What is next after
Trastuzumab?

Trastuzumab has improved outcomes for early-stage HER2+ breast cancer patients, but it has not eliminated the risk of recurrence. Up to one in four early-stage HER2+ breast cancer patients experience recurrence after treatment in the adjuvant setting (after surgery) with Trastuzumab.

Fortunately, there is a treatment available to help you further reduce the risk of recurrence. Neratinib is a kinase inhibitor indicated for the extended adjuvant treatment of adult patients with early-stage HER2 overexpressed/ amplified breast cancer, to follow adjuvant Trastuzumab-based therapy.

BEACON Pharma Introduces

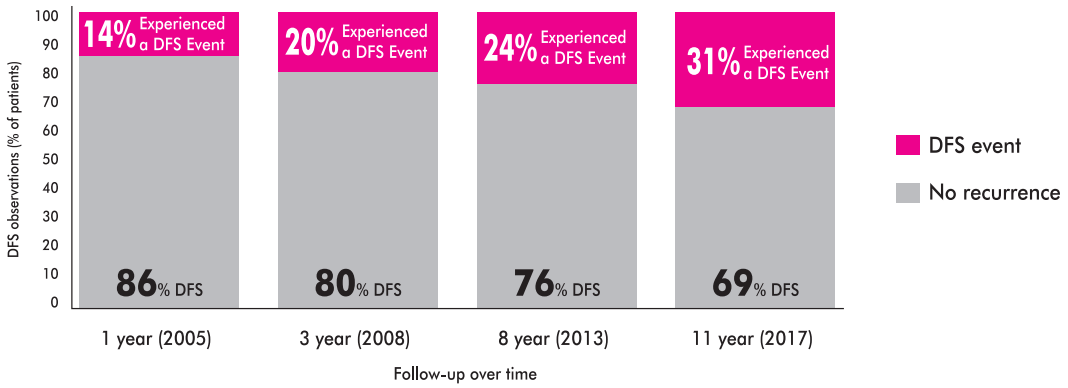
Hernix

Neratinib INN 40 mg tablet

Ensures relief from risk of recurrence

Trastuzumab has improved but not eliminated the risk of recurrence in early-stage HER2+ breast cancer

HERA trial long-term disease-free survival (DFS) outcomes



31 up to % face a disease-free survival event or death within 11 years as observed in the HERA trial.
A substantial inmet need still exists.

Ref: Ferlay J, et al. [Online]. Available from: http://globocan.iarc.fr [Accessed 15 September 2014]. 2. Wolff AC, et al. J Clin Oncol 2013;31(31):3997-4013.

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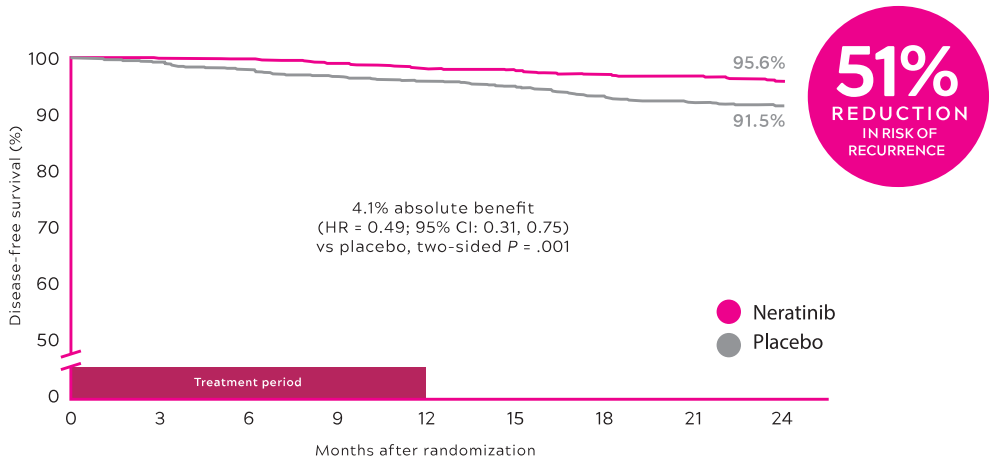
Significantly improve invasive disease-free survival (iDFS) versus placebo after adjuvant therapy

