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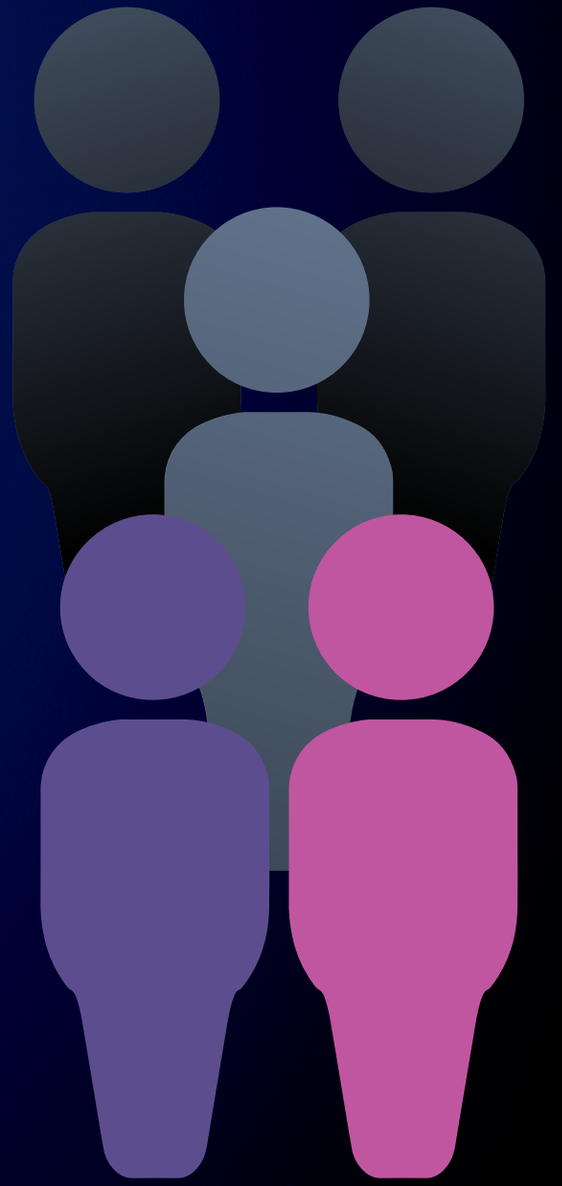
(neratinib) tablets

ExteNET patient outcomes in the ITT population and subgroups of clinical interest

Descriptive analyses of patients with HER2+ HR+ disease who initiated NERLYNX ≤1 year after trastuzumab-based therapy[1]



HER2+: human epidermal growth factor receptor 2-positive; HR+: hormone receptor-positive; ITT: intent to treat.

INDICATION: 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.

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.

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ExteNET was a pivotal phase 3, global, multicenter, randomized, double-blind, placebo-controlled study investigating 1 year of NERLYNX vs placebo after adjuvant trastuzumab-based therapy. The primary endpoint was iDFS at 2 years. Secondary endpoints included an event-driven OS analysis. Antidiarrheals were not protocol mandated.[1,2]

* ExteNET included patients with stages I to IIIC breast cancer.[2]

† Patients who initiated NERLYNX treatment within 1 year of completing trastuzumab-based therapy.[2]

eBC: early-stage breast cancer; HER2+: human epidermal growth factor receptor 2-positive; HR+: hormone receptor-positive; iDFS: invasive disease-free survival; ITT: intent to treat; OS: overall survival; pCR: pathologic complete response.

2840 patients with HER2+ eBC were in the ITT population of ExteNET[2,*]

NERLYNX arm: n=1420

ITT population

HER2+ HR+ ≤1-year patients†

HER2+ HR+ no-pCR ≤1-year patients†

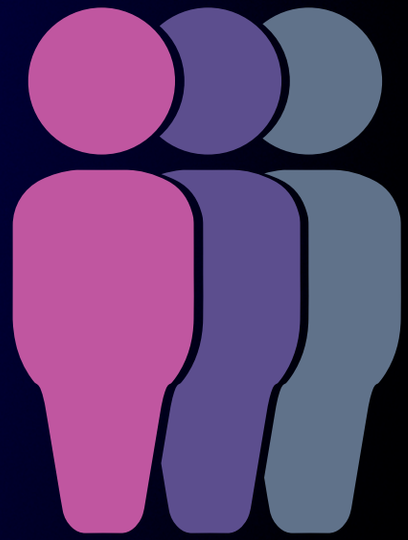
NERLYNX significantly reduced the risk of recurrence in HER2+ eBC[2,‡]

Primary endpoint of ExteNET: iDFS at 2 years in the ITT population (N=2840)[2,§]

34% **reduction in risk of recurrence at 2 years**
(HR=0.66; 95% CI: 0.49-0.90; *P*=0.008)

94.2% with NERLYNX (n=1420; 95% CI: 92.6%-95.4%) vs 91.9% with placebo (n=1420; 95% CI: 90.2%-93.2%)

2.3% absolute benefit in iDFS



After a median follow-up of 8 years, there was no statistically significant difference in OS between the NERLYNX arm and the placebo arm in the ITT population (HR=0.95; 95% CI: 0.75-1.21).[2]

‡ After previous trastuzumab therapy.

