Clinical Cancer Research

Neratinib: Inching Up on the Cure Rate of HER2$^+$ Breast Cancer?

Nisha Unni[1], Dhivya R. Sudhan[2], and Carlos L. Arteaga[1,3]

Neratinib was recently approved by the FDA for extended adjuvant treatment of HER2$^+$ breast cancer. The ExteNET trial showed improvement in invasive disease-free survival (iDFS) in the neratinib arm compared with placebo. The benefit was more pronounced in patients with estrogen receptor–positive (ER$^+$)/HER2$^+$ tumors, suggesting bidirectional cross-talk between the ER and HER pathways. *Clin Cancer Res; 24(15); 3483–5. ©2018 AACR.*

See related article by Singh et al., p. 3486

In this issue of *Clinical Cancer Research*, Singh and colleagues (1) summarize the FDA decision and data supporting the approval of neratinib for extended adjuvant treatment of early-stage HER2-amplified breast cancer following completion of 1 year of trastuzumab-based therapy. Neratinib is an irreversible, pan-HER tyrosine kinase inhibitor that blocks HER2 and EGFR phosphorylation and downstream signal transduction through the PI3K/AKT and RAS/RAF/MEK/ERK pathways. Clinical and preclinical studies have shown neratinib is a potent suppressor of HER2-mediated tumor growth and progression. Treatment of breast cancer cells with the combination of trastuzumab and neratinib has been shown to be an effective regimen to counteract both innate and acquired resistance to trastuzumab.

The approval of neratinib was based on the ExteNET trial, a multicenter, randomized, double-blind, and placebo-controlled phase III trial evaluating neratinib compared with placebo as an extended adjuvant therapy in patients with early-stage (stages I–III, which was modified later to stages II–III) HER2$^+$ breast cancer who had completed adjuvant treatment with trastuzumab up to 2 years before randomization. The primary endpoint was invasive disease-free survival (iDFS), which at 2 years was 94.2% [95% confidence interval (CI), 92.6–95.4] in the neratinib group and 91.9% (90.2–93.2) in the placebo group. Patients treated with neratinib had significantly fewer iDFS events than did those in the placebo group (70 vs. 109 events; stratified HR, 0.66; 95% CI, 0.49–0.90; $P = 0.008$; ref. 2). The updated results after a median follow-up of 5.2 years maintained this benefit, with a 5-year iDFS of 90.2% (95% CI, 88.3–91.8) from neratinib and 87.7% (85.7–89.4) in the placebo group (HR, 0.73; 95% CI, 0.57–0.92). The benefit of adjuvant neratinib was more pronounced in patients with estrogen receptor–positive (ER$^+$) breast cancer as well as those who started neratinib within 1 year of completion of trastuzumab. The HR for iDFS in the ER$^+$ subgroup was 0.60 (95% CI, 0.43–0.83) compared with the ER$^-$ subgroup versus placebo of 0.95 (0.66–1.35; ref. 3). As mentioned by Singh and colleagues (1), this was an exploratory subgroup analysis, not part of the initial study design. This is the first study that has shown benefit from extended adjuvant therapy with anti-HER2 therapy, as previously the HERA trial failed to demonstrate a benefit from 2 years versus 1 year of adjuvant trastuzumab.

The interaction between ER status and benefit from HER2-targeted drugs has not been uniformly observed in other adjuvant trials. For example, the TEACH trial did not show any difference in DFS in trastuzumab-naïve patients who received adjuvant lapatinib, especially in the ER$^+$ subgroup (4). The BCIRG 006 trial of adjuvant trastuzumab demonstrated no detectable difference in DFS between patients with ER$^+$ versus ER$^-$ tumors (5). Furthermore, in the recently published APHINITY trial (adjuvant trastuzumab ± pertuzumab for 1 year), there was no reported statistically significant difference in outcome between the ER$^+$ versus the ER$^-$ subgroup (6).

In patients with metastatic ER$^+$/HER2$^+$ breast cancer, the randomized phase III TAnDEM trial and the EGF 30008 trial showed a benefit from the addition of trastuzumab to anastrozole and of lapatinib to letrozole, respectively (7, 8). The results of these studies may apply to ExteNET considering 94% of patients with ER$^+$ tumors were on (nonprotocol) antiestrogens while on neratinib, thus suggesting HER2 inhibition enhances the response to endocrine therapy in metastatic breast cancer. However, we should note that in those trials, different to ExteNET, the endocrine therapy control arm did not include any chemotherapy.