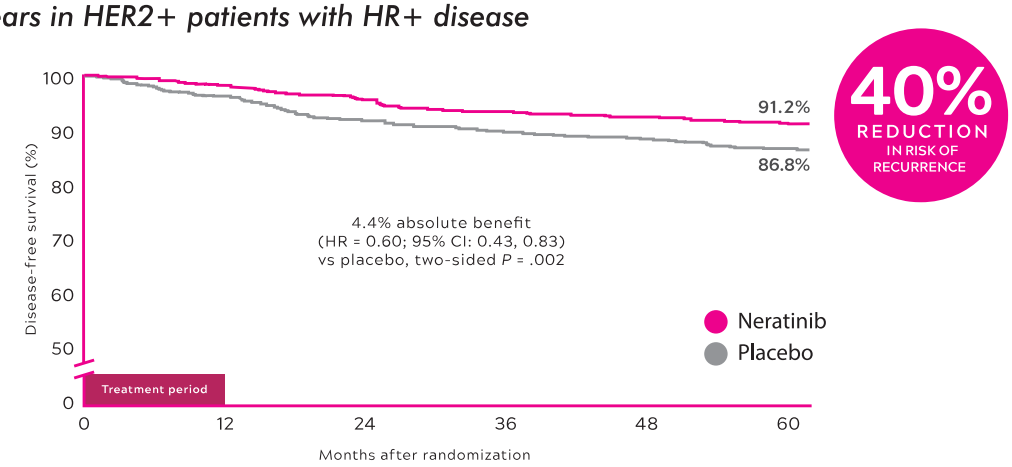
iDFS at 2 years in HER2+ patients with HR+ disease



*Ensures 51% reduction in risk of reoccurrence at **2** years follow-up*

Maintaines a significant treatment benefit at 5 years follow-up

iDFS at 5 years in HER2+ patients with HR+ disease



*Ensures 40% reduction in risk of reoccurrence at **5** years follow-up*

Ref.: Lancet Oncol. 2017;18(12):1688-1700

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Ensures relief from risk of recurrence

No evidence of cardiac or pulmonary toxicity or increased risk for secondary malignancy

	Neratinib n=1408		Placebo n=1408	
	All grades ≥ 10%	All grades ≥ 3%, ≥ 1%	All grades ≥ 10%	All grades ≥ 3%, ≥ 1%
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	6	0.1
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

Hernix is a once-daily oral therapy for 1 year

Recommended dosing is 240 mg once daily as 6 x 40 mg tablets taken by mouth with food

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Antidiarrheal Prophylaxis

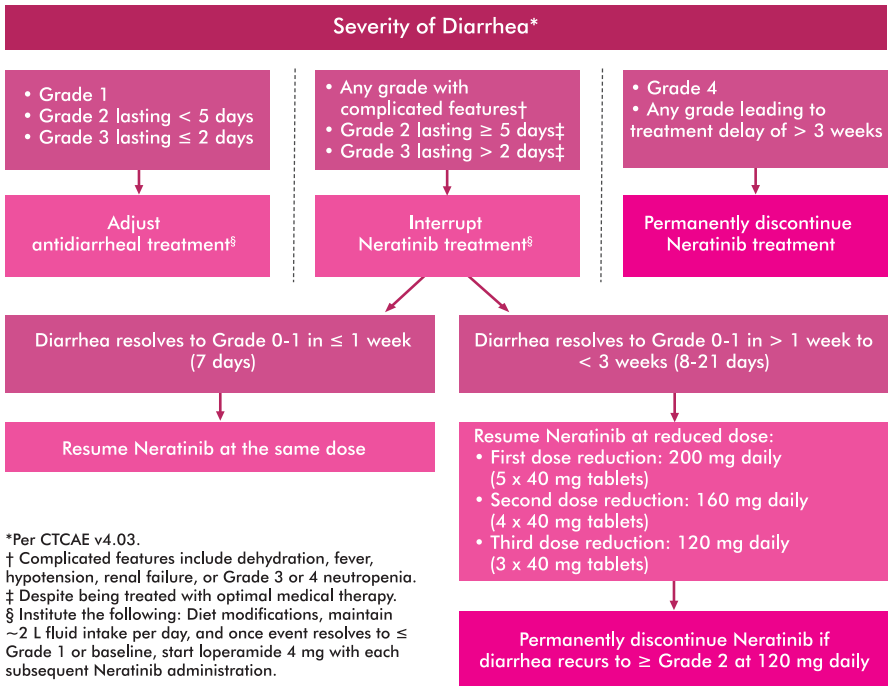
Prophylaxis with Loperamide

93% of patients had diarrhea in the first month. Prophylaxis with Loperamide has been shown to lower the incidence and severity of diarrhea. Start Loperamide with the first dose of Neratinib and continue during the first two cycles (56 days) of treatment. Continue Loperamide as shown below, titrating to 1-2 bowel movements per day. Additional antidiarrheal agents may be required to manage diarrhea in patients with Loperamide-refractory diarrhea

Time on Neratinib	Loperamide	Frequency
Weeks 1-2 (days 1-14)	4 mg	Three times daily
Weeks 3-8 (days 15-56)	4 mg	Twice daily
Weeks 9-52 (days 57-365)	4 mg	As needed (not to exceed 16 mg per day)

Neratinib dose modifications for patients with diarrhea

Diarrhea management requires the correct use of antidiarrheal medication, dietary changes, and appropriate dose modifications of Neratinib.



