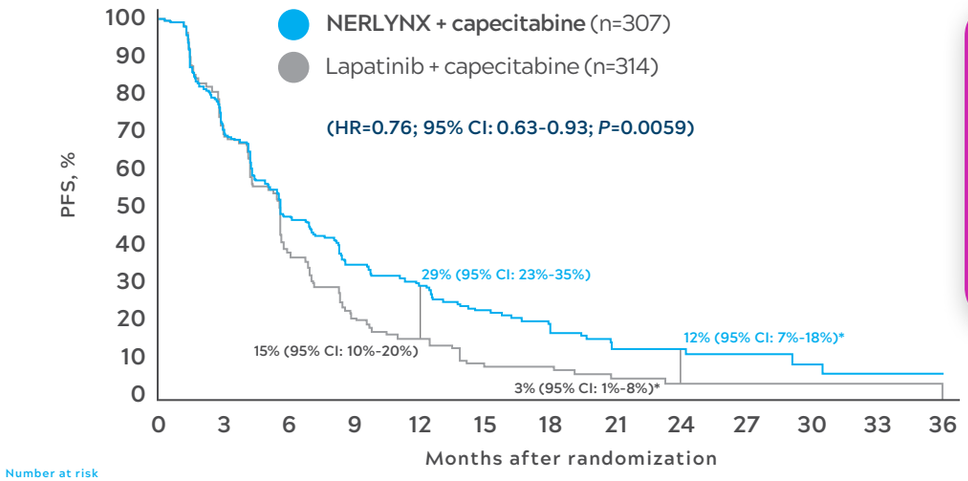
THE FIRST AND ONLY HER2-DIRECTED SMALL MOLECULE APPROVED IN BOTH EARLY-STAGE AND METASTATIC HER2+ BREAST CANCER[1]

nerlynx® (neratinib) tablets

PROTECT AGAINST PROGRESSION[1]

NERLYNX + CAPECITABINE INCREASED PFS

PFS IN PATIENTS WITH HER2+ mBC VS LAPATINIB[1]



Number at risk

NERLYNX + capecitabine	307	183	113	69	54	35	20	13	9	7	3	2	2
Lapatinib + capecitabine	314	183	82	39	24	9	8	3	2	2	2	2	1

29%

PFS RATE AT 12 MONTHS VS 15% WITH LAPATINIB + CAPECITABINE

24% reduction in risk of disease progression or death[1,2]

* The total number of patients remaining in study at 24 months was 11 (9 patients receiving NERLYNX + capecitabine, 2 patients receiving lapatinib + capecitabine).

CI: confidence interval; HER: human epidermal growth factor receptor; HR: hazard ratio; mBC: metastatic breast cancer; PFS: progression-free survival.

INDICATIONS: NERLYNX® (neratinib) tablets, for oral use, is a kinase inhibitor indicated:

- As a single agent, for the extended adjuvant treatment of adult patients with early-stage HER2-positive breast cancer, to follow adjuvant trastuzumab-based therapy.
- In combination with capecitabine, 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.

Select IMPORTANT SAFETY INFORMATION

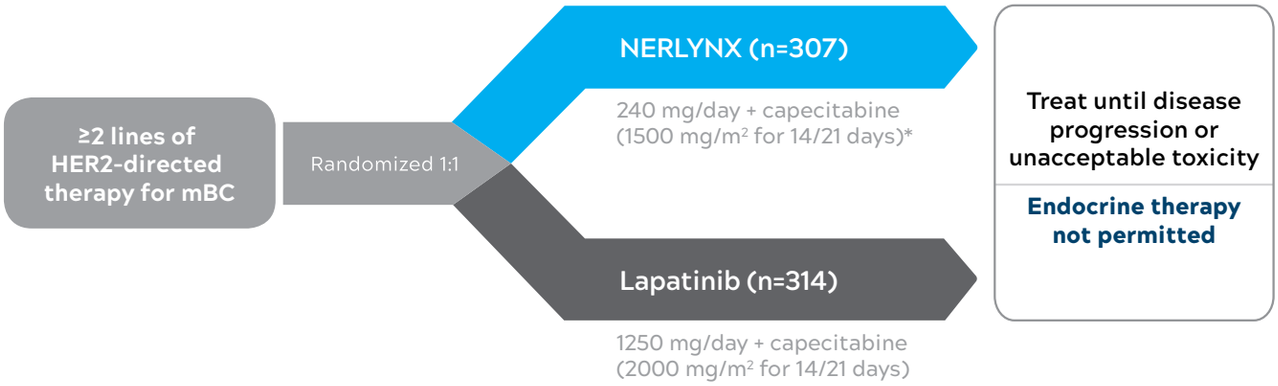
Diarrhea: Manage diarrhea through either NERLYNX dose escalation or loperamide prophylaxis. If diarrhea occurs despite recommended prophylaxis, treat with additional antidiarrheals, fluids, and electrolytes as clinically indicated.

