NERLYNX® (neratinib) Film-Coated Tablets 40 mg

1 INDICATIONS AND USAGE

1.1 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 HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy [*see Clinical Studies (13.1)*].

1.2 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 [*see Clinical Studies (13.2)*].

2 DOSAGE AND ADMINISTRATION

2.1 Premedication for Diarrhea

When not using dose escalation *[see Dosage and Administration (2.2)],* administer antidiarrheal prophylaxis during the first 56 days of treatment and initiate with the first dose of NERLYNX [*see Warnings and Precautions (5.1) and Adverse Reactions (6.1)*].

Instruct patients to take loperamide as directed in Table 1. Titrate Loperamide 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 diarrhea occurs despite prophylaxis, treat with additional antidiarrheals, fluids and electrolytes as clinically indicated. NERLYNX dose interruptions and dose reductions may also be required to manage diarrhea [*see Dosage and Administration (2.3)*].

2.2 Recommended Dose and Schedule

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. Treatment with NERLYNX should be initiated within 1 year after completion of trastuzumab therapy.

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.

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 *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

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 diarrhea occurs, treat with antidiarrheal medications, fluids, and electrolytes as clinically indicated. NERLYNX dose interruptions and dose reductions may also be required to manage diarrhea *[see Dosage and Administration (2.3)].*

Administration Instructions

Instruct patients to take NERLYNX at approximately the same time every day. NERLYNX tablets should be swallowed whole (tablets should not be chewed, crushed, or split prior to swallowing).

If a patient misses a dose, do not replace missed dose, and instruct the patient to resume NERLYNX with the next scheduled daily dose.

2.3 Dosage 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 adverse reactions that fail to recover to Grade 0-1 or baseline, with toxicities that result in a treatment delay > 3 weeks, or if 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
Diarrhea *[see Warnings and Precautions (5.1)]*	• Grade 1 diarrhea [increase of <4 stools per day over baseline] • Grade 2 diarrhea [increase of 4–6 stools per day over baseline] lasting ≤5 days • Grade 3 diarrhea [increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; limiting self-care activities of daily living] lasting ≤2 days	• Adjust antidiarrheal 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 diarrhea lasting longer than 5 days‡ • Grade 3 diarrhea lasting longer than 2 days‡	• Interrupt NERLYNX treatment • Diet modifications • Fluid intake of ~2 L/day should be maintained to avoid dehydration • If diarrhea resolves to ≤Grade 1 in one week or less, then resume NERLYNX treatment at the same dose • If diarrhea 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 diarrhea [life-threatening consequences; urgent intervention indicated]	• Permanently discontinue NERLYNX treatment
	• Diarrhea recurs to Grade 2 or higher at 120 mg per day	• Permanently discontinue NERLYNX treatment
Hepatotoxicity *[see Warnings and Precautions (5.2)]*	• 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.

Adverse Reaction	Severity†	Action/Dose Modification
	• Grade 4 ALT or AST (>20× ULN) OR • Grade 4 bilirubin (>10× ULN)	• Permanently discontinue NERLYNX • Evaluate alternative causes
Other *[see Adverse Reactions (6.1)]*	• 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
Diarrhea *[see Warnings and Precautions (5.1)]*	• Grade 1 Diarrhea [Increase of <4 stools per day over baseline] • Grade 2 Diarrhea [Increase of 4–6 stools per day over baseline] lasting ≤5 days • Grade 3 Diarrhea: [Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; limiting self-care and activities of daily living] lasting ≤2 days	• Adjust antidiarrheal 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 Diarrhea: lasting >5 days • Grade 3 Diarrhea lasting >2 days	• Adjust antidiarrheal treatment

Adverse Reaction	Severity†	Action/Dose Modification
	• Grade 4 Diarrhea [Life-threatening consequences; urgent intervention indicated]	• 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 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

Adverse Reaction	Severity†	Action/Dose Modification
Hepatotoxicity *[see Warnings and Precautions (5.2)]*	• 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 *[see Adverse Reactions (6.1)]*	• 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.

2.4 Dosage Modifications for Hepatic Impairment

No dose modifications are recommended for patients with mild to moderate hepatic impairment (Child Pugh A or B). Treatment of patients with severe hepatic impairment (Child Pugh C) is not recommended [*see Use in Specific Populations (8.6) and Clinical Pharmacology (11.3)*].

2.5 Concomitant Use with Gastric Acid Reducing Agents

Proton pump inhibitors (PPI): Avoid concomitant use with NERLYNX [*see Drug Interactions (7.1)*].

H2-receptor antagonists: Take NERLYNX at least 2 hours before the next dose of the H2-receptor antagonist or 10 hours after the H2-receptor antagonist [*see Drug Interactions (7.1)*].

Antacids: Separate dosing of NERLYNX by 3 hours after antacids [*see Drug Interactions (7.1)*].

3 DOSAGE FORMS AND STRENGTHS

Tablets: 40 mg neratinib (equivalent to 48.31 mg of neratinib maleate).

Film-coated, red, oval shaped and debossed with 'W104' on one side and plain on the other side.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Diarrhea

Severe diarrhea and sequelae, such as dehydration, hypotension, and renal failure, occurred during treatment with NERLYNX.

Diarrhea 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 antidiarrheal prophylaxis. In the NERLYNX arm, Grade 3 diarrhea occurred in 40% and Grade 4 diarrhea occurred in 0.1% of patients. The majority of patients (93%) had diarrhea in the first month of treatment, the median time to first onset of Grade ≥ 3 diarrhea was 8 days (range, 1-350), and the median cumulative duration of Grade ≥ 3 diarrhea was 5 days (range, 1-139) [*see Adverse Reactions (6.1)*].

Diarrhea 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-diarrheal prophylaxis in the first 21-day cycle. The majority of patients (70%) had diarrhea in the first 21-day of treatment, the median time to first onset of Grade ≥3 diarrhea was 11 days (range, 2–728) and the median cumulative duration of Grade ≥3 diarrhea was 3 days (range, 1–21). In the NERLYNX plus capecitabine arm, Grade 3 diarrhea occurred in 24% of patients *[see Adverse Reactions (6.1)]*.

