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Efficacy and safety outcomes in the ITT population and a select subgroup from the phase 3 ExteNET trial

Descriptive analyses of patients with HER2+ HR- early-stage breast cancer stratified by timing of NERLYNX initiation after trastuzumab-based therapy[1]

HER2+: human epidermal growth factor receptor 2-positive; HR-: hormone receptor-negative; 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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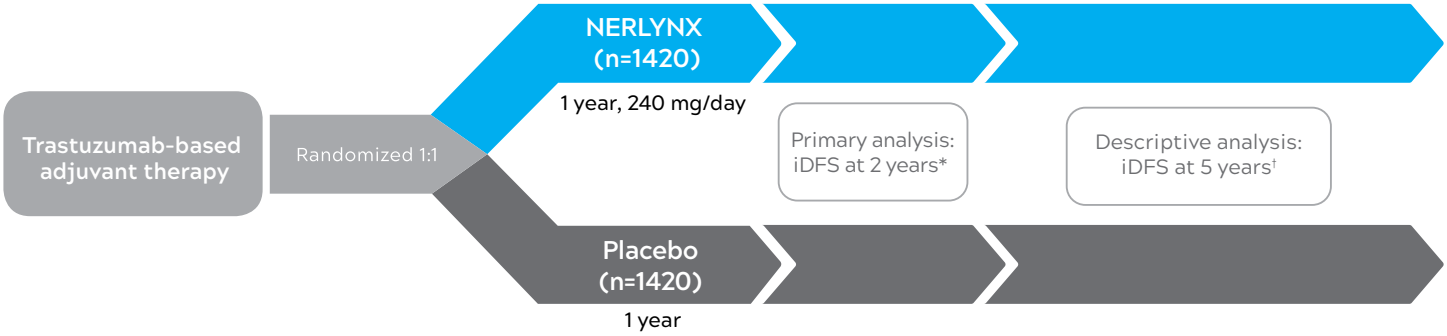
ExteNET TRIAL DESIGN AND PRIMARY ENDPOINT RESULTS

ExteNET was a phase 3, global, randomized, placebo-controlled study[2,3]



PRIMARY ENDPOINT: iDFS in the ITT population (N=2840)[4,*]

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

2.3% absolute benefit in iDFS
- 94.2% with NERLYNX (n=1420; 95% CI: 92.6%-95.4%)
- 91.9% with placebo (n=1420; 95% CI: 90.2%-93.2%)

- **Study population:** 2840 women with HER2+ eBC and locally confirmed hormone receptor status; all patients had prior trastuzumab-based therapy[2,3,‡]
- **Primary endpoint:** iDFS[1,*]
- **Secondary endpoints:** OS, DFS-DCIS, DDFS, time to distant recurrence, CNS metastases, safety[2,§]
- **Stratification:** positive nodes (0, 1-3, or 4+), hormone receptor status, concurrent vs sequential trastuzumab-based therapy[2]

* iDFS was defined as the 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.[2]

† 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.[2,3]

‡ Select exclusion criteria: clinically significant cardiac, gastrointestinal, or psychiatric comorbidities; inability to swallow pills.[3]

§ Antidiarrheal prophylaxis was not mandated in ExteNET.[4]

CI: confidence interval; CNS: central nervous system; DDFS: distant disease-free survival; DFS-DCIS: disease-free survival including ductal carcinoma in situ; eBC: early-stage breast cancer; HER2+: human epidermal growth factor receptor 2-positive; HR: hazard ratio; HR+: hormone receptor-positive; iDFS: invasive disease-free survival; ITT: intent to treat; OS: overall survival.

