nerlynx®
(neratinib) tablets

The **FIRST AND ONLY** HER2-directed small molecule approved in both early-stage and metastatic HER2+ breast cancer[1]

PROTECT AGAINST PROGRESSION IN HER2+ METASTATIC BREAST CANCER[1,*]

After ≥2 prior anti-HER2–based regimens in the metastatic setting

* Median PFS of 5.6 months with NERLYNX + capecitabine vs 5.5 months with lapatinib + capecitabine (HR=0.76; 95% CI: 0.63-0.93; *P*=0.0059).[1]

CI: confidence interval; HER2+: human epidermal growth factor receptor 2-positive; HR: hazard ratio; 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.

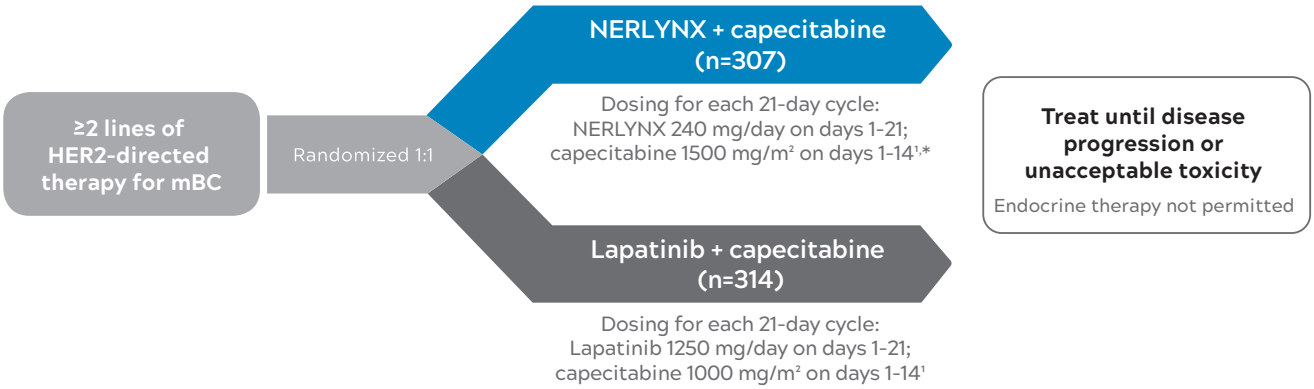
Select IMPORTANT SAFETY INFORMATION

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. 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.

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

NALA: a pivotal phase 3, global, multicenter, randomized, open-label study[2]

STUDY COMPARED NERLYNX + CAPECITABINE WITH 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[1]
- **Co-primary endpoints:** PFS (confirmed centrally) and OS[2]
- **Secondary endpoints:** PFS (confirmed locally), ORR, DoR, CBR, time to intervention for CNS metastases, safety, health-related quality of life[2]
- **Stratification:** number of prior HER2-directed therapies for mBC, HR status, disease location (visceral vs nonvisceral), geographic location[2]

Patients in NALA were heavily pretreated: All patients in the NERLYNX + capecitabine treatment arm received prior trastuzumab. Patients may have received other HER2-directed therapies for mBC prior to receiving NERLYNX (51.8% received prior trastuzumab emtansine; 40.4% received prior pertuzumab; and 32.9% received prior trastuzumab emtansine, pertuzumab, and trastuzumab).[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.[2]

CBR: clinical benefit rate; CNS: central nervous system; DoR: duration of response; HER2+: human epidermal growth factor receptor 2-positive; HR: hormone receptor; mBC: metastatic breast cancer; ORR: objective response rate; OS: overall survival; PFS: progression-free survival.