Antidiarrheal prophylaxis with loperamide has been shown to lower the incidence and severity of diarrhea. Instruct patients to initiate antidiarrheal prophylaxis with loperamide along with the first dose of NERLYNX and continue during the first two cycles (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 Dosage and Administration (2.1)*]. Consider adding other agents to loperamide as clinically indicated *[see Adverse Reactions (6.1)]*.

Alternatively, a 2-week NERLYNX dose escalation approach prior to initiation of the recommended treatment regimen with NERLYNX can also be considered for diarrhea management *[see Dosage and Administration (2.2)]*. For patients who used NERLYNX dose escalation, the median time to first onset of Grade ≥3 diarrhea was 45 days (range, 15–132) and the median cumulative duration of Grade ≥3 diarrhea was 2.5 days (range, 1–6). Grade 3 diarrhea occurred in 13% of patients who used NERLYNX dose escalation *[see Adverse Reactions (6.1)]*.

Monitor patients for diarrhea and treat with additional antidiarrheals as needed. When severe diarrhea with dehydration occurs, administer fluid and electrolytes as needed, interrupt NERLYNX, and reduce subsequent doses [*see Dosage and Administration (2.3)*]. Perform stool cultures as clinically indicated to exclude infectious causes of Grade 3 or 4 diarrhea or diarrhea of any grade with complicating features (dehydration, fever, neutropenia).

5.2 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 increase > 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 increase >3× ULN, 2% experienced an ALT or AST increase >5× ULN, 7% experienced a bilirubin increase >1.5×

ULN, and 1.3% experienced a bilirubin increase >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 diarrhea or any signs or symptoms of hepatotoxicity, such as worsening of fatigue, nausea, vomiting, right upper quadrant tenderness, fever, rash, or eosinophilia [*see Dosage and Administration (2.3) and Adverse Reactions (6.1)*].

5.3 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, NERLYNX can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of neratinib to pregnant rabbits during organogenesis caused abortions, embryo-fetal death and fetal abnormalities in rabbits at maternal AUCs approximately 0.2 times the AUC in patients receiving the recommended dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for at least 1 month after the last dose. [*see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (11.1)*].

5.4 Left Ventricular Dysfunction

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.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Diarrhea [*see Warnings and Precautions (5.1)*]
- Hepatotoxicity [*see Warnings and Precautions (5.2)*]

6.1 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 antidiarrheal agents to prevent the NERLYNX-related diarrhea. 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 diarrhea, accounting for 17% of NERLYNX-treated patients.

The most common adverse reactions (≥5%) were diarrhea, 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 diarrhea, vomiting, nausea, and abdominal pain.

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

Table 7 summarizes the adverse reactions in ExteNET.

Table 7: 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						
Diarrhea	95	40	0.1	35	2	0
Nausea	43	2	0	22	0.1	0
Abdominal pain[1]	36	2	0	15	0.4	0
Vomiting	26	3	0	8	0.4	0
Stomatitis[2]	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
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[3]	18	0.6	0	9	0	0
Dry skin	6	0	0	2	0	0
Nail disorder[4]	8	0.3	0	2	0	0
Skin fissures	2	0.1	0	0.1	0	0

[1] Includes abdominal pain, abdominal pain upper, and abdominal pain lower

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

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

[4] 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-positive 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 NERLYNX 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%), diarrhea (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 diarrhea, 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 diarrhea, nausea, vomiting, fatigue, and decreased appetite.

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

Table 8 summarizes the adverse reactions in NALA.

Table 8: 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						
Diarrhea	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

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 (%)
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 Diarrhea

CONTROL

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-diarrheal 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 *[see Dosage and Administration (2.1)].* 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 *[see Dosage and Administration (2.2)]*.

Table 9 summarizes the diarrhea adverse reactions for NERLYNX with loperamide prophylaxis and NERLYNX dose escalation.

Table 9: Diarrhea in Patients Treated with NERLYNX with Antidiarrheal 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 Diarrhea, %		
Any Grade	78	98
Grade 2	25	45
Grade 3	32	13
Action Taken, %		

	Loperamide Prophylaxis n=109	NERLYNX Dose Escalation n=60
Discontinuation due to diarrhea	18	3.3

6.2 Post-Marketing Experience

Post marketing analysis has shown that syncope has been reported with a frequency of ≥ 1/100 to < 1/10 (common).

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on NERLYNX

Table 10 includes drug interactions that affect the pharmacokinetics of neratinib.

Table 10: Drug Interactions That Affect NERLYNX

Gastric Acid Reducing Agents	
Clinical Impact	Concomitant use of NERLYNX with a proton pump inhibitor (PPI), H2-receptor antagonist, or antacid may decrease neratinib AUC *[see Clinical Pharmacology (11.3)],* which may reduce NERLYNX activity.
Prevention or Management [see Dosage and Administration (2.5)]	Avoid concomitant use of PPIs.
	Separate administration of NERLYNX at least 2 hours before or 10 hours after the H2-receptor antagonist dose.
	Separate administration of NERLYNX by at least 3 hours after antacids.
Strong CYP3A4 Inhibitors	
Clinical Impact	Concomitant use of NERLYNX with a strong CYP3A4 inhibitor increased neratinib C_{max} and AUC *[see Clinical Pharmacology (11.3)]*, which may increase the risk of NERLYNX toxicity.
Prevention or Management	Avoid concomitant use of NERLYNX with strong CYP3A4 inhibitors.
P-gp and Moderate CYP3A4 Dual Inhibitors	
Clinical Impact	Concomitant use of NERLYNX with a P-gp and moderate CYP3A4 dual inhibitor may increase neratinib C_{max} and AUC *[see Clinical Pharmacology (11.3)]*, which may increase the risk of NERLYNX toxicity.
Prevention or Management	Avoid concomitant use of NERLYNX with P-gp and moderate CYP3A4 dual inhibitors.
Strong or Moderate CYP3A4 Inducers	
Clinical Impact	Concomitant use of NERLYNX with a strong CYP3A4 inducer reduced neratinib C_{max} and AUC *[see Clinical Pharmacology (11.3)]*, which may reduce NERLYNX activity.

