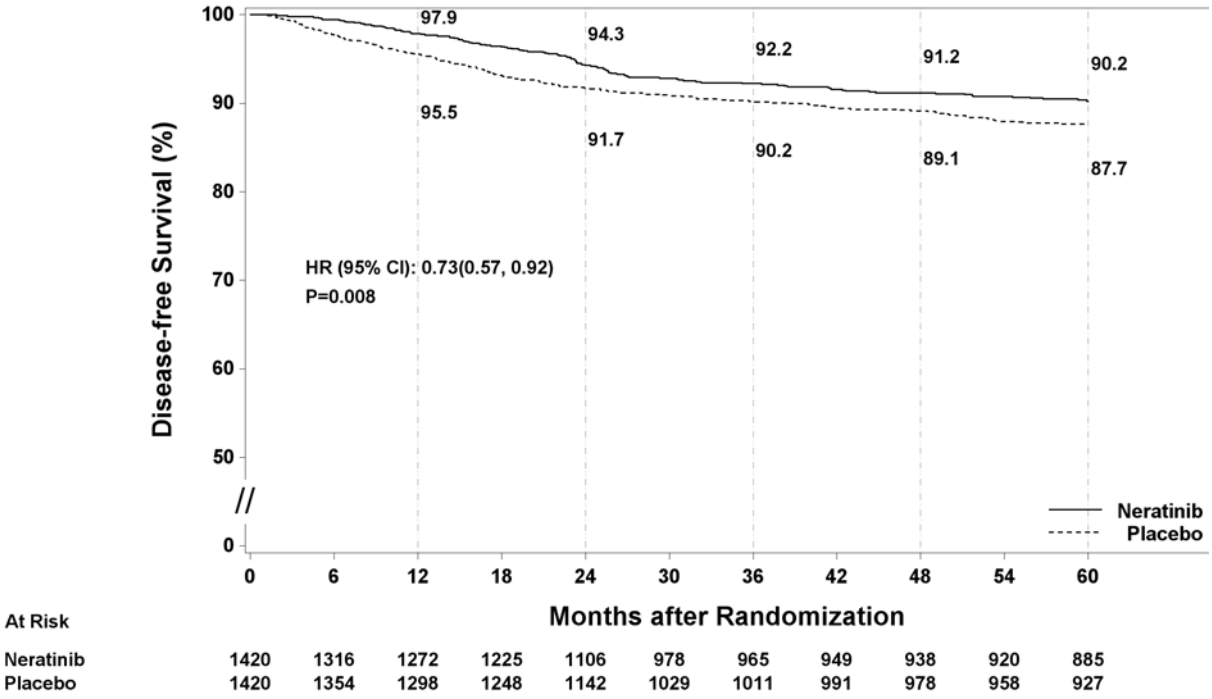
Figure 2. Disease-Free Survival by Patient Subgroup[a]



Approximately 75% of patients were re-consented for extended follow-up beyond 24 months. This exploratory analysis confirms that the iDFS results at 5 years are durable and consistent with the 2-year iDFS results.

Figure 3 shows a descriptive analysis of the 5-year iDFS that demonstrated the durability of the treatment effect on efficacy. The Hazard Ratio is 0.73 (95% CI 0.57, 0.92) for the ITT population.