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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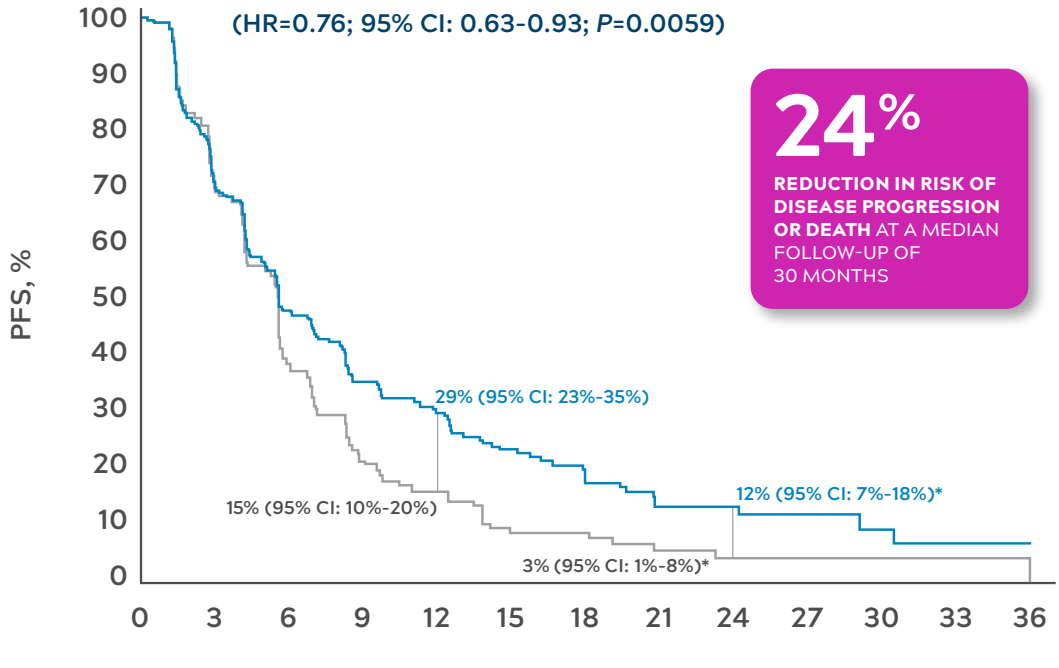
NERLYNX + capecitabine helps protect patients with HER2+ mBC against progression[1,2]

CENTRALLY CONFIRMED PFS IN PATIENTS WITH HER2+ mBC TREATED WITH NERLYNX + CAPECITABINE VS LAPATINIB + CAPECITABINE[1,2]



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

NERLYNX + capecitabine (n=307) Lapatinib + capecitabine (n=314)

29% PFS RATE AT 12 MONTHS WITH NERLYNX + CAPECITABINE VS 15% WITH LAPATINIB + CAPECITABINE[1]

- **NERLYNX + capecitabine significantly improved median PFS vs lapatinib + capecitabine:** 5.6 months with NERLYNX + capecitabine vs 5.5 months with lapatinib + capecitabine (HR=0.76; 95% CI: 0.63-0.93; *P*=0.0059)[1]
- **There was no significant difference in OS between NERLYNX + capecitabine vs lapatinib + capecitabine:** 21.0 months with NERLYNX + capecitabine vs 18.7 months with lapatinib + capecitabine (HR=0.88; 95% CI: 0.72-1.07; *P*=0.2086)[1]

*The total number of patients remaining in the study at 24 months was 11 (9 patients receiving NERLYNX + capecitabine, 2 patients receiving lapatinib + capecitabine).[1]

CI: confidence interval; HER2+: human epidermal growth factor receptor 2-positive; HR: hazard ratio; mBC: metastatic breast cancer; PFS: progression-free survival.

Select IMPORTANT SAFETY INFORMATION

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 and Full Prescribing Information.