Prevention or Management	Avoid concomitant use of NERLYNX with strong or moderate CYP3A4 inducers.

AUC=Area Under Curve; C_{max}=Maximum Concentration

7.2 Effect of NERLYNX on Other Drugs

Certain P-glycoprotein (P-gp) Substrates

Concomitant use of NERLYNX increased concentrations of a P-gp substrate, [*see Clinical Pharmacology (11.3)*], which may increase the risk of adverse reactions of these substrates. Monitor for adverse reactions of certain P-gp substrates for which minimal concentration changes may lead to serious adverse reactions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and the mechanism of action, NERLYNX can cause fetal harm when administered to a pregnant woman [*see Clinical Pharmacology (11.1)*].

There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of neratinib to pregnant rabbits during organogenesis resulted in abortions, embryo-fetal death and fetal abnormalities in rabbits at maternal exposures (AUC) approximately 0.2 times exposures in patients at the recommended dose (*see Data*). Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies in the U.S. general population.

Data

Animal Data

In a fertility and early embryonic development study in female rats, neratinib was administered orally for 15 days before mating to Day 7 of pregnancy, which did not cause embryonic toxicity at doses up to 12 mg/kg/day in the presence of maternal toxicity. A dose of 12 mg/kg/day in rats is approximately 0.5 times the maximum recommended dose of 240 mg/day in patients on a mg/m^2 basis.

In an embryo-fetal development study in rats, pregnant animals received oral doses of neratinib up to 15 mg/kg/day during the period of organogenesis. No effects on embryo-fetal development or survival were observed. Maternal toxicity was evident at 15 mg/kg/day (approximately 0.6 times the AUC in patients receiving the maximum recommended dose of 240 mg/day).

In an embryo-fetal development study in rabbits, pregnant animals received oral doses of neratinib up to 9 mg/kg/day during the period of organogenesis. Administration of neratinib at doses ≥ 6 mg/kg/day resulted in maternal toxicity, abortions and embryo-fetal death (increased resorptions). Neratinib administration resulted in increased incidence of fetal gross external (domed head), soft tissue (dilation of the brain ventricles and ventricular septal defect), and skeletal (misshapen anterior fontanelles and enlarged anterior and/or posterior fontanelles) abnormalities at ≥ 3 mg/kg/day. The $AUC_{(0-t)}$ at 6 mg/kg/day and 9 mg/kg/day in rabbits were approximately 0.5 and 0.8 times, respectively, the AUCs in patients receiving the maximum recommended dose of 240 mg/day.

In a peri and postnatal development study in rats, oral administration of neratinib from gestation day 7 until lactation day 20 resulted in maternal toxicity at ≥ 10 mg/kg/day (approximately 0.4 times the maximum

recommended dose of 240 mg/day in patients on a mg/m^2 basis) including decreased body weights, body weight gains, and food consumption. Effects on long-term memory were observed in male offspring at maternal doses ≥ 5 mg/kg/day (approximately 0.2 times the maximum recommended dose of 240 mg/day in patients on a mg/m^2 basis).

8.2 Lactation

Risk Summary

No data are available regarding the presence of neratinib or its metabolites in human milk or its effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in breastfed infants from NERLYNX, advise lactating women not to breastfeed while taking NERLYNX and for at least 1 month after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy

Based on animal studies, NERLYNX can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*]. Females of reproductive potential should have a pregnancy test prior to starting treatment with NERLYNX.

Contraception

Females

Based on animal studies, NERLYNX can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during treatment with NERLYNX and for at least 1 month after the last dose.

Males

Based on findings in animal reproduction studies, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of NERLYNX [*see Use in Specific Populations (8.1)*].

8.4 Pediatric Use

The safety and efficacy of NERLYNX in pediatric patients has not been established.

8.5 Geriatric Use

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%), diarrhea (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 age group were diarrhea (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.

8.6 Hepatic Impairment

No dose modifications are recommended for patients with mild to moderate hepatic impairment (Child Pugh A or B). Patients with severe, pre-existing hepatic impairment (Child Pugh Class C) experienced a reduction in neratinib clearance and an increase in C_{max} and AUC. Treatment of patients with severe hepatic impairment (Child Pugh C) is not recommended [*see Dosage and Administration (2.3) and Clinical Pharmacology (11.3)*].

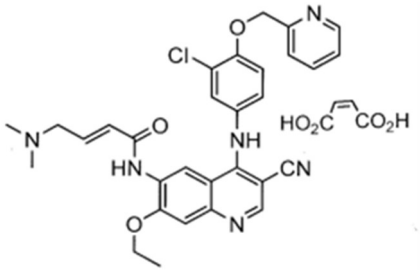
9 OVERDOSAGE

There is no specific antidote, and the benefit of hemodialysis 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 overdose. The adverse reactions experienced by these patients were diarrhea, nausea, vomiting, and dehydration. The frequency and severity of gastrointestinal disorders (diarrhea, abdominal pain, nausea and vomiting) appear to be dose related.

10 DESCRIPTION

NERLYNX (neratinib) immediate release, film-coated tablets for oral administration contain 40 mg of neratinib, equivalent to 48.31 mg neratinib maleate. Neratinib is a member of the 4-anilino quinolidine class of protein kinase inhibitors. The molecular formula for neratinib maleate is $C_{30}H_{29}ClN_6O_3 \bullet C_4H_4O_4$ and the molecular weight is 673.11 Daltons. The chemical name is (E)-N-{4-[3-chloro-4-(pyridin-2-yl methoxy)anilino]-3-cyano-7-ethoxyquinolin-6-yl}-4-(dimethylamino)but-2-enamide maleate, and its structural formula is:



Neratinib maleate is an off-white to yellow powder with pK_as of 7.65 and 4.66. The solubility of neratinib maleate increases dramatically as neratinib becomes protonated at acidic pH. Neratinib maleate is sparingly soluble at pH 1.2 (32.90 mg/mL) and insoluble at approximate pH 5.0 and above (0.08 mg/mL or less).