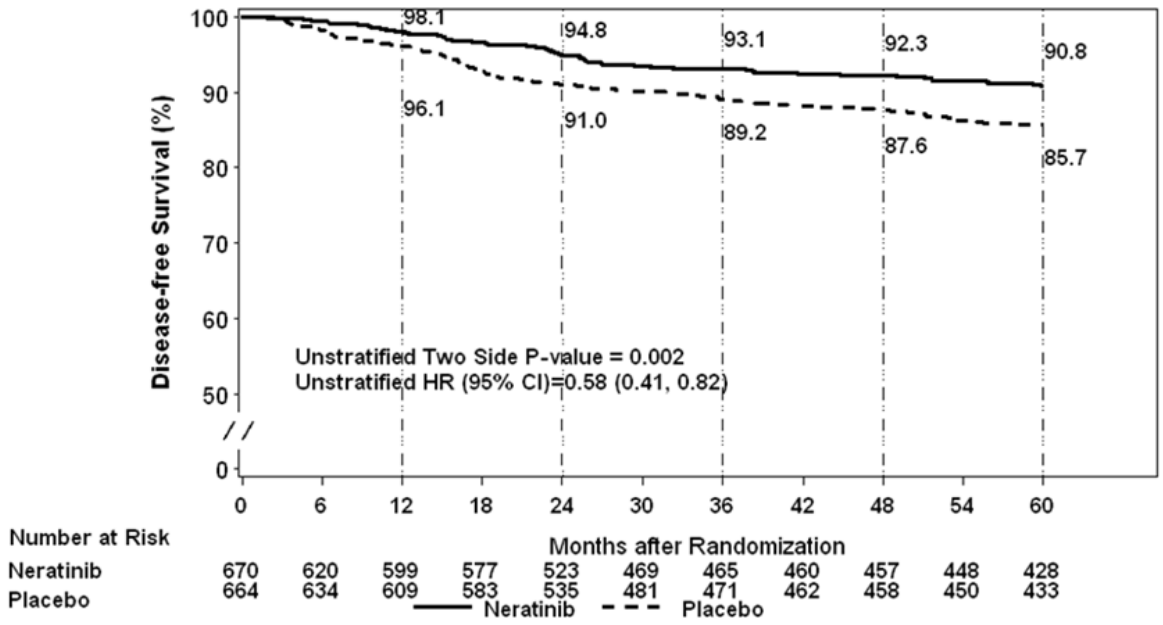
Figure 3. Kaplan-Meier plot of 5-year disease-free survival - ITT population



Of the 2840 women in the ITT population (NERLYNX, n=1420; placebo, n=1420), 1334 had HR+ tumours and were randomised to start study treatment within 1 year of completing trastuzumab (NERLYNX, n=670; placebo, n=664). A protocol-defined subgroup analysis of ExteNET after 2 years showed greater benefit with NERLYNX in patients with HR+ breast cancer, which was also durable at 5 years as shown in the Kaplan-Meier curves below.

Among patients with HR+ tumours who started NERLYNX within 1 year of completing trastuzumab, there was an absolute iDFS benefit of 4.5% with NERLYNX after 2 years' follow-up [hazard ratio 0.49; 95% CI 0.30–0.78; p=0.002]. Treatment benefit was durable with an absolute iDFS benefit of 5.1% with NERLYNX after 5 years' follow-up [hazard ratio 0.58; 95% CI 0.41-0.82; p=0.002]. Kaplan-Meier curves for iDFS (2 and 5 years) separated early and maintained separation (Figure 4).

Figure 4: ITT Population: 5-Year Analysis, Invasive Disease Free Survival (iDFS) Hormone Receptor Positive Patients (Who Completed Trastuzumab within 1 Year of Initiating NERLYNX Therapy)



Of the 1334 women who had HR+ tumours, an exploratory subset of patients (n=295) were randomised to start study treatment within 1 year of completing trastuzumab and did not achieve pathological complete response (pCR) after neoadjuvant therapy (NERLYNX, n=131; placebo, n=164). Baseline characteristics for this subgroup are described in Table 12.

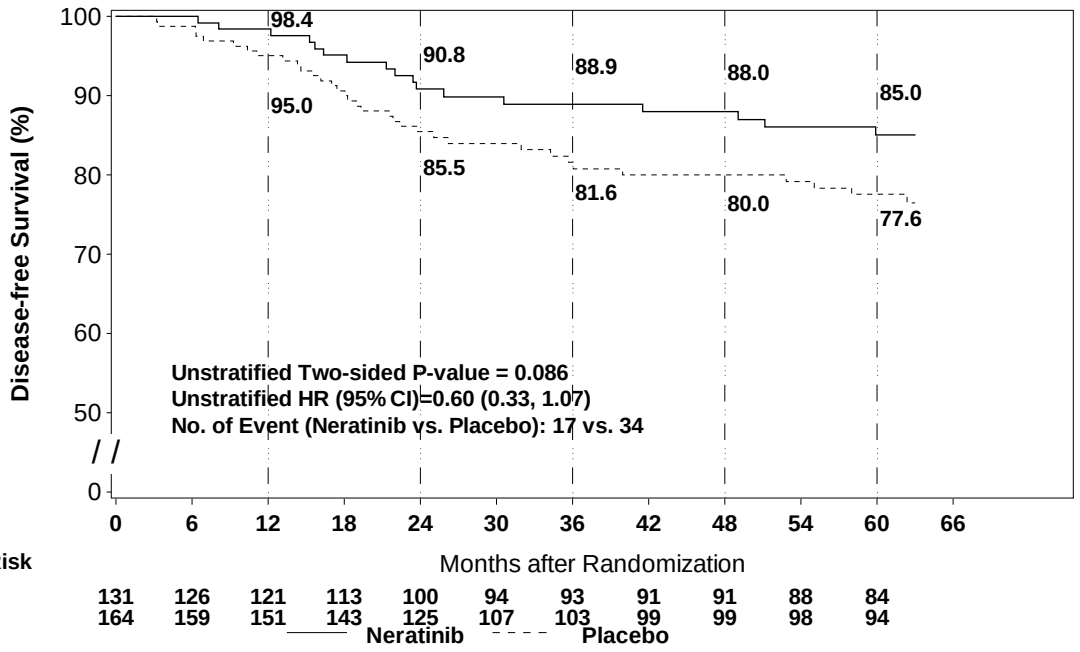
Table 12 Baseline disease characteristics in the ExteNET trial; ITT population versus subgroup of patients who are HR+ and ≤1 year from last dose of trastuzumab to randomisation and did not achieve pCR after neoadjuvant therapy