§ "Recurrence" was defined as time from randomization to first occurrence of invasive ipsilateral tumor recurrence, invasive contralateral breast cancer, local/regional invasive recurrence, distant recurrence, or death from any cause.[1]

CI: confidence interval; eBC: early-stage breast cancer; HER2+: human epidermal growth factor receptor 2-positive; HR: hazard ratio; iDFS: invasive disease-free survival; ITT: intent to treat; OS: overall survival.

Select IMPORTANT SAFETY INFORMATION

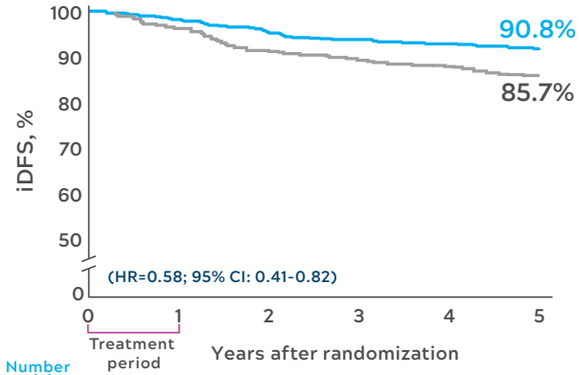
Hepatotoxicity: Monitor liver function tests monthly for the first 3 months of treatment, then every 3 months while on treatment and as clinically indicated. Withhold NERLYNX in patients experiencing Grade 3 liver abnormalities and permanently discontinue NERLYNX in patients experiencing Grade 4 liver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

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

1334 patients were in the HER2+ HR+ ≤1 year subgroup[1]

iDFS

iDFS AT 5 YEARS[1,*]



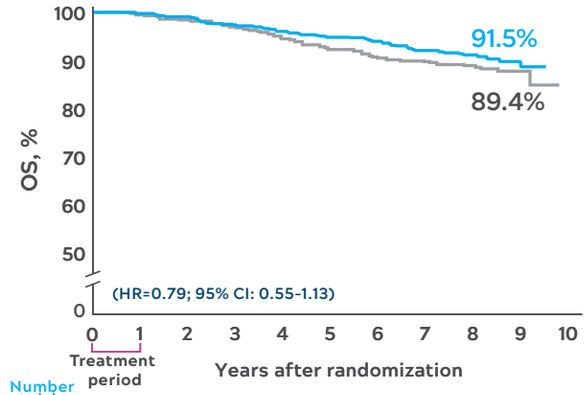
Number at risk											
NERLYNX	670	620	599	577	523	469	465	460	457	448	428
Placebo	664	634	609	583	535	481	471	462	458	450	433

NERLYNX (n=670) Placebo (n=664)

5.1% ABSOLUTE BENEFIT IN iDFS AT 5 YEARS

OS

OS AT 8 YEARS[1,*]



Number at risk											
NERLYNX	670	640	620	578	567	556	534	490	315	78	0
Placebo	664	645	630	589	574	560	537	497	335	78	0

NERLYNX (n=670) Placebo (n=664)

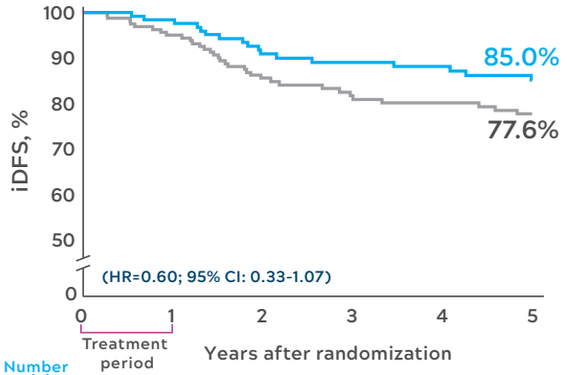
2.1% ABSOLUTE BENEFIT IN OS AT 8 YEARS

Descriptive analyses, not prespecified or powered.[1]

295 patients were in the HER2+ HR+ no-pCR ≤1 year subgroup[1]

iDFS

iDFS AT 5 YEARS[1,*]