Inactive ingredients: Tablet Core: colloidal silicon dioxide, mannitol, microcrystalline cellulose, crospovidone, povidone, magnesium stearate, and purified water. Coating: red film coat: polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide red.

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

11 CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

Neratinib is an intracellular kinase inhibitor that irreversibly binds to Epidermal Growth Factor Receptor (EGFR), Human Epidermal Growth Factor Receptor 2 (HER2), and HER4. *In vitro*, neratinib reduces EGFR and HER2 autophosphorylation, downstream MAPK and AKT signaling pathways, and showed antitumor activity in EGFR and/or HER2 expressing carcinoma cell lines. Neratinib human metabolites M3, M6, M7 and M11 inhibited the activity of EGFR, HER2 and HER4 *in vitro*. *In vivo*, oral administration of neratinib inhibited tumor growth in mouse xenograft models with tumor cell lines expressing HER2 and EGFR.

11.2 Pharmacodynamics

Neratinib exposure-response relationships and the time course of pharmacodynamic response are unknown.

Cardiac Electrophysiology

The effect of NERLYNX on the QTc interval was evaluated in a randomized, placebo and positive controlled, double-blind, single-dose, crossover study in 60 healthy subjects. At 140% the therapeutic exposures of NERLYNX, there was no clinically relevant effect on the QTc interval.

11.3 Pharmacokinetics

Neratinib AUC increases in less than dose proportional manner over a daily dose range of 40 to 400 mg (0.17 to 1.7 times the maximum approved recommended dosage).

Absorption

Peak concentrations of neratinib and major active metabolites M3, M6 and M7 are reached in the range of 2 to 8 hours after oral administration.

Effect of Food

A high-fat meal (approximately 55% fat, 31% carbohydrate, and 14% protein) increased neratinib C_{max} and AUC_{inf} by 70% (90% CI: 1.1 - 2.7) and 120% (90% CI: 1.4 - 3.5), respectively, in healthy subjects compared to fasting conditions. A standard breakfast (approximately 50% carbohydrate, 35% fat, and 15% protein) increased the C_{max} and AUC_{inf} by 20% (90% CI: 0.97 - 1.42) and 10% (90% CI: 1.02 - 1.24), respectively, in healthy subjects. [*See Dosage and Administration (2.2)*]

Distribution

The mean (%CV) apparent volume of distribution at steady-state (V_{ss}/F) was 6433 (19%) L in patients. *In vitro* protein binding of neratinib was greater than 99%, predominantly to serum albumin and alpha-1 acid glycoprotein, and was independent of concentration.

Elimination

The mean (%CV) plasma half-life of neratinib, M3, M6, and M7 was 14.6 (38%), 21.6 (77%), 13.8 (50%) and 10.4 (33%) hours, respectively, in healthy subjects. The mean elimination half-life of neratinib ranged from 7 to 17 hours following a single oral dose in patients. The mean (%CV) CL/F after first dose and at steady state (day 21) were 216 (34%) and 281 (40%) L/hour, respectively, in patients.

Metabolism

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

Neratinib represents the most prominent component in plasma. The systemic exposures (AUC) of the active metabolites M3, M6, M7 and M11 were 15%, 33%, 22% and 4% of the systemic neratinib exposure (AUC), respectively, at steady state in healthy subjects.

Excretion

After oral administration of radiolabeled neratinib 200 mg (0.83 times of maximum approved recommended dosage), fecal excretion accounted for approximately 97% and urinary excretion accounted for 1.1% of the total dose. Sixty-one percent of the excreted radioactivity was recovered within 96 hours and 98% was recovered after 10 days.

Specific Populations

Age, sex, race and renal function do not have a clinically significant effect on neratinib pharmacokinetics.

Patients with Hepatic Impairment

Neratinib exposures in patients with mild (Child Pugh A) and moderate hepatic impairment (Child Pugh B) were similar to that in healthy subjects with normal hepatic function. Neratinib C_{max} and AUC increased by 173% and 181%, respectively, in patients with severe hepatic impairment (Child Pugh C) as compared to subjects with normal hepatic function. [*see Dosage and Administration (2.4) and Use in Specific Populations (8.6)*].

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Gastric Acid Reducing Agents: Concomitant use with lansoprazole (proton pump inhibitor) decreased neratinib C_{max} by 71% and AUC by 65%. When NERLYNX was administered 2 hours after ranitidine (H2- receptor antagonist), the neratinib C_{max} was reduced by 57% and AUC by 48%. When NERLYNX was administered 2 hours prior to ranitidine, neratinib C_{max} was reduced by 44% and AUC by 32%. [*See Dosage and Administration (2.5) and Drug Interactions (7.1)*].

Strong CYP3A4 Inhibitors: Concomitant use of ketoconazole (strong inhibitor of CYP3A4 and P-gp inhibitor), increased neratinib C_{max} by 221% and AUC by 381% *[see Drug Interactions (7.1)]*.

P-gp and moderate CYP3A4 Dual Inhibitors: Verapamil (moderate CYP3A4 and P-gp dual inhibitor) increased the C_{max} and AUC of neratinib by 203% and 299%, respectively *[see Drug Interactions (7.1)]*.

Moderate CYP3A4 Inhibitors: Fluconazole (moderate CYP3A4 inhibitor) increased the C_{max} and AUC of neratinib by 30% and 68%, respectively.

Strong and Moderate CYP3A4 Inducers: Concomitant use of rifampin (strong CYP3A4 inducer) decreased neratinib C_{max} by 76% and AUC by 87%. The AUC of active metabolites M6 and M7 were also reduced by 37–49% when compared to NERLYNX administered alone. Efavirenz (moderate CYP3A4 inducer) decreased the C_{max} of neratinib by 36% and AUC by 52% *[see Drug Interactions (7.1)]*.

Effect of NERLYNX on P-gp Transporters: Concomitant use of NERLYNX increased the mean digoxin (P-gp substrate) C_{max} by 54% and AUC by 32% *[see Drug Interactions (7.2)]*.

