

Neratinib extends adjuvant treatment of patients with HER2-positive breast cancer

The small-molecule tyrosine kinase inhibitor neratinib is now approved for the extended adjuvant treatment of patients with early-stage HER2 [human epidermal growth factor receptor]-positive breast cancer following postoperative trastuzumab. Trastuzumab is a HER2-targeted monoclonal antibody that has become standard of care in combination with chemotherapy for the treatment of this patient population in which it significantly improves survival. However, disease recurrence will occur in about a quarter of trastuzumab-treated patients owing to the development of resistance.

Neratinib may help overcome trastuzumab resistance thanks to its potent inhibition of the downstream phosphorylation of HER2 and other members of the HER family. Its approval was based on the phase 3 ExteNET trial, in which extended adjuvant treatment with neratinib was compared with placebo among 2,840 patients who remained disease free after 1 year of adjuvant trastuzumab.¹

The ExteNET trial was performed at 495 centers in Europe, Asia, Australia, New Zealand, and South America. Patients aged 18 years or older (≥ 20 years in Japan), with stage 1-3 HER2-positive breast cancer, who completed neoadjuvant and adjuvant trastuzumab therapy up to 1 year before randomization were eligible. Patients also had an Eastern Cooperative Oncology Group Performance Status of 0 or 1 (range, 0-5; 0, fully active, and 5, dead), normal organ function, and a left ventricular ejection fraction within normal institutional range. Patients with clinically significant cardiac, gastrointestinal or psychiatric comorbidities and those who were not able to swallow oral medication were excluded from the study.

Patients randomly received oral neratinib 240 mg per day or matching placebo, and randomization was stratified according to HR status (positive or negative), nodal status (0, 1-3, or ≥ 4) and trastuzumab-adjuvant regimen (sequentially or concurrently with chemotherapy).

The primary outcome was invasive disease-free survival (iDFS). The 2-year iDFS rate was 93.9% for neratinib, compared with 91.6% for placebo (hazard ratio [HR], 0.66; $P < .008$). Recently, a 5-year analysis of the ExteNET trial showed that after a median follow-up of 5.2 years, the iDFS rates were 90.2% vs 87.7% (HR, 0.73; $P = .0083$).²

What's new, what's important

The approval of neratinib for the extended adjuvant treatment of early-stage HER2-positive breast cancer after postoperative trastuzumab therapy may help overcome trastuzumab resistance. The approval was based on the phase 3 ExteNET trial, in which extended adjuvant treatment with neratinib was compared with placebo among 2,840 patients who remained disease free after 1 year of adjuvant trastuzumab. The primary outcome was invasive disease-free survival. The 2-year iDFS rate was 93.9% for neratinib, compared with 91.6% for placebo (hazard ratio [HR], 0.66; $P < .008$). A 5-year analysis of the ExteNET trial showed that after a median follow-up of 5.2 years, the iDFS rates were 90.2% vs 87.7% (HR, 0.73; $P = .0083$).

The most common AE was diarrhea, in 95% of patients (40% grade 3 diarrhea, leading to dose reduction in 26% of patients and discontinuation in 16.8% of patients). Serious AEs occurred in 7% of patients in the neratinib and 6% of those in the placebo arms. The prescribing information warns of diarrhea, hepatotoxicity, and embryofetal toxicity.

Total bilirubin, aspartate and alanine aminotransferase, and alkaline phosphatase levels should be measured before starting treatment, every 3 months during therapy, or as indicated. Pregnant women should be advised of the risk to the fetus and patients of reproductive potential should be counselled on the need for effective contraception during treatment and for at least 1 month after the last dose.

— Jame Abraham, MD, FACP (abrahamj5@ccf.org)

Adverse events

The most common adverse event (AE) was diarrhea, in 95% of patients, 40% of whom had grade 3 diarrhea, leading to dose reduction in 26% of patients and discontinuation in 16.8% of patients. Serious AEs occurred in 7% of patients in the neratinib and 6% of those in the placebo arms. In the 5-year analysis, there was no evidence of increased risk of long-term toxicity or adverse consequences of neratinib-associated diarrhea. Furthermore, the ongoing, open-label phase 2 CONTROL trial suggests that the occurrence and severity of neratinib-associated diarrhea can be effectively controlled with antidiarrheal prophylaxis, with drugs such as loperamide.³

At the January 2017 cut-off, 137 patients treated with

Mechanism of action: neratinib

Overcoming trastuzumab resistance. The human epidermal growth factor receptor 2 (HER2) is a member of a family of tyrosine kinase receptors that play a key role in coordinating cell growth, proliferation, survival and differentiation via multiple signal transduction pathways. HER2 is commonly overexpressed in many different cancer types as a means of driving some of the hallmark features of cancer cells.