Hepatotoxicity: Monitor liver function tests monthly for the first 3 months of treatment, then every 3 months while on treatment and as clinically indicated.

Embryo-Fetal Toxicity: NERLYNX can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception.

Please see additional IMPORTANT SAFETY INFORMATION throughout this brochure and accompanying Full Prescribing Information.

NALA: a pivotal phase 3, global, multicenter, randomized, open-label study of NERLYNX + capecitabine vs lapatinib + capecitabine[1,2]



- **STUDY POPULATION:** 621 patients with HER2+ mBC (HER2 status was confirmed centrally); all patients had ≥2 prior lines of HER2-directed therapy for mBC; asymptomatic or stable brain metastases permitted
- **CO-PRIMARY ENDPOINTS:** PFS (confirmed centrally) and OS
- **SECONDARY ENDPOINTS:** PFS (confirmed locally), ORR, DoR, time to intervention for symptomatic CNS metastases, safety, health outcomes
- **STRATIFICATION:** Number of prior HER2-directed therapies for mBC; hormone receptor status; disease location; geographic location

Patients in NALA were heavily pretreated: All patients in the NERLYNX + capecitabine treatment arm received prior trastuzumab. In addition, 51.8% of patients received prior trastuzumab emtansine, 40.4% of patients received prior pertuzumab, and 32.9% of patients received trastuzumab emtansine, pertuzumab, and trastuzumab for mBC prior to NERLYNX.[3]

* Loperamide was administered for the first 21 days of treatment with NERLYNX + capecitabine: 4 mg with the first dose of NERLYNX, followed by 2 mg every 4 hours for the first 3 days, followed by 2 mg every 6 to 8 hours through day 21.

CNS: central nervous system; DoR: duration of response; HER: human epidermal growth factor receptor; mBC: metastatic breast cancer; ORR: objective response rate; OS: overall survival; PFS: progression-free survival.

Select IMPORTANT SAFETY INFORMATION

Diarrhea: Manage diarrhea through either NERLYNX dose escalation or loperamide prophylaxis. If diarrhea occurs despite recommended prophylaxis, treat with additional antidiarrheals, fluids, and electrolytes as clinically indicated. Withhold NERLYNX in patients experiencing severe and/or persistent diarrhea. Permanently discontinue NERLYNX in patients experiencing Grade 4 diarrhea or Grade ≥2 diarrhea that occurs after maximal dose reduction.

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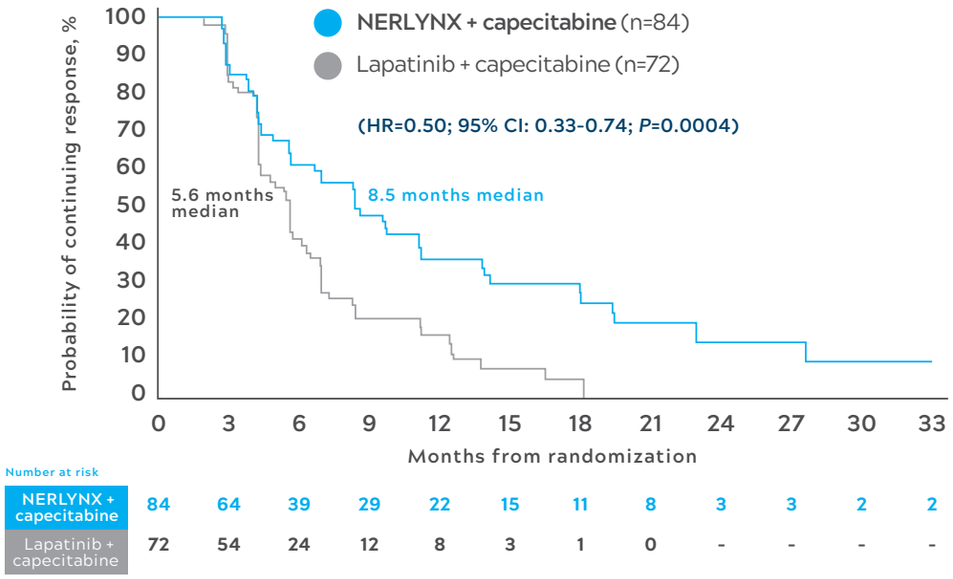
NERLYNX + capecitabine prevents tumor growth[2]

DURATION OF RESPONSE WAS LONGER WITH NERLYNX + CAPECITABINE VS LAPATINIB + CAPECITABINE[2]