12 NONCLINICAL TOXICOLOGY

12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A two-year carcinogenicity study was conducted in rats at oral neratinib doses of 1, 3, and 10 mg/kg/day. Neratinib was not carcinogenic in male and female rats at exposure levels > 25 times the AUC in patients receiving the maximum recommended dose of 240 mg/day. Neratinib was not carcinogenic in a 26-week study in Tg.rasH2 transgenic mice when administered daily by oral gavage at doses up to 50 mg/kg/day in males and 125 mg/kg/day in females.

Neratinib was not mutagenic in an *in vitro* bacterial reverse mutation (AMES) assay or clastogenic in an *in vitro* human lymphocyte chromosomal aberration assay or an *in vivo* rat bone marrow micronucleus assay.

In a fertility study in rats, neratinib administration up to 12 mg/kg/day (approximately 0.5 times the maximum recommended dose of 240 mg/day in patients on a mg/m^2 basis) caused no effects on mating or the ability of animals to become pregnant. In repeat-dose toxicity studies in dogs with oral administration of neratinib daily for up to 39 weeks, tubular hypoplasia of the testes was observed at ≥ 0.5 mg/kg/day. This finding was observed at AUCs that were approximately 0.4 times the AUC in patients at the maximum recommended dose of 240 mg.

13 CLINICAL STUDIES

13.1 Extended Adjuvant Treatment in 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.

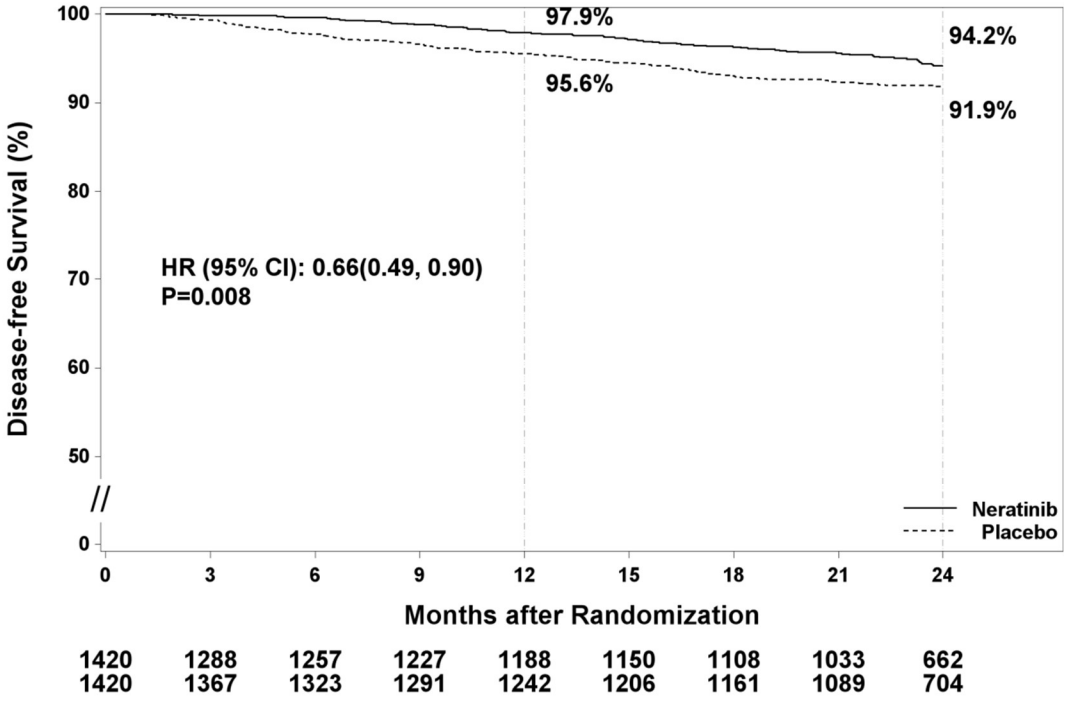
Table 11: Primary efficacy analyses – ITT population

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).

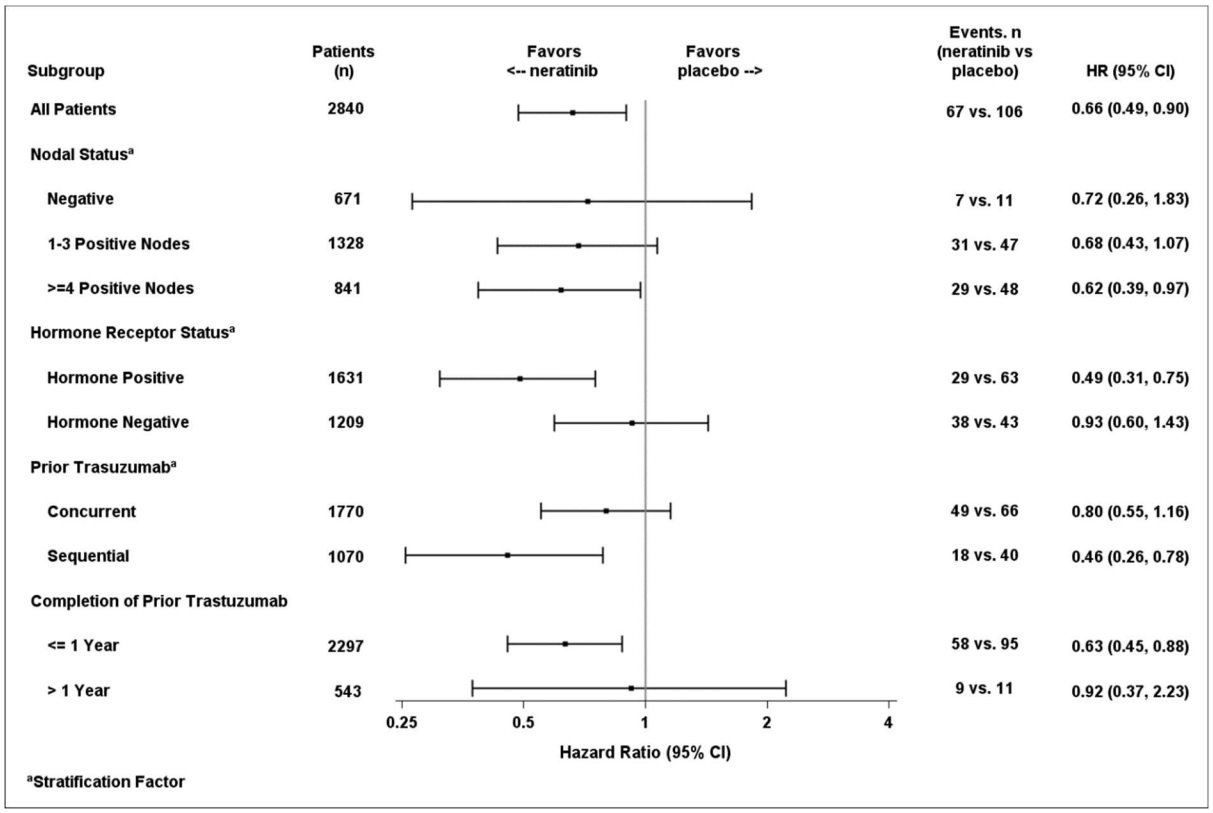
Figure 1: Kaplan-Meier plots for iDFS for the ITT population of study ExteNET (3004)