Several translational studies suggest a mechanistic explanation for the observed benefit from neratinib. In the laboratory, HER2-amplified breast cancers that acquire resistance to trastuzumab exhibit increased levels of EGFR and ERBB ligands as well as activated EGFR/HER3 and EGFR/HER2 dimers. This is consistent with data showing that trastuzumab is unable to block ligand-induced HER2-containing heterodimers. Along these lines, patients with breast cancer with high EGFR levels did not benefit from adjuvant trastuzumab in NSABP 9831 (9). Thus, with neratinib being a potent inhibitor of EGFR, it is plausible that blockade of an EGFR-dependent mechanism of early recurrence

[1]Department of Medicine, UT Southwestern Medical Center, Dallas, Texas. [2]Department of Medicine, Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, Tennessee. [3]Harold C. Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, Texas.

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Corresponding Author: Carlos L. Arteaga, UT Southwestern Harold C. Simmons Comprehensive Cancer Center, 5323 Harry Hines Boukevard, Dallas, TX 75390-8590. Phone: 214-648-1677; Fax: 214-648-7084; E-mail: carlos.arteaga@utsouthwestern.edu

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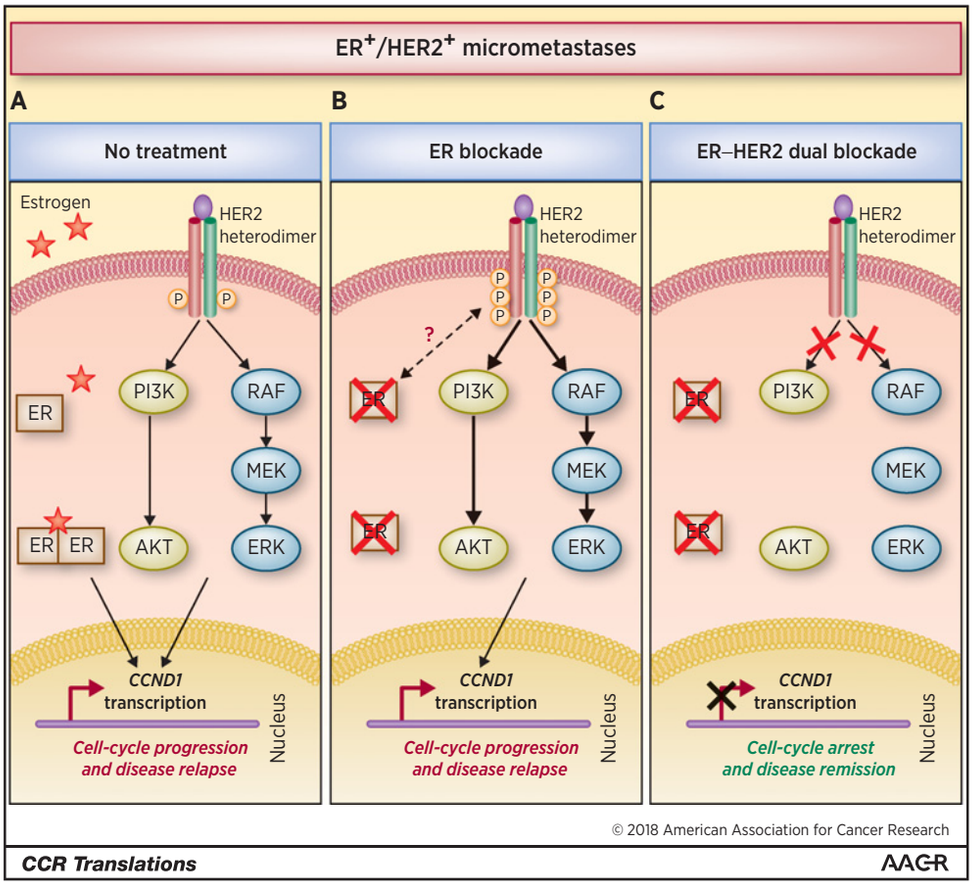

Figure 1.