*Per CTCAE v4.03.
† Complicated features include dehydration, fever, hypotension, renal failure, or Grade 3 or 4 neutropenia.
‡ Despite being treated with optimal medical therapy.
§ Institute the following: Diet modifications, maintain ~2 L fluid intake per day, and once event resolves to ≤ Grade 1 or baseline, start loperamide 4 mg with each subsequent Neratinib administration.

Ref: Cancer Research 77(13 Supplement):CT128-CT128 · July 2017

Hernix

Neratinib INN 40 mg tablet

Ensures relief from risk of recurrence

- Reduces the risk of recurrence following Trastuzumab-based therapy
- Significantly improve invasive disease-free survival (iDFS)
- Maintaines significant treatment benefit at 5 years follow-up
- No evidence of cardiac or pulmonary toxicity or increased risk for secondary malignancy
- Once-daily oral therapy for 1 year

Abridged Prescribing Information

COMPOSITION: ***Hernix Tablet:*** Each film coated tablet contains Neratinib Maleate INN equivalent to Neratinib 40 mg **THERAPEUTIC CLASS:** Anti Cancer **CLINICAL PHARMACOLOGY Mechanism of action:** Neratinib is a 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. **Pharmacodynamics:** *Cardiac Electrophysiology:* The effect of Neratinib on the QTc interval was evaluated in a randomized, placebo and positive controlled, double-blind, single-dose, crossover study in 60 healthy subjects. At 2.4-fold the therapeutic exposures of Neratinib, there was no clinically relevant effect on the QTc interval. **Pharmacokinetics:** *Absorption:* Neratinib exhibits a non-linear PK profile with less than dose proportional increase of AUC with the increasing daily dose over the range of 40 to 400 mg. The Neratinib and major active metabolites M3, M6 and M7 peak concentrations are reached in the range of 2 to 8 hours after oral administration. *Effect of Food:* The food-effect assessment was conducted in healthy volunteers who received Neratinib 240 mg under fasting conditions and with high fat food (approximately 55% fat, 31% carbohydrate, and 14% protein) or standard breakfast (approximately 50% carbohydrate, 35% fat, and 15% protein). A high fat meal increased Neratinib C_{max} and AUC_{inf} by 1.7-fold (90% CI: 1.1- 2.7) and 2.2-fold (90% CI: 1.4- 3.5), respectively. A standard breakfast increased the C_{max} and AUC_{inf} by 1.2-fold (90% CI: 0.97- 1.42) and 1.1-fold (90% CI: 1.02- 1.24), respectively. *Distribution:* In patients, following multiple doses of Neratinib, the mean (%CV) apparent volume of distribution at steady-state (Vss/F) was 6433 (19%) L. *In vitro* protein binding of Neratinib in human plasma was greater than 99% and independent of concentration. Neratinib bound predominantly to human serum albumin and human alpha-1 acid glycoprotein. *Elimination:* Following 7 days of daily 240 mg oral doses of Neratinib in healthy subjects, 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. The mean elimination half-life of Neratinib ranged from 7 to 17 hours following a single oral dose in patients. Following multiple doses of Neratinib at once-daily 240 mg in cancer patients, the mean (%CV) CL/F after first dose and at steady state (day 21) were 216 (34%) and 281 (40%) L/hour, respectively. *Metabolism:* Neratinib is metabolized primarily in the liver by CYP3A4 and to a lesser extent by flavin-containing monooxygenase (FMO).After oral administration of Neratinib, Neratinib represents the most prominent component in plasma. At steady state after 240 mg daily oral doses of Neratinib in a healthy subject study (n=25), the systemic exposures (AUC) of the active metabolites M3, M6, M7 and M11were 15%, 33%, 22% and 4% of the systemic Neratinib exposure (AUC) respectively. *Excretion:* After oral administration of 200 mg (0.83 times of approved recommended dosage) radiolabeled Neratinib oral formulation, fecal excretion accounted for approximately 97.1% and urinary excretion accounted for 1.13% of the total dose. Sixty-one percent of the excreted radioactivity was recovered within 96 hours and 98% was recovered after 10 days. **INDICATIONS:** Neratinib is indicated for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer, to follow adjuvant Trastuzumab based therapy. **DOSAGE & ADMINISTRATION:** ***Antidiarrheal Prophylaxis:*** Antidiarrheal prophylaxis is recommended during the first 2 cycles (56 days) of treatment and should be initiated with the first dose of Neratinib. Instruct patients to take Loperamide as directed in Table 1, titrating to 1-2 bowel movements per day. Additional antidiarrheal agents may be required to manage diarrhea