At Risk									
Neratinib	1420	1288	1257	1227	1188	1150	1108	1033	662
Placebo	1420	1367	1323	1291	1242	1206	1161	1089	704

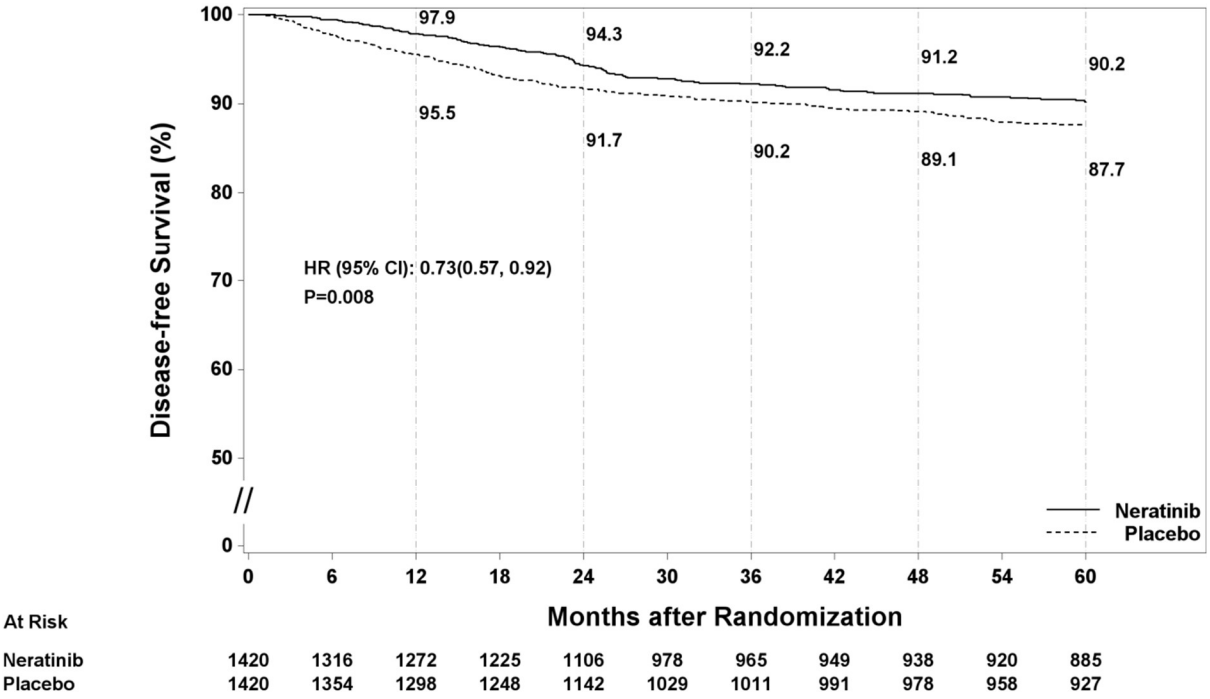
Figure 2 shows the Forrest Plot for iDFS by pre-specified patient subgroup.

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



The benefits of NERLYNX were more apparent in subgroups of patients with hormone receptor-positive disease and in patients who were treated with NERLYNX within 1 year after completion of trastuzumab. 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.

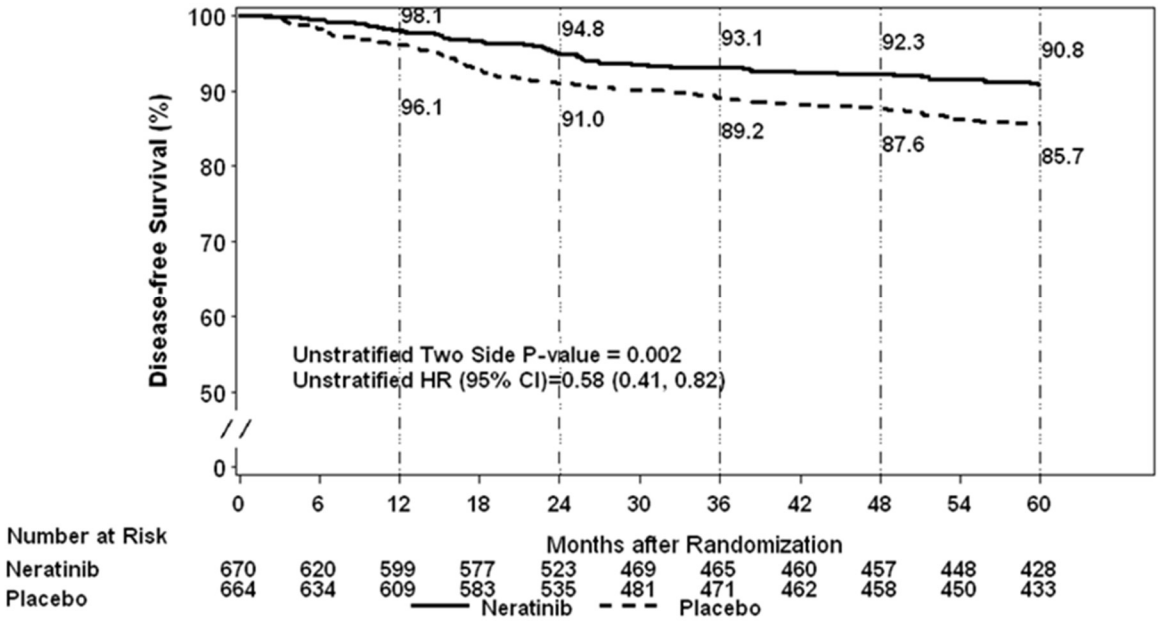
Figure 3: Kaplan-Meier plot of 5-year disease-free survival – ITT population



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)



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)].