Response of $ER^+/HER2^+$ tumors to anti-ER therapy versus ER–ERBB inhibition. **A,** Activation of ER and ERBB receptors by cognate ligands triggers various pathways that culminate in cyclin D1 transcription. **B,** ER blockade leads to enhanced HER2 phosphorylation and upregulation of downstream signal transduction resulting in cyclin D1 maintenance and cell-cycle progression. **C,** Simultaneous ER and HER2 blockade ablates cyclin D1 transcription and tumor cell viability, thus potentially limiting recurrence of $ER^+/HER2^+$ tumors.

could explain, at least in part, the results of ExteNET. As it applies to the results in the $ER^+/HER2^+$ subgroup, other studies have reported bidirectional cross-talk between ER and HER2 (10) and that blockade of either axis is followed by compensatory activation of the other signaling pathway. Sudhan and colleagues recently simulated the clinical outcome of extended adjuvant neratinib in a human-in-mouse model of $ER^+/HER2^+$ breast cancer (11). Mice bearing $ER^+/HER2^+$ xenografts that were maintained on endocrine therapy following complete tumor responses to trastuzumab and chemotherapy exhibited rapid tumor recurrences, which were ablated by extended adjuvant neratinib. Tumor relapses were associated with marked upregulation of HER2 signaling despite ER suppression. $ER^+/HER2^+$ tumors escaped ER blockade primarily through HER2-mediated induction of CCND1 (cyclin D1). In fact, cyclin D1 has been shown to be an important mediator of the oncogenic effects of HER2, and, conversely, cyclin D1 ablation seems vital to the antitumor effects of HER2-targeted agents. Thus, we speculate that in $ER^+/HER2^+$ breast cancers, endocrine therapy alone might result in incomplete suppression of cyclin D1; hence, simultaneous blockade of ER and HER2, as in ExteNET, may ablate cyclin D1 and maintain tumor suppression (Fig. 1). Whether the benefit of neratinib is limited or predominant in $ER^+/HER2^+$ cancers that also harbor CCND1 amplification or overexpression will require additional prospective investigation.

On the basis of the observed benefits from neratinib, the relative risks, and consideration of expert opinion, the FDA approved neratinib for extended adjuvant treatment of all patients with early $HER2^+$ breast cancer. Whether this indication is too broad and should instead be limited to patients with ER^+ tumors is challenged by the fact that the analysis of this subgroup was not preplanned in the study design. On the other hand, however, biological differences between ER^+ and ER^- tumors, which may provide plausibility to the difference in outcome between both subgroups, cannot be ignored. Indeed, the FDA chose to include the results of the subgroup analyses in the product label in light of the related discussion during the ODAC meeting (available from: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM575431.pdf and https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208051s000lbl.pdf). It would be incumbent upon providers to review and use these data to make informed decisions regarding their patients with early-stage $HER2^+$ breast cancer.

The role of neratinib is being explored further in neoadjuvant trials and in patients with metastatic disease. Using a Bayesian efficacy threshold in an adaptive randomization design, the neoadjuvant I-SPY2 trial showed a benefit of neratinib over placebo in women with operable ER$^-$/HER2$^+$ breast cancer (12). The phase III NALA trial comparing neratinib plus capecitabine versus lapatinib plus capecitabine in patients with advanced HER2$^+$ breast cancer has completed accrual. These and other trials using neratinib in combination will further define its place within the anti-HER2 therapeutic armamentarium.

Finally, ExteNET was conducted and completed in the prepertuzumab era, and, for that reason, none of these patients received dual HER2 blockade. With the increasing use of pertuzumab along with trastuzumab in the neoadjuvant and adjuvant settings, it is unclear whether there will still be a sizable subgroup of HER2-driven recurrences that can be abrogated by extended adjuvant neratinib. Until further studies can validate the benefit described in ExteNET, it would be appropriate for providers to discuss this as an option of extended adjuvant neratinib in patients with high-risk features and who do not achieve a pathologic complete response after neoadjuvant therapy.

Neratinib is the fifth HER2-targeted drug to be approved in the United States. Additional research as well as increasing clinical use and familiarity with the management of neratinib's toxicity profile will eventually contribute to finding its niche in the treatment of HER2$^+$ breast cancer.

Disclosure of Potential Conflicts of Interest

C.L. Arteaga is a consultant for Puma Biotechnology, Inc. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: N. Unni, D.R. Sudhan, C.L. Arteaga.
Development of methodology: N. Unni, D.R. Sudhan.
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): N. Unni, D.R. Sudhan.
Writing, review, and/ or revision of the manuscript: N. Unni, D.R. Sudhan, C.L. Arteaga.
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): N. Unni.
Study supervision: N. Unni, D.R. Sudhan.
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