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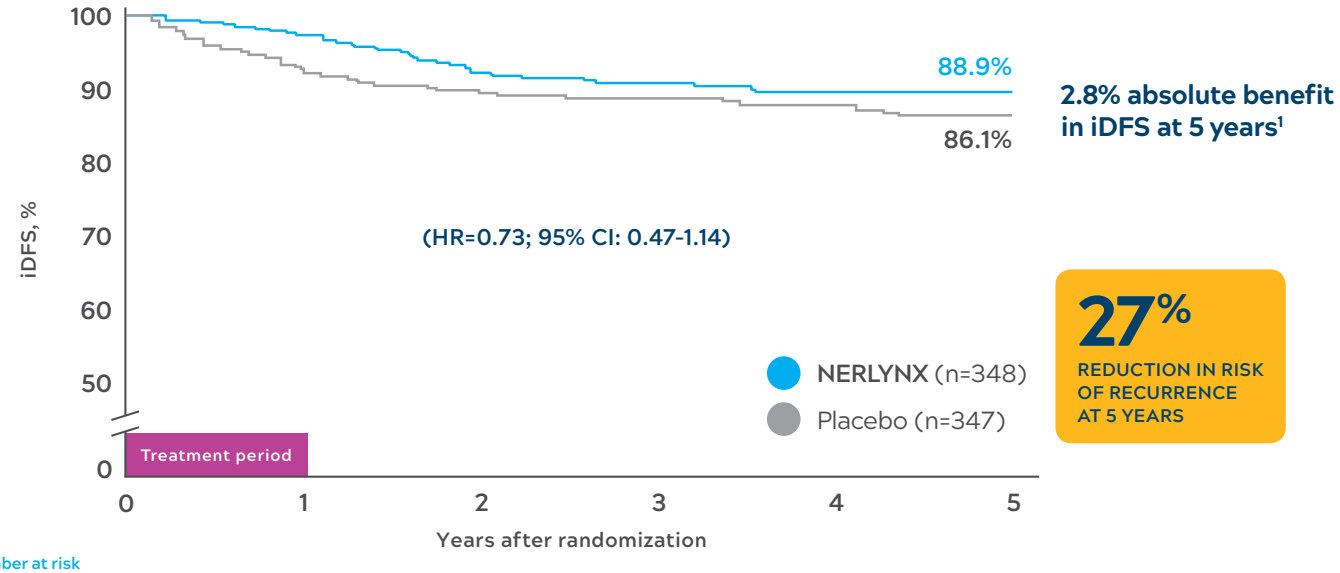
DATA FROM ExteNET DESCRIPTIVE ANALYSES

iDFS in the HER2+ HR− subgroup that initiated NERLYNX within 6 months of completing prior trastuzumab-based therapy[1]

DESCRIPTIVE ANALYSIS OF 5-YEAR iDFS IN THE HER2+ HR- ≤6 MONTHS POST-TRASTUZUMAB SUBGROUP (n=695)[1,*]



2.8% absolute benefit in iDFS at 5 years[1]

27% REDUCTION IN RISK OF RECURRENCE AT 5 YEARS

Number at risk

NERLYNX	348	321	312	299	266	232	230	227	222	216	205
Placebo	347	324	310	296	276	255	252	248	244	235	224

Additional descriptive analyses of iDFS at 5 years in patients with HER2+ HR- disease[1,*]:

- All HER2+ HR- patients (n=1209): 88.8% with NERLYNX, 88.9% with placebo; HR=0.95 (95% CI: 0.66-1.35)
- HER2+ HR- >6 months post-trastuzumab subgroup (n=514): 88.7% with NERLYNX, 92.7% with placebo; HR=1.52 (95% CI: 0.82-2.88)

Descriptive analyses, not prespecified or powered.

* Results of ExteNET are supported by descriptive analyses after 5 years of follow-up, with 75% of patients (2117/2840) reconsented.[2,3]

CI: confidence interval; HER2+: human epidermal growth factor receptor 2-positive; HR: hazard ratio; HR−: hormone receptor-negative; iDFS: invasive disease-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.