13.2 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 12, Figure 5, and Figure 6.

Table 12: 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

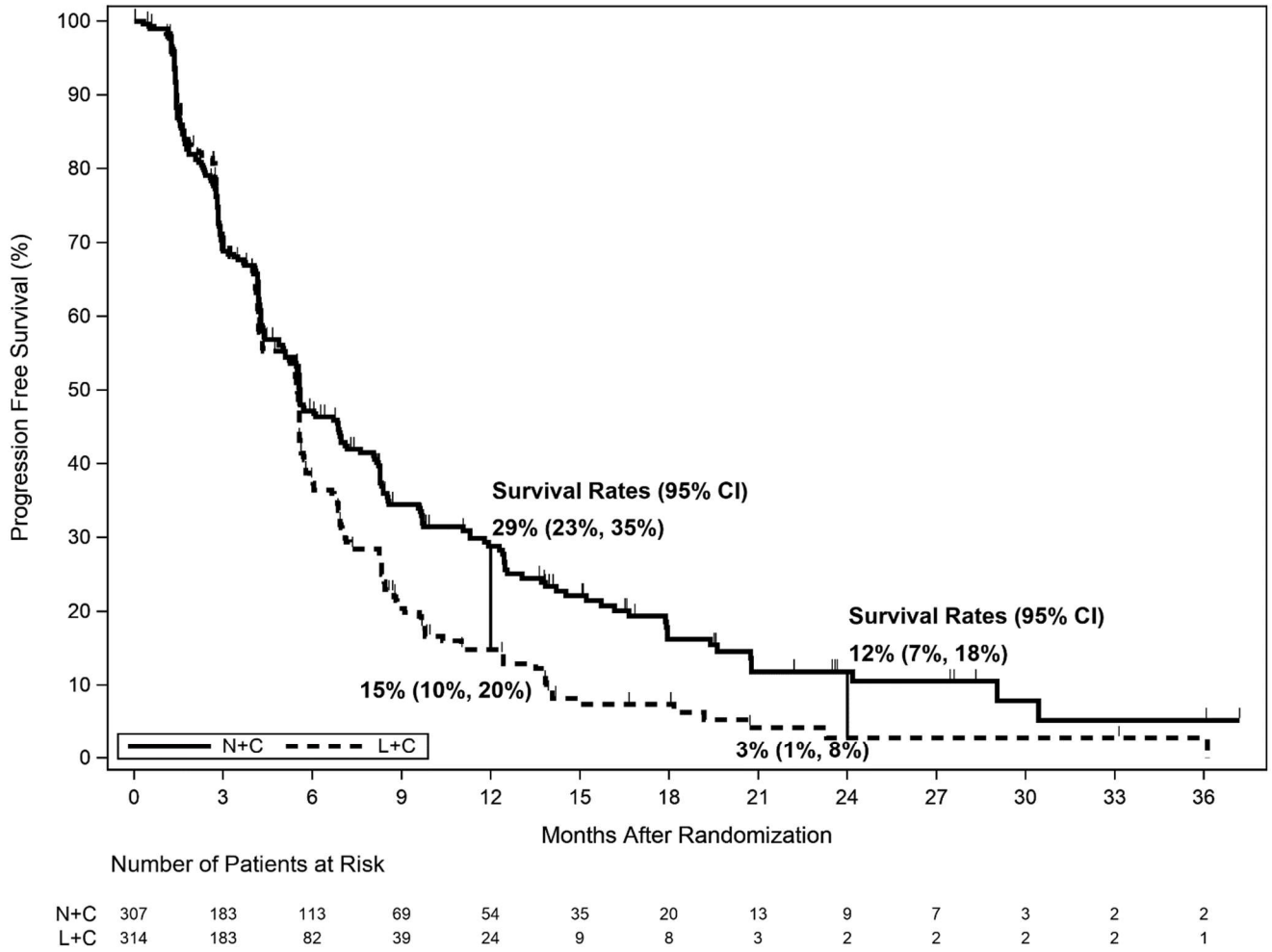
* Hazard ratio is presented as NERLYNX plus Capecitabine (N+C) vs Lapatinib plus Capecitabine (L+C).

† 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.