Characteristic	ITT population		HR+ and ≤1 year from last dose of trastuzumab to randomisation without achieving pCR after neoadjuvant therapy	
	NERLYNX (N=1408)	Placebo (N=1408)	NERLYNX (N=131)	Placebo (N=164)
Nodal Status, n (%)				
Negative	335 (24)	336 (24)	15 (11)	20 (12)
Positive	1085 (76)	1084 (76)	116 (89)	144 (88)
Hormone Receptor Status, n (%)				
Positive	816 (57.5)	815 (57.4)	131 (100)	164 (100)
Negative	604 (42.5)	605 (42.6)	–	–
Prior trastuzumab regimen, n (%)				
Concurrent	884 (62)	886 (62)	90 (69)	111 (68)
Sequential	536 (38)	534 (38)	41 (31)	53 (32)
Median (range) time from last trastuzumab dose to randomisation, months	4.4 (0.2, 30.9)	4.6 (0.3, 40.6)	3.0 (0.4, 12.0)	2.8 (0.3, 11.9)

Source: CSR 3144A2-3004-WW Table 13, pages 109–110; Gnant et al. (2018) Table 1

In patients who had received prior neoadjuvant therapy and did not achieve a pCR, there was an absolute iDFS benefit of 4.6% with NERLYNX at 2 years [hazard ratio 0.64; 95% CI 0.30, 1.29], and 7.4% with NERLYNX after 5-year follow-up [hazard ratio 0.60; 95% CI 0.33, 1.07] (Figure 5).

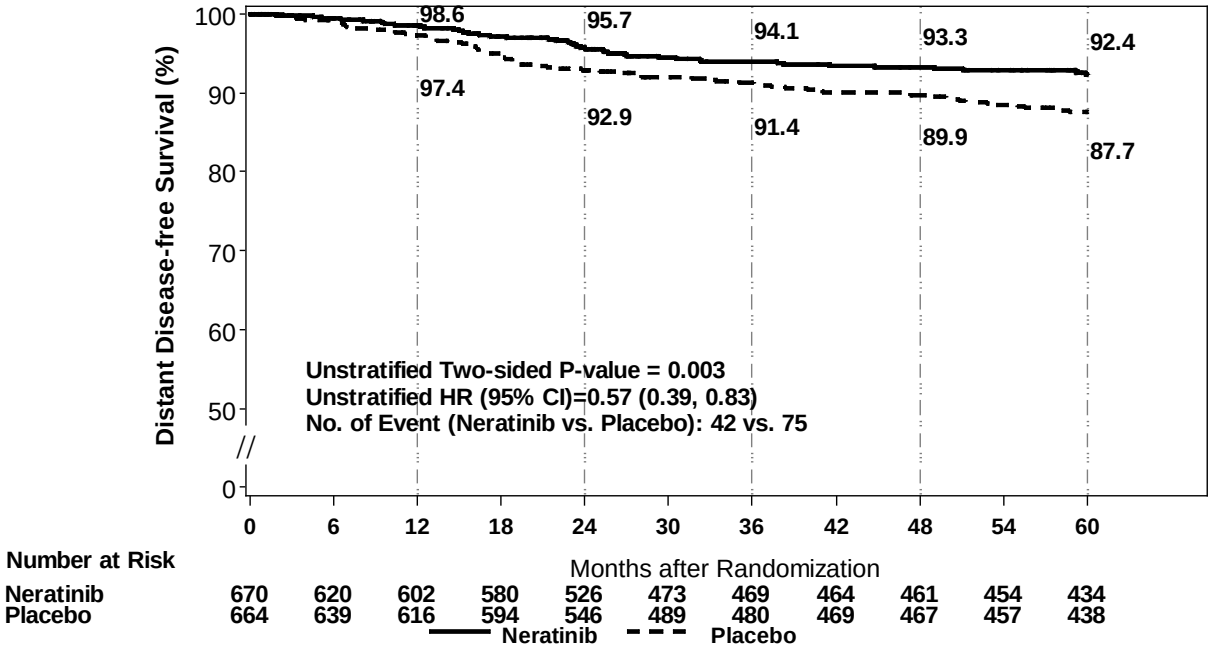
Figure 5 **5-year invasive disease-free survival in patients with HR+ tumours who started treatment within 1 year of completing trastuzumab and who did not have a pCR after neoadjuvant therapy (exploratory subset) (n=295)**