Number at risk

NERLYNX + capecitabine	84	64	39	29	22	15	11	8	3	3	2	2
Lapatinib + capecitabine	72	54	24	12	8	3	1	0	-	-	-	-

2.9 MONTH
INCREASE IN MEDIAN DURATION OF RESPONSE WITH NERLYNX + CAPECITABINE

50% reduction in relative risk

- NALA was a pivotal phase 3, global, multicenter, randomized, open-label study of NERLYNX 240 mg/day + capecitabine 1500 mg/m^2 for 14/21 days* (n=307) vs lapatinib 1250 mg/day + capecitabine 2000 mg/m^2 for 14/21 days (n=314)[1,2]

* Loperamide was administered for the first 21 days of treatment with NERLYNX + capecitabine: 4 mg with the first dose of NERLYNX, followed by 2 mg every 4 hours for the first 3 days, followed by 2 mg every 6 to 8 hours through day 21.

CI: confidence interval; HR: hazard ratio.

Select IMPORTANT SAFETY INFORMATION

Hepatotoxicity: Monitor liver function tests monthly for the first 3 months of treatment, then every 3 months while on treatment and as clinically indicated. Withhold NERLYNX in patients experiencing Grade 3 liver abnormalities and permanently discontinue NERLYNX in patients experiencing Grade 4 liver abnormalities.

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NERLYNX safety in NALA[1]

MOST COMMON ADVERSE REACTIONS (≥5%)[1]

	NERLYNX + capecitabine (n=303)		Lapatinib + capecitabine (n=311)	
	All grades, %	Grades ≥3, %	All grades, %	Grades ≥3, %
Diarrhea	83	25*	66	13*
Nausea	53	4.3	42	2.9
Vomiting	46	4	31	1.9
Fatigue/asthenia	45	6	40	4.5
Decreased appetite	35	2.6	22	2.3
Constipation	31	1	13	0
Weight decreased	20	0.3	13	0.6
Dizziness	14	0.3	10	0.6
Back pain	10	0.3	8	0.3
Arthralgia	10	0	6	1
Urinary tract infection	9	0.7	4.2	0.6
Upper respiratory infection	8	0.3	4.5	0.3
Abdominal distention	8	0.3	3.2	0.6
Renal impairment†	7	2 (Grade 3) 0.3 (Grade 4)	1	0 (Grade 3) 0.3 (Grade 4)
Muscle spasms	5	0	1.9	0

* No grade 4 diarrhea.
† Renal impairment includes acute kidney injury, blood creatinine increased, renal failure, and renal impairment.

Please see additional IMPORTANT SAFETY INFORMATION throughout this brochure and accompanying Full Prescribing Information.

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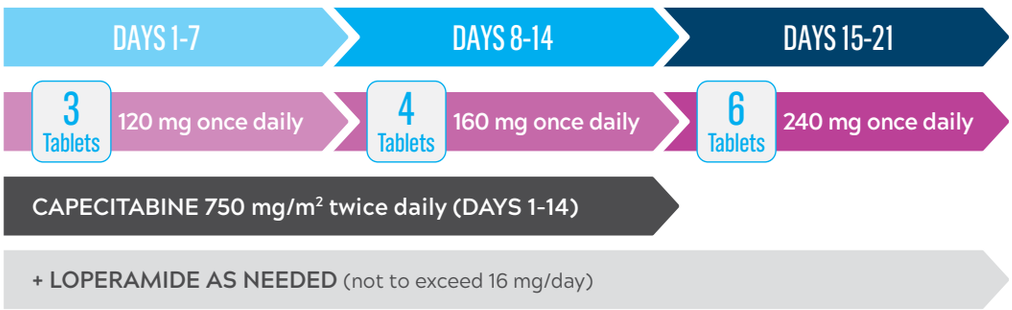
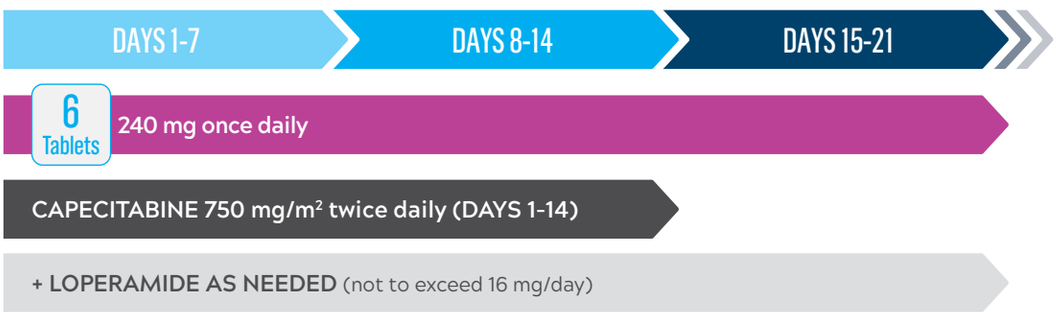
Approach to managing diarrhea: Dose escalation in HER2+ mBC[1]