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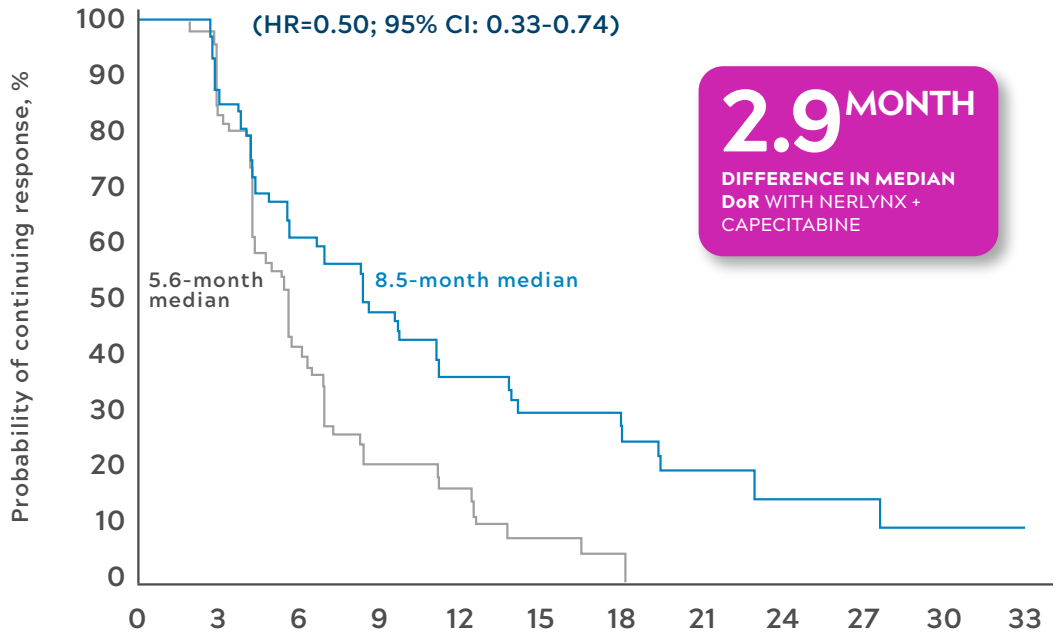
Median DoR observed in patients with HER2+ mBC treated with NERLYNX + capecitabine[2,*]

DoR IN PATIENTS WITH HER2+ mBC TREATED 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	-	-	-	-

NERLYNX + capecitabine (n=84) Lapatinib + capecitabine (n=72)

* Centrally confirmed objective response rate in patients with measurable disease at screening: 32.8% with NERLYNX + capecitabine (n=256; 95% CI: 27.1%-38.9%) vs 26.7% with lapatinib + capecitabine (n=270; 95% CI: 21.5%-32.4%).[1]

CI: confidence interval; DoR: duration of response; HER2+: human epidermal growth factor receptor 2-positive; HR: hazard ratio; mBC: metastatic breast cancer.

Select IMPORTANT SAFETY INFORMATION

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

- 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.

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

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NERLYNX safety for patients with HER2+ mBC in NALA[1]

MOST COMMON ADVERSE REACTIONS REPORTED IN ≥5% OF NERLYNX + CAPECITABINE PATIENTS[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 tract 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

- Discontinuation of NERLYNX or lapatinib due to any adverse event occurred in 10.9% of patients treated with NERLYNX + capecitabine vs 14.5% of patients treated with lapatinib + capecitabine[2]
- The USPI Warnings and Precautions do not include cardiac, pulmonary, or hematologic toxicities, or increased risk for secondary malignancy[1]

DRUG INTERACTIONS[1]

- 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

*No grade 4 diarrhea.[1]

†Renal impairment includes acute kidney injury, blood creatinine increased, renal failure, and renal impairment.[1]

HER2+: human epidermal growth factor receptor 2-positive;
mBC: metastatic breast cancer.