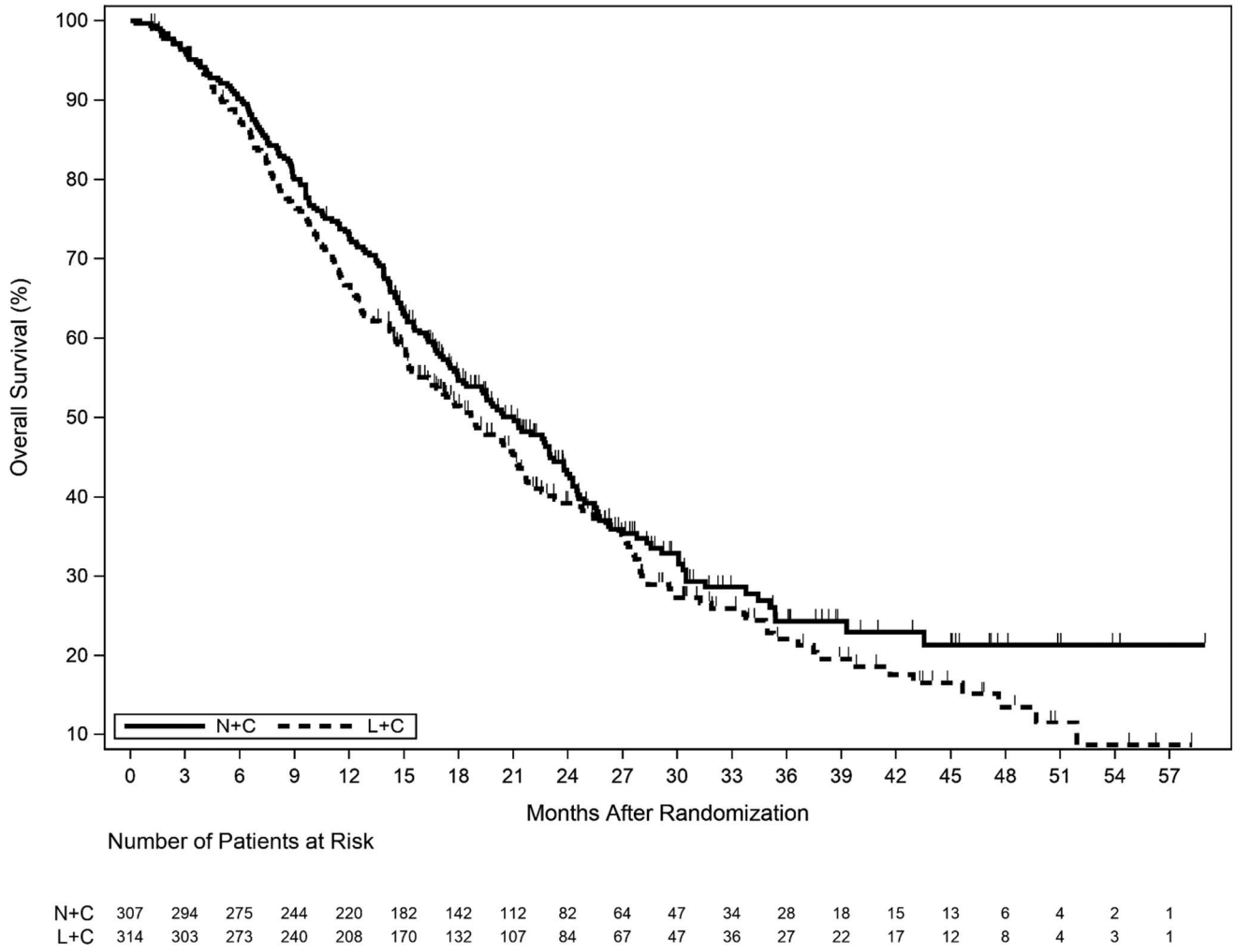
§ Confirmed ORR in patients with measurable disease at screening (256 in the N+C arm and 270 in the L+C arm).

Figure 5: 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 6: Overall Survival (ITT Population)



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

Table 13: 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)
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

14 HOW SUPPLIED/STORAGE AND HANDLING

NERLYNX 40 mg film-coated tablets are red, oval shaped and debossed with 'W104' on one side and plain on the other side.

NERLYNX is available in: HDPE Bottles of 180 tablets

Store at 30ºC or below. Keep the bottle tightly closed. Protect from moisture.

The bottle contains a desiccant canister. Do not swallow the canister

15 PATIENT COUNSELING INFORMATION

Diarrhea

- Inform patients that NERLYNX has been associated with diarrhea which may be severe in some cases.
- When not using dose escalation, instruct patients to initiate antidiarrheal prophylaxis with the first dose of NERLYNX.
- When using dose escalation, instruct patients to initiate 2 weeks of lower dose NERLYNX prior to receiving the recommended full dose of NERLYNX.
- Instruct patients to maintain 1-2 bowel movements per day and on how to use anti-diarrheal treatment regimens.

- Advise patients to inform their healthcare provider immediately if severe (≥Grade 3) diarrhea or diarrhea associated with weakness, dizziness, or fever occurs during treatment with NERLYNX [*see Dosage and Administration (2.1, 2.2) and Warnings and Precautions (5.1)*].

Hepatotoxicity

- Inform patients that NERLYNX has been associated with hepatotoxicity which may be severe in some cases.
- Inform patients that they should report signs and symptoms of liver dysfunction to their healthcare provider immediately [*see Warnings and Precautions (5.2)*].

Embryo-Fetal Toxicity

- Advise females to inform their healthcare provider if they are pregnant or become pregnant. Inform female patients of the risk to a fetus and potential loss of the pregnancy [*see Use in Specific Populations (8.1)*].
- Advise females of reproductive potential to use effective contraception during treatment and for 1 month after receiving the last dose of NERLYNX [*see Warnings and Precautions (5.3) and Use in Specific Populations (8.1, 8.3)*].
- Advise lactating women not to breastfeed during treatment with NERLYNX and for at least 1 month after the last dose [*see Use in Specific Populations (8.2)*].

Drug Interactions

- NERLYNX may interact with many drugs; therefore, advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products [*see Dosage and Administration (2.5) and Clinical Pharmacology (11.3)*].
- NERLYNX may interact with gastric acid reducing agents. Advise patients to avoid concomitant use of proton pump inhibitors. When patients require gastric acid reducing agents, use an H2-receptor antagonist or antacid. Advise patients to separate the dosing of NERLYNX by 3 hours after antacid medicine, and to take NERLYNX at least 2 hours before or 10 hours after a H2-receptor antagonist. [*see Dosage and Administration (2.5) and Drug Interactions (7.1)*].
- NERLYNX may interact with grapefruit. Advise patients to avoid taking NERLYNX with grapefruit products [*see Drug Interactions (7.1)*].

Dosing and Administration

- For patients undergoing extended adjuvant treatment for early-stage breast cancer, instruct patients to take NERLYNX with food at approximately the same time each day consecutively until disease recurrence or for up to one year.
- For patients undergoing treatment for metastatic breast cancer, instruct patients to take NERLYNX with food on days 1–21 of a 21-day cycle, with capecitabine on Days 1–14 of a 21-day cycle until disease progression or unacceptable toxicities.
- If a patient misses a dose, instruct the patient not to replace the missed dose, and to resume NERLYNX with the next scheduled daily dose [*see Dosage and Administration (2.2)*].

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