In the subgroup of patients with HR+ disease who commenced NERLYNX ≤ one year after completing trastuzumab therapy, an absolute DDFS benefit of 3.2% was evident with NERLYNX after 2 years [hazard ratio 0.53; 95% CI 0.31–0.88; p=0.015], and 4.7% after 5 years [hazard ratio 0.57; 95% CI 0.39–0.83; p=0.003] (Figure 6).

The number of CNS recurrence events was low at both 2 years (NERLYNX, n=2; placebo, n=6) and 5 years (NERLYNX, n=4; placebo, n=12); the cumulative incidence of CNS recurrences at 2 years was 0.34% with NERLYNX and 1.01% with placebo (p=0.187), and at 5 years was 0.69% and 2.09% (p=0.055), respectively (subgroup of patients with HR+ disease who started treatment less than one year from completing trastuzumab therapy).

Figure 6 **5-year distant disease free survival in patients with HR+ tumours and ≤1 year from last dose of trastuzumab (n=1334)**



At a median follow-up of 8.06 years, there was no statistically significant difference in OS between the NERLYNX and the placebo arm [HR 0.96 (95% CI: 0.75, 1.22)] in the ITT population. A trend favouring the NERLYNX arm was observed in the HR+ population who were less than one year from completion of trastuzumab [HR 0.83 (95% CI, 0.58, 1.18)].

Advanced or Metastatic Breast Cancer

The safety and efficacy of NERLYNX in combination with capecitabine was studied in NALA (NCT01808573), a randomized, multicenter, open-label clinical trial in patients (n=621) with metastatic HER2 positive breast cancer who had received 2 or more prior anti-HER2 based regimens in the metastatic setting. HER2 expression was based on archival tissue tested at a central laboratory prior to enrollment. HER2 positivity was defined as a HER2 immunohistochemistry (IHC) score of 3+ or IHC 2+ with confirmatory in situ hybridization (ISH) positive. Fifty-nine percent of these patients were hormone receptor positive (HR+) and 41% were hormone receptor negative (HR-); 69% had received two prior anti-HER2 based regimens, 31% had received three or more prior anti-HER2 based regimens, 81% had visceral disease, and 19% had non-visceral-only disease. Patients with asymptomatic or stable brain metastases were included in NALA trial (16%).

Patients were randomized (1:1) to receive NERLYNX 240 mg orally once daily on Days 1–21 in combination with capecitabine 750 mg/m^2 given orally twice daily on Days 1–14 for each 21–day cycle (n=307) or lapatinib 1250 mg orally once daily Days 1–21 in combination with capecitabine 1000 mg/m^2 given orally twice daily on Days 1–14 for each 21-day cycle (n=314). Patients were treated until disease progression or unacceptable toxicity.

The efficacy results from the NALA trial are summarized in Table 13, Figure 7, and Figure 8.