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

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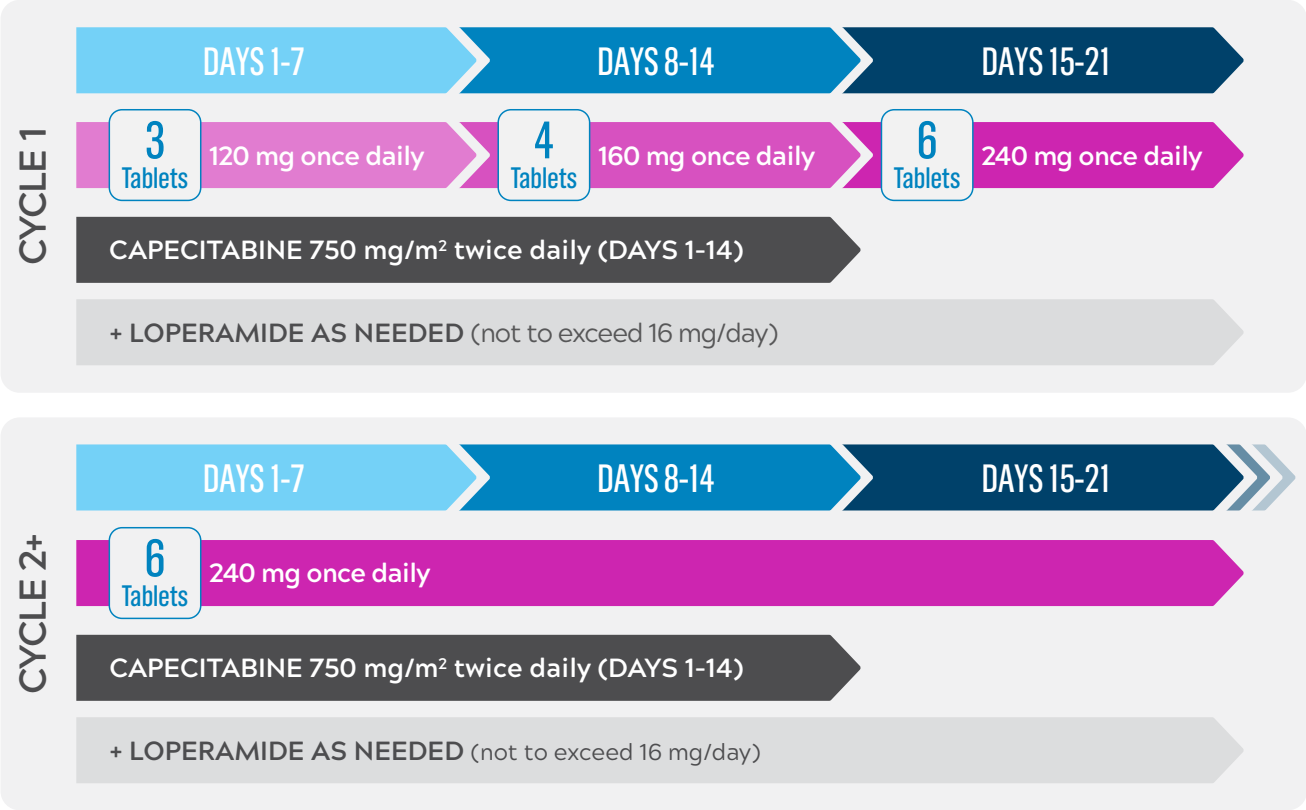
Start NERLYNX at a lower dose and titrate up to the full recommended dose to help manage diarrhea[1]

NERLYNX + CAPECITABINE IS ADMINISTERED IN A 21-DAY DOSING CYCLE[1]



- NERLYNX is an oral once-daily therapy taken continuously until disease progression or unacceptable toxicities[1]
- Capecitabine is taken 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.

DOSE ESCALATION MAY HELP MANAGE AND REDUCE DIARRHEA AND IMPROVE PATIENT TOLERANCE OF NERLYNX[1]

Select IMPORTANT SAFETY INFORMATION

Lactation: Advise women not to breastfeed.

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

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Once-daily oral dosing with NERLYNX[1]

IMPORTANT DOSING AND ADMINISTRATION INFORMATION[1]

- The recommended dose is 240 mg once daily*
- A 2-week dose escalation for NERLYNX may also be initiated
- 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 HER2+ mBC 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

NERLYNX IS AVAILABLE IN A 133-TABLET BOTTLE FOR PATIENTS STARTING DOSE ESCALATION

National Drug Code (NDC) for NERLYNX 40 mg film-coated tablets

Package size	NDC
133 tablets	NDC 70437-240-33
180 tablets	NDC 70437-240-18

Use the 133-tablet NDC for the first month of treatment when initiating dose escalation for NERLYNX.

* If diarrhea occurs, treat with antidiarrheal medications, fluids, and electrolytes as clinically indicated.[1]

mBC: metastatic breast cancer.