in patients with loperamide-refractory diarrhea. Neratinib dose interruptions and dose reductions may also be required to manage diarrhea. ***Recommended Dose and Schedule:*** The recommended dose of Neratinib is 240 mg (six tablets) given orally once daily with food, continuously for one year. Instruct patients to take Neratinib at approximately the same time every day. Neratinib 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 Neratinib with the next scheduled daily dose. **Dose Modifications** ***Dose Modifications for Diarrhea:*** Diarrhea management requires the correct use of antidiarrheal medication, dietary changes, and appropriate dose modifications of Neratinib. Guidelines for adjusting doses of Neratinib in the setting of diarrhea. ***Dose Modifications for Hepatic Impairment:*** Reduce the Neratinib starting dose to 80 mg in patients with severe hepatic impairment (Child Pugh C). No dose modifications are recommended for patients with mild to moderate hepatic impairment (Child Pugh A or B). ***Dose Modifications for Hepatotoxicity:*** Guidelines for dose adjustment of Neratinib in the event of liver toxicity are shown in Table 5. Patients who experience Grade 3 diarrhea requiring IV fluid treatment or any signs or symptoms of hepatotoxicity, such as worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia, should be evaluated for changes in liver function tests. Fractionated bilirubin and prothrombin time should also be collected during hepatotoxicity evaluation. **USE IN SPECIFIC POPULATIONS:** ***Pregnancy:*** Based on findings from animal studies and the mechanism of action, Neratinib can cause fetal harm when administered to a pregnant woman. Administration of Neratinib during pregnancy may have potential risk to the fetus. ***Lactation:*** 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 Neratinib, advise lactating women not to breastfeed while taking Neratinib and for at least 1 month after the last dose. **Females and Males of Reproductive Potential** *Pregnancy:* Based on animal studies, Neratinib can cause fetal harm when administered to a pregnant woman.Females of reproductive potential should have a pregnancy test prior to starting treatment with Neratinib. *Contraception: Females;* Based on animal studies, Neratinib can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with Neratinib 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 Neratinib. ***Pediatric Use:*** The safety and efficacy of Neratinib in pediatric patients has not been established. ***Geriatric Use:*** In the Clinical trial, the mean age was 52 years in the Neratinib 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 Neratinib arm, the percentages were 44.8% compared with 25.2%, respectively, and in the placebo arm 6.4% and 5.3%, respectively. The incidence of serious adverse reactions in the Neratinib arm vs. placebo arm was 7.0% vs. 5.7% (< 65 years-old) and 9.9% vs. 8.1% (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%). ***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. Reduce the Neratinib dosage for patients with severe hepatic impairment. **ADVERSE REACTIONS:** The most common adverse reactions (> 5%) were diarrhea, nausea, abdominal pain, fatigue, vomiting, rash, stomatitis, decreased appetite, muscle spasms, dyspepsia, AST or ALT increase, nail disorder, dry skin, abdominal distention, weight decreased and urinary tract infection. **OVERDOSAGE:** There is no specific antidote, and the benefit of hemodialysis in the treatment of Neratinib overdose is unknown. In the event of an overdose, administration should be withheld and general supportive measures undertaken. **DRUG INTERACTIONS:** Gastric acid reducing agents: Avoid concomitant use with proton pump inhibitors (PPI) and H2-receptor antagonists. Separate Neratinib by 3 hours after antacid dosing. • Strong or moderate CYP3A4 inhibitors: Avoid concomitant use. • Strong or moderate CYP3A4 inducers: Avoid concomitant use. • P-glycoprotein (P-gp) substrates: Monitor for adverse reactions of narrow therapeutic agents that are P-gp substrates when used concomitantly with Neratinib. **PHARAMCEUTICAL INFORMATIONS: Storage Conditions:** Store at below 30°C and dry place, away from light and moisture. Keep out of the reach of children. **Presentation & Packaging: Hernix Tablet:** Each commercial box contains 180 tablets in a bottle.

Manufactured By:

BEACON® Pharmaceuticals Limited

Light for life

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Caring Global Patients

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