NERLYNX + CAPECITABINE IS ADMINISTERED IN A 21-DAY DOSING CYCLE

Cycle 1—NERLYNX dose escalation[1]



Cycle 2 and beyond—full recommended NERLYNX dose[1]



- NERLYNX is an oral, once-daily therapy taken continuously until disease progression or unacceptable toxicities[1]
- Instruct patients to take capecitabine with water within 30 minutes after a meal on days 1 to 14 of each 21-day cycle[3,*]
- If diarrhea occurs, treat with antidiarrheal medications, fluids, and electrolytes as clinically indicated[1]

* Refer to the capecitabine Prescribing Information when NERLYNX is used in combination with capecitabine.

HER: human epidermal growth factor receptor; mBC: metastatic breast cancer.

Important Dosing Information[1]: The recommended dose is 240 mg once daily.† Instruct patients to take NERLYNX with food at approximately the same time every day. NERLYNX tablets should be swallowed whole (not be chewed, crushed, or split prior to swallowing).

Patients with metastatic HER2+ breast cancer should take NERLYNX until disease progression or unacceptable toxicities. If a patient misses a dose, do not replace a missed dose, and instruct the patient to resume NERLYNX with the next scheduled daily dose. Dose interruptions and/or dose reductions are recommended based on individual safety and tolerability. Hepatic impairment: reduce the starting dose to 80 mg in patients with severe hepatic impairment.

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.

† When not using dose escalation, start loperamide with the first dose of NERLYNX and continue during the first 2 cycles (56 days) of treatment. Titrate loperamide dosing to achieve 1-2 bowel movements per day.[1]

Please see additional IMPORTANT SAFETY INFORMATION throughout this brochure and accompanying Full Prescribing Information.

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IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS:

- **Diarrhea:** Manage diarrhea through either NERLYNX dose escalation or loperamide prophylaxis. If diarrhea occurs despite recommended prophylaxis, treat with additional antidiarrheals, fluids, and electrolytes as clinically indicated. Withhold NERLYNX in patients experiencing severe and/or persistent diarrhea. Permanently discontinue NERLYNX in patients experiencing Grade 4 diarrhea or Grade ≥2 diarrhea that occurs after maximal dose reduction.
- **Hepatotoxicity:** Monitor liver function tests monthly for the first 3 months of treatment, then every 3 months while on treatment and as clinically indicated. Withhold NERLYNX in patients experiencing Grade 3 liver abnormalities and permanently discontinue NERLYNX in patients experiencing Grade 4 liver abnormalities.
- **Embryo-Fetal Toxicity:** NERLYNX can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception.

UPDATED PRESCRIBING INFORMATION[1]:

- Dose escalation in HER2+ eBC and mBC
- 133-tablet bottle to support dose escalation

ADVERSE REACTIONS: The most common adverse reactions (reported in ≥5% of patients) were:

- NERLYNX as a single agent: 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.
- NERLYNX in combination with capecitabine: 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.

To report SUSPECTED ADVERSE REACTIONS, contact Puma Biotechnology, Inc. at 1-844-NERLYNX (1-844-637-5969) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS:

- Gastric acid reducing agents: Avoid concomitant use with proton pump inhibitors. Separate NERLYNX by at least 2 hours before or 10 hours after H_2-receptor antagonists. Or separate NERLYNX by at least 3 hours after antacids.
- Strong CYP3A4 inhibitors: Avoid concomitant use.
- P-gp and moderate CYP3A4 dual inhibitors: Avoid concomitant use.
- Strong or moderate CYP3A4 inducers: Avoid concomitant use.
- Certain P-gp substrates: Monitor for adverse reactions of P-gp substrates for which minimal concentration change may lead to serious adverse reactions when used concomitantly with NERLYNX.

USE IN SPECIFIC POPULATIONS:

- **Lactation:** Advise women not to breastfeed.

Please see accompanying Full Prescribing Information.

eBC: early-stage breast cancer; HER: human epidermal growth factor receptor; mBC: metastatic breast cancer.

References: 1. NERLYNX [package insert]. Los Angeles, CA: Puma Biotechnology, Inc. **2.** Saura C, Oliveira M, Feng Y-H, et al. Neratinib plus capecitabine versus lapatinib plus capecitabine in HER2-positive metastatic breast cancer previously treated with ≥ 2 HER2-directed regimens: phase III NALA trial. *J Clin Oncol.* 2020;38(27):3138-3149. doi:10.1200/JCO.20.00147 **3.** Puma Biotechnology, Inc. Data on file.

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