Table 13. Efficacy Results – NALA Trial (Central Assessment)

	NERLYNX + Capecitabine (n=307)	**Lapatinib + Capecitabine (n=314)**
Progression-Free Survival (PFS)		
Number of Events (%)	210 (68.4)	223 (71.0)
Median PFS, months (95% CI)	5.6 (4.9, 6.9)	5.5 (4.3, 5.6)
HR (95% CI)*	0.76 (0.63,0.93)	
p-value†	0.0059	
PFS rates at 12 months, % (95% CI)	29 (23, 35)	15 (10, 20)
PFS rates at 24 months, % (95% CI)‡	12 (7, 18)	3 (1, 8)
Overall Survival (OS)		
Number of Events (%)	192 (62.5)	218 (69.4)
Median OS, months (95% CI)	21.0 (17.7, 23.8)	18.7 (15.5, 21.2)
HR (95% CI)*	0.88 (0.72, 1.07)	
p-value†	0.2086	
Objective Response Rate (ORR)§		
ORR, % (95% CI)	32.8 (27.1, 38.9)	26.7 (21.5, 32.4)
Duration of Response (DOR)		
Median DOR, months (95% CI)	8.5 (5.6, 11.2)	5.6 (4.2, 6.4)

HR=Hazard Ratio

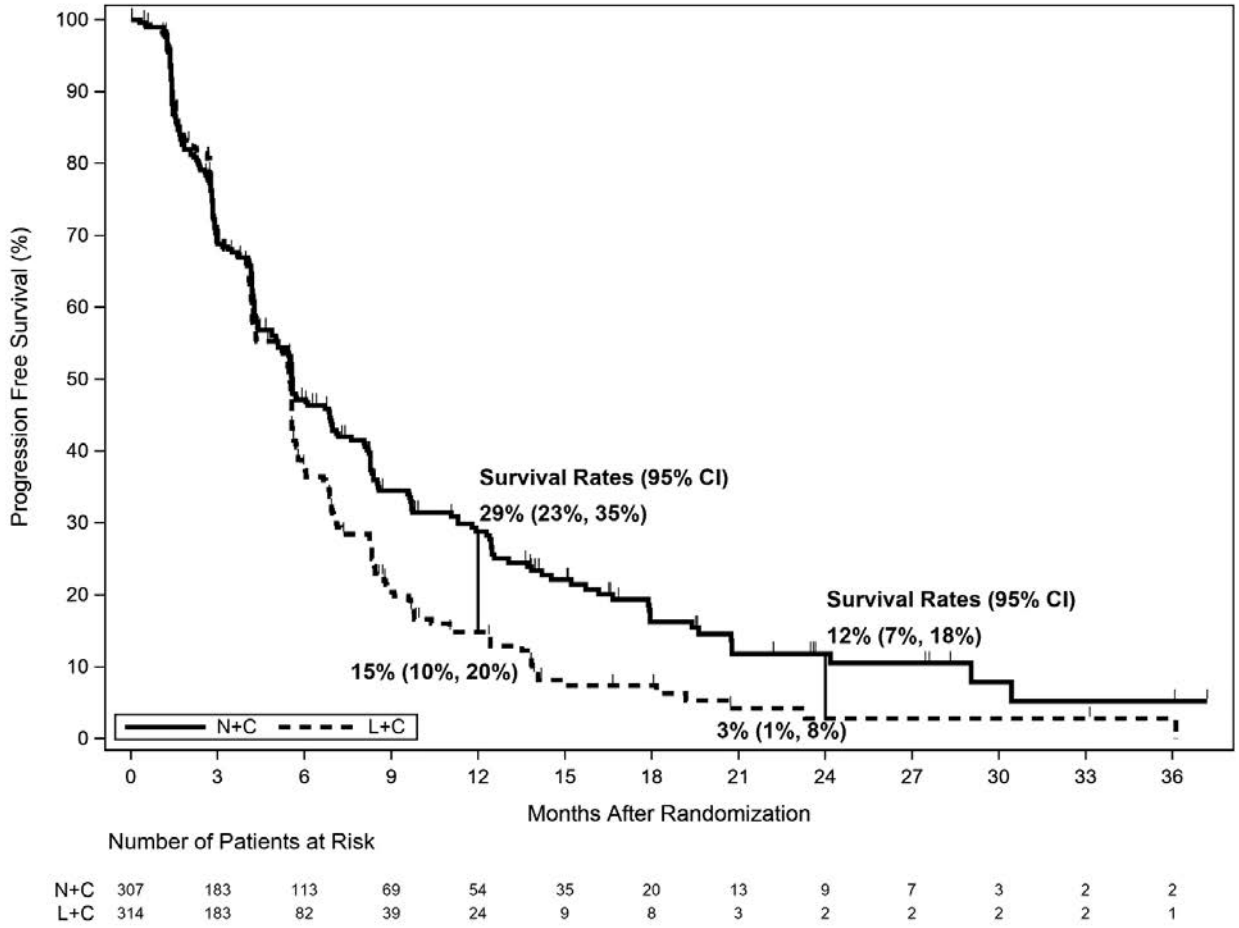
* Hazard ratio is presented as NERLYNX plus Capecitabine (N+C) vs Lapatinib plus Capecitabine (L+C).