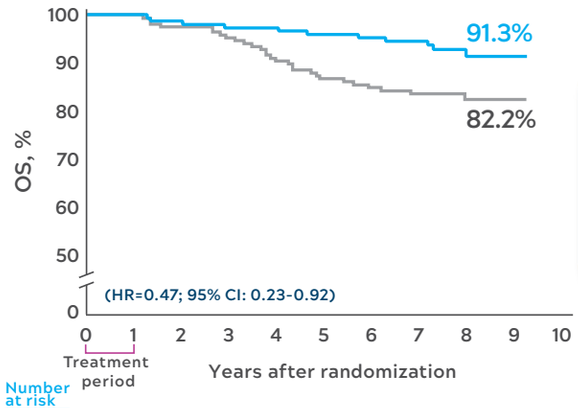
Number at risk											
NERLYNX	131	126	121	113	100	94	93	91	91	88	84
Placebo	164	159	151	143	125	107	103	99	99	98	94

NERLYNX (n=131) Placebo (n=164)

7.4% ABSOLUTE BENEFIT IN iDFS AT 5 YEARS

OS

OS AT 8 YEARS[1,*]



Number at risk											
NERLYNX	131	126	121	116	113	110	106	100	60	14	0
Placebo	164	161	156	143	135	129	123	115	65	12	0

NERLYNX (n=131) Placebo (n=164)

9.1% ABSOLUTE BENEFIT IN OS AT 8 YEARS

Descriptive analyses, not prespecified or powered.[1]

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* Results of ExteNET are supported by descriptive analyses after 5 years of follow-up, with 75% of patients (2117/2840) reconsented. 95% of the patients with HER2+ HR+ disease had concomitant endocrine therapy.[1,3]

CI: confidence interval; HER2+: human epidermal growth factor receptor 2-positive; HR: hazard ratio; HR+: hormone receptor-positive; iDFS: invasive disease-free survival; OS: overall survival; pCR: pathologic complete response.

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.

DOSE ESCALATION IN HER2+ eBC

Start NERLYNX at a lower dose and titrate up to the full recommended dose to help manage diarrhea[2]

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NERLYNX DOSE ESCALATION[2]

DAYS 1-7	DAYS 8-14	DAY 15+
3 Tablets: 120 mg once daily	4 Tablets: 160 mg once daily	6 Tablets: 240 mg once daily

+ LOPERAMIDE AS NEEDED (not to exceed 16 mg/day)*,†

NERLYNX is available in a 133-tablet bottle for patients starting dose escalation[2]

A CROSS-STUDY, DESCRIPTIVE ANALYSIS OF THE DOSE-ESCALATION ARM IN CONTROL (n=60) VS NERLYNX ARM IN ExteNET (n=1408)[2]

>65%

reduction in rate of grade 3 diarrhea[2,*]

Rate of grade 3 diarrhea: 13% with NERLYNX dose escalation vs 40% with NERLYNX in ExteNET.

50%

reduction in median days of grade ≥3 diarrhea[2,*]

Median cumulative days of grade ≥3 diarrhea: 2.5 days with NERLYNX dose escalation vs 5 days with NERLYNX in ExteNET.

>80%

reduction in rate of discontinuations due to diarrhea[2,*]

Treatment discontinuations due to diarrhea: 3.3% with NERLYNX dose escalation vs 17% with NERLYNX in ExteNET.

CONTROL was a phase 2, open-label, nonrandomized, multicenter, multinational study to evaluate the effect of dose escalation or antidiarrheal prophylaxis on diarrhea associated with NERLYNX. NERLYNX dose-escalation arm in CONTROL: n=60.[4]

ExteNET was a pivotal phase 3, global, multicenter, randomized, double-blind, placebo-controlled study. NERLYNX arm in ExteNET: n=1408. Antidiarrheals were not protocol mandated.[1,2]

* Dose-escalation arm (n=60): NERLYNX 120 mg/day on days 1-7, 160 mg/day on days 8-14, 240 mg/day from days 15-364.[4]

† If diarrhea occurs, treat with antidiarrheal medications, fluids, and electrolytes as clinically indicated.[2]

eBC: early-stage breast cancer.

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Indication and Important Safety Information

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INDICATION: 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.

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.

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. Chan A, Moy B, Mansi J, et al. Final efficacy results of neratinib in HER2-positive hormone receptor-positive early-stage breast cancer from the phase III ExteNET trial. *Clin Breast Cancer*. 2021;21(1):80-91.e7. doi:10.1016/j.clbc.2020.09.014 **2.** NERLYNX [package insert]. Los Angeles, CA: Puma Biotechnology, Inc. **3.** Martin M, Holmes FA, Ejlertsen B, et al. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2017;18(12):1688-1700. doi:10.1016/S1470-2045(17)30717-9 **4.** Barcenas CH, Hurvitz SA, Di Palma JA, et al. Improved tolerability of neratinib in patients with HER2-positive early-stage breast cancer: the CONTROL trial. *Ann Oncol*. 2020;31(9):1223-1230. doi:10.1016/j.annonc.2020.05.012

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