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SAFETY IN ExteNET

NERLYNX safety profile[4]

MOST COMMON ADVERSE REACTIONS (≥5%)	NERLYNX (n=1408)		Placebo (n=1408)	
	All grades, %	Grades ≥3, %	All grades, %	Grades ≥3, %
Diarrhea	95	40 (Grade 3) 0.1 (Grade 4)	35	2
Nausea	43	2	22	0.1
Abdominal pain*	36	2	15	0.4
Fatigue	27	2	20	0.4
Vomiting	26	3	8	0.4
Rash†	18	0.6	9	0
Stomatitis‡	14	0.6	6	0.1
Decreased appetite	12	0.2	3	0
Muscle spasms	11	0.1	3	0.1
Dyspepsia	10	0.4	4	0
ALT increased	9	1 (Grade 3) 0.2 (Grade 4)	3	0.2
Nail disorder§	8	0.3	2	0
AST increased	7	0.5 (Grade 3) 0.2 (Grade 4)	3	0.3
Dry skin	6	0	2	0
Abdominal distention	5	0.3	3	0
Epistaxis	5	0	1	0.1
Weight decreased	5	0.1	0.5	0
Urinary tract infection	5	0.1	2	0

DRUG INTERACTIONS[4]

- 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-glycoprotein (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

The USPI warnings and precautions do not include cardiac, pulmonary, or hematologic toxicities, or increased risk for secondary malignancy.[4]

* Includes abdominal pain, abdominal pain upper, and abdominal pain lower.[4]

† 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 stomatitis, aphthous stomatitis, mouth ulceration, oral mucosal blistering, mucosal inflammation, oropharyngeal pain, oral pain, glossodynia, glossitis, and cheilitis.[4]

§ Includes nail disorder, paronychia, onychoclasis, nail discoloration, nail toxicity, nail growth abnormal, and nail dystrophy.[4]

ALT: alanine aminotransferase; AST: aspartate aminotransferase.

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ExteNET PATIENT CHARACTERISTICS

Baseline patient characteristics of the HER2+ HR− subgroup and ITT population[1]

CHARACTERISTIC	HR- subgroup		ITT population	
	NERLYNX (n=604)	Placebo (n=605)	NERLYNX (n=1420)	Placebo (n=1420)
Median age, years (range)	54 (27-81)	54 (28-82)	52 (25-83)	52 (23-82)
Race, n (%)				
White	475 (79)	460 (76)	1165 (82)	1135 (80)
Asian	99 (16)	99 (16)	188 (13)	197 (14)
Black or African American	12 (2)	22 (4)	27 (2)	47 (3)
Other	18 (3)	24 (4)	40 (3)	41 (3)
Region, n (%)				
North America	216 (36)	202 (33)	519 (37)	477 (34)
Western Europe, Australia, and South Africa	200 (33)	213 (35)	487 (34)	532 (38)
Asia Pacific, Eastern Europe, and South America	188 (31)	190 (31)	414 (29)	411 (29)
Nodal status, n (%)				
Negative	148 (25)	148 (24)	335 (24)	336 (24)
1-3 positive nodes	271 (45)	270 (45)	664 (47)	664 (47)
≥4 positive nodes	185 (31)	187 (31)	421 (30)	420 (30)
Prior trastuzumab regimen, n (%)				
Concurrent	378 (63)	378 (62)	884 (62)	886 (62)
Sequential	226 (37)	227 (38)	536 (38)	534 (38)
Median time from last trastuzumab to randomization, months (range)	4.4 (0.4-26.9)	4.4 (0.3-24.3)	4.4 (0.2-30.9)	4.7 (0.3-40.6)
Prior neoadjuvant therapy, n (%)	152 (25)	162 (27)	342 (24)	379 (27)

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

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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Indication and Important Safety Information

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 accompanying Full Prescribing Information.

Learn more at nerlynxHCP.com

References: 1. Ejlertsen B, Barrios C, Gokmen E, et al. Timing of initiation of neratinib after trastuzumab-based adjuvant therapy in early stage HER2+ hormone receptor-negative breast cancer: exploratory analyses from the phase III ExteNET trial. Poster presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; June 1-5, 2018. **2.** 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 **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.** NERLYNX [package insert]. Los Angeles, CA: Puma Biotechnology, Inc.