† Stratified log-rank test

‡ The total number of patients remaining on study at 24 months is 11; with 9 patients on N+C and 2 patients on L+C.

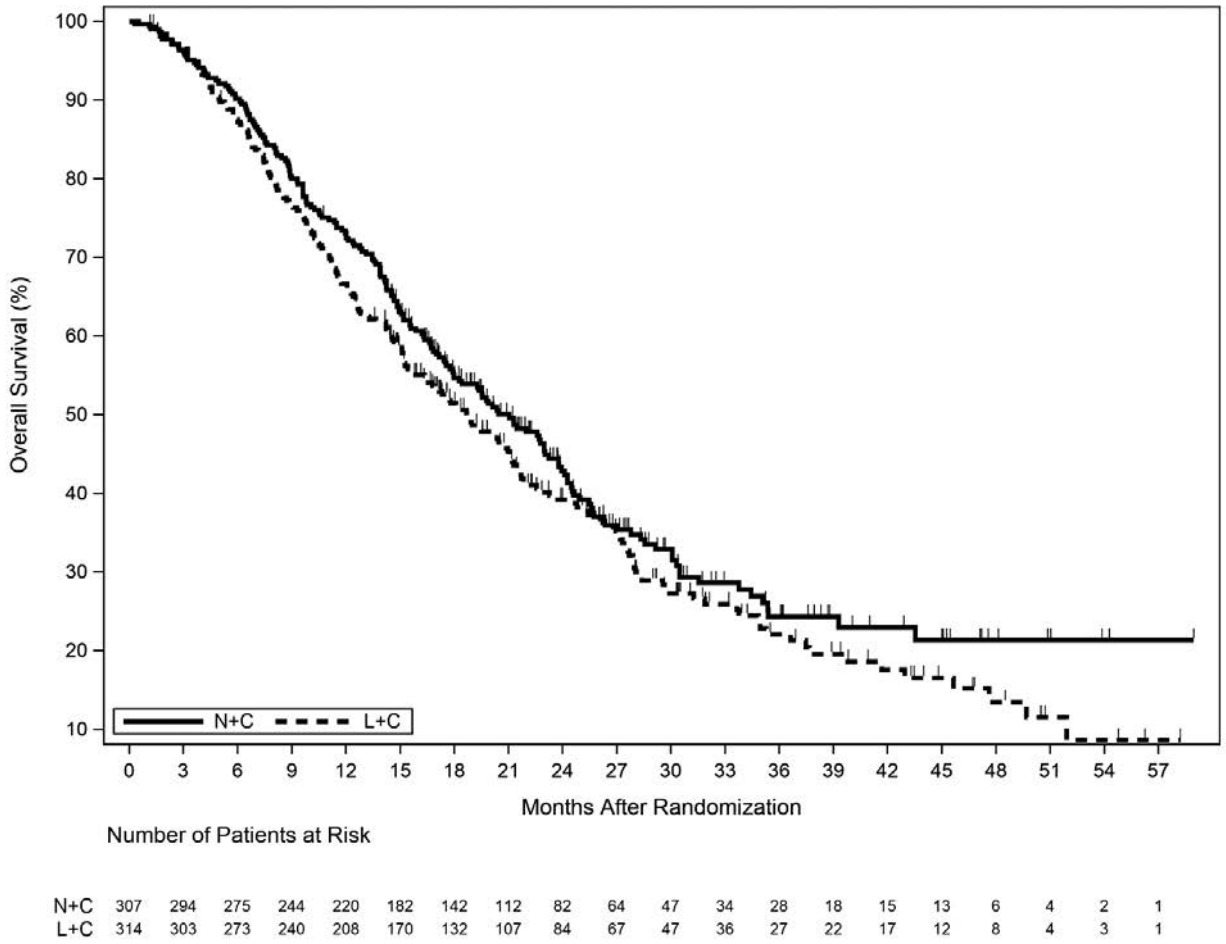
§ Confirmed ORR in patients with measurable disease at screening (256 in the N+C arm and 270 in the L+C arm).

