Original Investigation

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Neratinib Plus Paclitaxel vs Trastuzumab Plus Paclitaxel in Previously Untreated Metastatic ERBB2-Positive Breast Cancer The NEfERT-T Randomized Clinical Trial

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Author Interviews(17:31)

Neratinib vs Trastuzumab for Untreated Metastatic ERBB2-Positive Breast Cancer (JAMA Oncology)

Key Points

Question Does neratinib plus paclitaxel improve progression-free survival compared with trastuzumab plus paclitaxel as first-line therapy in recurrent and/or metastatic ERBB2-positive breast cancer?

Findings In this randomized clinical trial that included 479 women, median progression-free survival was 12.9 months with neratinib-paclitaxel and 12.9 months with trastuzumab-paclitaxel with no statistically significant difference between groups. The incidence of central nervous system (CNS) recurrences was significantly lower and time to CNS metastases significantly delayed with neratinib-paclitaxel.

Meaning Neratinib-paclitaxel is not superior to trastuzumab-paclitaxel in terms of progression-free survival in previously untreated women with ERBB2-positive metastatic breast cancer, and the CNS findings warrant further clinical investigation.

Abstract

Importance Efficacious ERBB2 (formerly HER2 or HER2/neu)-directed treatments, in addition to trastuzumab and lapatinib, are needed.

Objective To determine whether neratinib, an irreversible pan-ERBB tyrosine kinase inhibitor, plus paclitaxel improves progression-free survival compared with trastuzumab plus paclitaxel in the first-line treatment of recurrent and/or metastatic ERBB2-positive breast cancer.

Design, Setting, and Participants In the randomized, controlled, open-label NEfERT-T trial conducted from August 2009 to December 2014 at 188 centers in 34 countries in Europe, Asia, Africa, and North America, 479 women with previously untreated recurrent and/or metastatic ERBB2-positive breast cancer were randomized to 1 of 2 treatment arms (neratinib-paclitaxel [n = 242] or trastuzumab-

paclitaxel [n = 237]). Women with asymptomatic central nervous system metastases were eligible, and randomization was stratified by prior trastuzumab and lapatinib exposure, hormone-receptor status, and region.

Interventions Women received neratinib (240 mg/d orally) or trastuzumab (4 mg/kg then 2 mg/kg weekly), each combined with paclitaxel (80 mg/m^2 on days 1, 8, and 15 every 28 days). Primary prophylaxis for diarrhea was not mandatory.

Main Outcome and Measures The primary outcome was progression-free survival. Secondary end points were response rate, clinical benefit rate, duration of response, frequency, and time to symptomatic and/or progressive central nervous system lesions, and safety.

Results The intent-to-treat population comprised 479 women 18 years or older (neratinib-paclitaxel, n = 242; trastuzumab-paclitaxel, n = 237) randomized and stratified in their respective treatment arms by prior trastuzumab and lapatinib exposure, hormone-receptor status, and region. Median progression-free survival was 12.9 months (95% CI, 11.1-14.9) with neratinib-paclitaxel and 12.9 months (95% CI, 11.1-14.8) with trastuzumab-paclitaxel (hazard ratio [HR], 1.02; 95% CI, 0.81-1.27; *P* =.89). With neratinib-paclitaxel, the incidence of central nervous system recurrences was lower (relative risk, 0.48; 95% CI, 0.29-0.79; *P* = .002) and time to central nervo

us system metastases delayed (HR, 0.45; 95% CI, 0.26-0.78; *P* = .004). Common grade 3 to 4 adverse events were diarrhea (73 of 240 patients [30.4%] with neratinib-paclitaxel and 9 of 234 patients [3.8%] with trastuzumab-paclitaxel), neutropenia (31 patients [12.9%] vs 34 patients [14.5%]) and leukopenia (19 patients [7.9%] vs 25 patients [10.7%]); no grade 4 diarrhea was observed.

Conclusions and Relevance In first-line ERBB2-positive metastatic breast cancer, neratinib-paclitaxel was not superior to trastuzumab-paclitaxel in terms of progression-free survival. In spite of similar overall efficacy, neratinib-paclitaxel may delay the onset and reduce the frequency of central nervous system progression, a finding that requires a larger study to confirm.