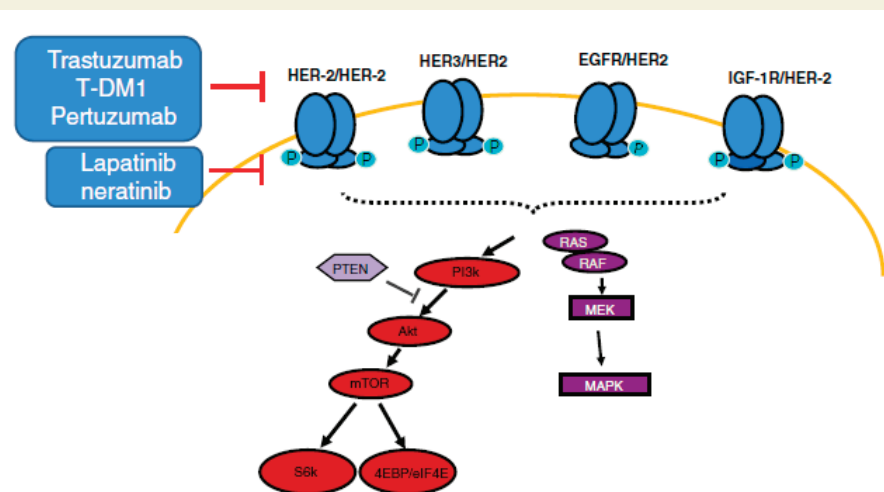
HER2-targeted drugs have been particularly successfully implemented in the treatment of HER2-positive breast cancer. Historically, the 18%-20% of breast cancers that are HER2-positive (displaying amplification of the *HER2* gene or overexpression of its protein product) were associated with a poorer patient prognosis. The monoclonal antibody trastuzumab, which has become standard of care in this disease setting, has altered the natural history of HER2-positive disease. Trastuzumab-treated patients with HER2-positive breast cancer now have a better prognosis than their HER2-negative counterparts.

However, not all patients respond to trastuzumab and, among those that do, tumor recurrence often occurs, as a result of *de novo* or acquired resistance to this drug. A number of other HER2-targeted drugs have been developed in an effort to help overcome trastuzumab resistance. Like trastuzumab, the monoclonal antibody pertuzumab and the antibody-drug conjugate ado-trastuzumab emtansine bind to the part of the HER2 protein that protrudes from

the cell and prevent it from binding to the ligands that activate it.

Alternatively, small-molecule tyrosine kinase inhibitors have also been developed that bind to the tyrosine kinase domain of the HER2 protein that is located inside the cell membrane. The latter prevent the receptor from transducing its signal by activating downstream signaling proteins.

Neratinib is an oral, irreversible, small-molecule tyrosine kinase inhibitor that has been shown to reduce the activity of all 4 HER receptors and to inhibit their downstream signaling. Its complementary mechanism of action may help to overcome some of the mechanisms by which breast cancer cells become resistant to trastuzumab, in particular the compensatory expression of other members of the HER family.



HER2-targeted drugs take the form of monoclonal antibodies or antibody-drug conjugates that bind to the extracellular portion of the HER2 protein and prevent ligand binding and receptor activation, or small molecule inhibitors that bind to the intracellular tyrosine kinase domain and block activation of downstream signaling pathways. Their distinct mechanism of action means that tyrosine kinase inhibitors like neratinib could help to overcome resistance to HER2-targeted monoclonal antibodies.

neratinib (240 mg/day) for 1 year had also received treatment with loperamide monotherapy, 64 patients had received loperamide and budesonide, and 10 patients had received loperamide and colestipol. The safety data from the loperamide monotherapy arm were compared with the safety data from the ExteNET trial, which was based in a similar population of patients who did not receive antidiarrheal prophylaxis. The incidence of all-grade diarrhea was 77% vs 95%, respectively, for those who received antidiarrheal prophylaxis in the CONTROL trial compared with those in the ExteNET trial who did not, and the respective rates of grade 3 diarrhea were 31% and 40%. The rate of dose reductions and holds owing to diarrhea were also lower among those who received antidiarrheal prophylaxis, but the rate of

discontinuation due to diarrhea was higher in the loperamide-treated cohort.

Warnings and precautions

Neratinib is marketed as Nerlynx by Puma Biotechnology Inc. The prescribing information describes warnings and precautions relating to diarrhea, hepatotoxicity, and embryofetal toxicity. Patients should be monitored for diarrhea and treated with antidiarrheals as needed. Severe diarrhea with dehydration should be treated with fluids and electrolytes as needed, treatment should be interrupted and resumed at a reduced dose. For grade 3/4 diarrhea or diarrhea with complicating features (eg, dehydration, fever, neutropenia), stool cultures should be performed to rule out infectious causes.

Total bilirubin, aspartate and alanine aminotransferase, and alkaline phosphatase levels should be measured before starting treatment, every 3 months during treatment, or as clinically indicated. Neratinib can cause fetal harm, so

pregnant women should be advised of the risk to the fetus and patients of reproductive potential should be counseled on the need for effective contraception during treatment and for at least 1 month after the last dose.⁴

References

1. Chan A, Delaloge S, Holmes FA, et al. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2016;17: 367-377.
2. Martin M, Holmes FA, Ejlertsen B, et al. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): a 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2017;18(12):1688-1700.
3. Ibrahim E, Tripathy D, Wilkinson M, et al. Effects of adding budesonide or colestipol to loperamide prophylaxis on neratinib-associated diarrhea in patients (pts) with HER2+ early-stage breast cancer (EBC): The CONTROL trial. *Cancer Res.* 2017; 77(13 supplement): Abstract CT128.
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