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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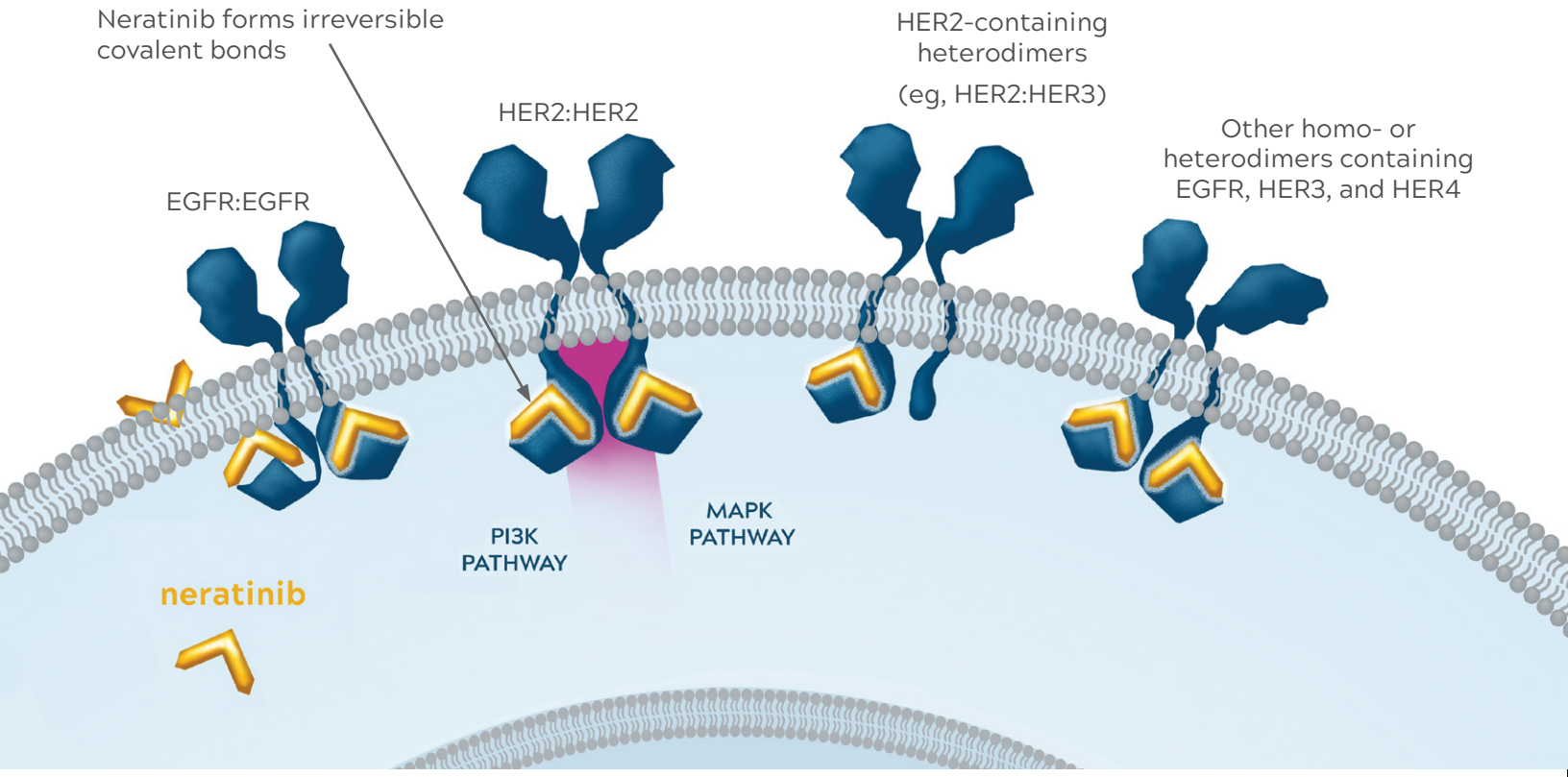
NERLYNX is a small molecule that demonstrates irreversible intracellular pan-HER signaling inhibition[1,4]



PAN-HER RECEPTOR TARGETING WITH NERATINIB[1,4,5]