Figure 7. Progression-Free Survival (Central Assessment - ITT Population)



CI=Confidence Interval; ITT=Intent to Treat; L+C=Lapatinib plus Capecitabine; N+C=NERLYNX plus Capecitabine

Figure 8. Overall Survival (ITT Population)



ITT=Intent to Treat; L+C=Lapatinib plus Capecitabine; N+C=NERLYNX plus Capecitabine

Table 14. Progression-Free Survival Rates - Subgroup Analyses[α]

Population	Number of Events/Total N (%)		PFS Rates (%) at 12 Months (95% CI)	
	NERLYNX + Capecitabine	Lapatinib + Capecitabine	NERLYNX + Capecitabine	Lapatinib + Capecitabine
Disease Location				
Visceral	181/247 (73.3)	185/253 (73.1)	23 (17, 30)	14 (10, 20)
Non Visceral	29/60 (48.3)	38/61 (62.3)	53 (38, 66)	18 (7, 32)
Hormone Receptor Status				
Positive	128/181 (70.7)	115/186 (61.8)	27 (19, 34)	23 (15, 31)
Negative	82/126 (65.1)	108/128 (84.4)	32 (23, 41)	5 (2, 11)

Population	Number of Events/Total N (%)		PFS Rates (%) at 12 Months (95% CI)	
	NERLYNX + Capecitabine	**Lapatinib + Capecitabine**	**NERLYNX + Capecitabine**	**Lapatinib + Capecitabine**
Previous HER2 regimens				
2 regimens	148/215 (68.8)	151/215 (70.2)	26 (20, 33)	13 (8, 19)
≥3 regimens	62/92 (67.4)	72/99 (72.7)	34 (24, 45)	19 (11, 29)

CI=Confidence Interval; PFS=Progression-Free Survival
α Exploratory Analysis

5.2 Pharmacokinetic properties

The mass balance after administration of a single oral dose of 200 mg of neratinib was studied in six healthy subjects.

Absorption
Following oral administration of 240 mg neratinib, absorption was slow and peak plasma concentrations of neratinib occurred around 7 hours after administration. A single dose of 240 mg neratinib taken with food increased C_{max} and AUC by approximately 17% and 23%, respectively, compared with administration in the fasting state. A single oral dose of 240 mg neratinib taken with a meal high in fat increased both C_{max} and AUC by approximately 100%.

Distribution
Binding of neratinib to human plasma proteins, including covalent binding to human serum albumin (HSA), was greater than 98% and independent of concentration. Neratinib bound predominantly to HSA and human alpha-1 acid glycoprotein (AAG). *In vitro, neratinib inhibited P-gp and BCRP at concentrations similar to the expected intestinal concentrations of neratinib.* Neratinib produced no clinically-relevant inhibitory activity towards the transporters, BSEP, OATP1B1*1a, OATP1B3, OAT1, OAT3, OCT1 and OCT2.

Metabolism
Neratinib is metabolised primarily in liver microsomes by CYP3A4 and to a lesser extent by flavin-containing monooxygenase (FMO).

Metabolite profiling in human plasma indicates that after oral administration, neratinib undergoes oxidative metabolism through CYP3A4. Circulating metabolites include neratinib pyridine N-oxide (M3), N-desmethyl neratinib (M6), neratinib dimethylamine N-oxide (M7) and traces of hydroxyl neratinib N-oxide and neratinib bis-N-oxide (M11). Neratinib represents the most prominent component in plasma and systemic exposure to the metabolites (M3, M6, M7 and M11) after oral administration of neratinib is between 10% and 33% lower than parent in healthy subjects. The neratinib metabolites M3, M6, M7 and M11 were shown to have similar or lower potencies to neratinib in either *in vitro* enzyme (binding assays) or cell based assays against cells expressing ERBB1, ERBB2 (HER2) and ERBB4.

Excretion
Following single doses of neratinib, the mean apparent plasma half-life of neratinib was 17 hours in patients.

Following the administration of a single radiolabelled dose of 200 mg neratinib oral solution,

97.1% and 1.1% of the administered dose was recovered in the faeces and urine, respectively. The excretion was rapid and complete, with the majority of the radioactivity (61%) recovered within 96 hours and 98% recovered after 10 days. It is not known if elimination is as unchanged medicine or metabolites.

Pharmacokinetic/pharmacodynamic relationship(s)

Renal impairment
Pharmacokinetic studies in patients with renal impairment or undergoing dialysis have not been carried out. Population pharmacokinetic modelling revealed that creatinine clearance did not explain the variability between patients, hence, no dose modifications are recommended for patients with mild to moderate renal impairment.

Hepatic impairment
Neratinib is extensively metabolised in the liver. In subjects with severe pre-existing hepatic impairment (Child Pugh Class C) without cancer, the clearance of neratinib was decreased by 36% and exposure to neratinib increased by about 3-fold as compared to healthy volunteers.

5.3 Preclinical safety data

Adverse reactions not observed in clinical studies but seen in animals at exposure levels like clinical exposure levels and with possible relevance to clinical use were as follows:

Genotoxicity
NERLYNX was neither clastogenic nor mutagenic in the standard battery of genotoxicity studies.

Neratinib metabolites M3, M6, M7 and M11 are negative in the standard battery of *in vitro* genotoxicity studies.

Carcinogenicity
Neratinib was not carcinogenic in rats up to 10 mg/kg/day (18-30 x the clinical AUC) administered by oral route for 24 months. Neratinib did not show any carcinogenic potential in Tg.rasH2 transgenic mice when administered at oral doses up to $\leq$ 50 mg/kg/day in males and $\leq$125 mg/kg/day in females, resulting in exposures 9-35 x the clinical AUC.

6 PHARMACEUTICAL PARTICULARS

6.1 Incompatibilities

Refer to section **4.5 Interactions with other medicines and other forms of interactions** for further information.

6.2 Shelf life

3 years from manufacturing date

6.3 Special precautions for storage

Store below 30°C. Keep the bottle tightly closed in order to protect from moisture.

6.4 Nature and contents of container

White, 60 mL high density polyethylene (HDPE) round bottle with child-resistant, polypropylene closure, and foil induction inner seal.

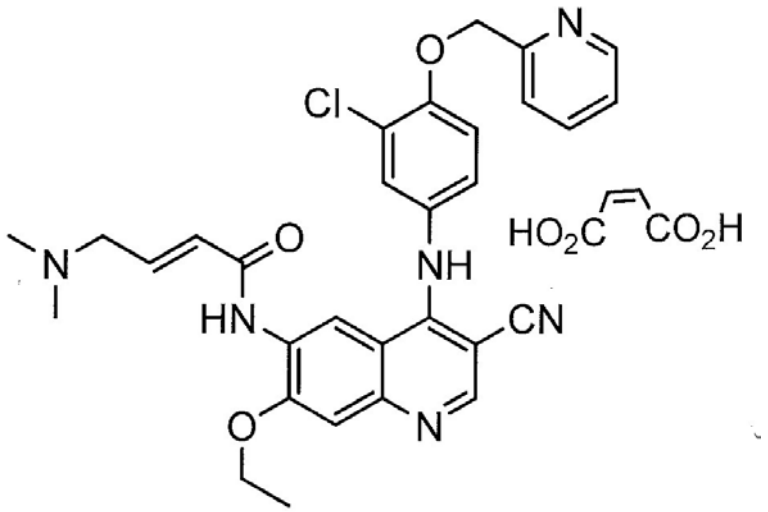
An HDPE desiccant canister with 1 g silica gel is enclosed with the tablets in each bottle.
Each bottle contains either 133 tablets or 180 tablets.

6.5 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.6 Physicochemical properties

Chemical Structure



Chemical Name:
(*E*)-*N*-{4-[3-chloro-4-(pyridin-2-yl methoxy)anilino]-3-cyano-7-ethoxyquinolin-6-yl}-4-(dimethylamino)but-2-enamide maleate

Molecular Weight
673.1 (neratinib maleate)
557.1 (neratinib)

CAS Number
915942-22-2 (neratinib maleate)
698387-09-6 (neratinib)

The active ingredient, Neratinib maleate, is an off-white to yellow powder. Its solubility decreases as pH increases over the range 1.2 - 9.6; it is insoluble at pH above 5.0 (e.g., in water). The API is slightly soluble in ethanol and sparingly soluble in methanol. The dissociation constant is pKa 7.65 and pKa 4.66. The partition coefficient is logP 4.72 and logP 4.47.

7 DATE OF REVISION

04 DECEMBER 2024

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Singapore 498770

Importer
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Bangkok, Thailand