- Irreversibly inhibits HER1 (EGFR), HER2, and HER4 signaling
- Also inhibits active HER3 heterodimer signaling and downstream signaling

ANTI-TUMOR ACTIVITY OF NERATINIB[1,4]

- Intracellular binding to the receptor tyrosine kinase signaling domain leads to sustained inhibition of signaling, inducing cell cycle arrest and apoptosis
- Inhibition of downstream signaling reduces tumor growth and proliferation and induces tumor cell death in vitro

NERATINIB AND THE BLOOD-BRAIN BARRIER[6]

- Neratinib passed through a cellular model of the blood-brain barrier, reducing the growth of HER2+ breast cancer cells*,†

*** In vitro model consisted of brain and endothelial cells, which were observed over 72 hours.[6]**

† The impact of neratinib on the blood-brain barrier has not been shown in clinical studies. Any impact is hypothesized, and no potential efficacy or safety implications can be drawn.[6]

EGFR: epidermal growth factor receptor; HER: human epidermal growth factor receptor; HER2+: human epidermal growth factor receptor 2-positive; MAPK: mitogen-activated protein kinase; PI3K: phosphatidylinositol 3-kinase.

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.

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

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Indications and Important Safety Information

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.

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.

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 Full Prescribing Information.

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. **4.** Segovia-Mendoza M, González-González ME, Barrera D, Díaz L, García-Becerra R. Efficacy and mechanism of action of the tyrosine kinase inhibitors gefitinib, lapatinib and neratinib in the treatment of HER2-positive breast cancer: preclinical and clinical evidence. *Am J Cancer Res*. 2015;5(9):2531-2561. **5.** Canonici A, Gijsen M, Mullooly M, et al. Neratinib overcomes trastuzumab resistance in HER2 amplified breast cancer. *Oncotarget*. 2013;4(10):1592-1605. doi:10.18632/oncotarget.1148 **6.** Martin T, Alani AS, Connors FA, Bryce RP, Jiang WG. Neratinib as a putative therapy in metastatic brain disease. Poster presented at: San Antonio Breast Cancer Symposium (SABCS); December 5-9, 2017; San Antonio, TX. **7.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Central Nervous System Cancers V1.2023. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed March 24, 2023. To view the most recent and complete version of the guideline, go online to NCCN.org. **8.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V4.2023. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed March 23, 2023. To view the most recent and complete version of the guideline, go online to NCCN.org.

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Guideline recommendations for neratinib (NERLYNX®) tablets[7,8]

NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY (NCCN GUIDELINES®)

NCCN Guidelines® for Central Nervous System Cancers Category 2A* recommended option in combination with capecitabine for HER2+ breast cancer brain metastases[7]

Phase 3 trial

Consider neratinib (NERLYNX) + capecitabine to treat patients with stable, asymptomatic HER2+ breast cancer brain metastases

NALA (NCT01808573)†

Phase 2 trial

Consider neratinib (NERLYNX) + capecitabine to treat patients with progressive HER2+ breast cancer brain metastases

TBCRC 022 (NCT01494662)‡

NCCN Guidelines for Breast Cancer Category 2A* recommended option in combination with capecitabine as a fourth-line and beyond treatment option for HER2+ mBC[8]

NCCN makes no warranties of any kind whatsoever regarding its content, use, or application and disclaims any responsibility for how its content is applied or used, in any way.

*Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.[8]

†A phase 3 trial of neratinib + capecitabine vs lapatinib + capecitabine for patients with HER2+ breast cancer after ≥2 HER2-directed regimens in the metastatic setting.[2]

‡A phase 2 trial of neratinib and capecitabine for patients with HER2+ breast cancer and brain metastases.

The NCCN Guidelines are developed and controlled by an independent third party and may contain information that may differ from or is not included in the Full Prescribing Information for neratinib (NERLYNX).

HER2+: human epidermal growth factor receptor 2-positive; mBC: metastatic breast cancer.

SCAN THE CODE TO DISCOVER THE FULL DATA

Select IMPORTANT SAFETY INFORMATION

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