Lessons from breast cancer trials of HER2-kinase inhibitors

The clinical development of the HER2-specific monoclonal antibody trastuzumab is an oncology success story. Adding trastuzumab to chemotherapy markedly improves survival for patients with both early and advanced HER2-positive breast cancer. Despite this success, trastuzumab regimens are not effective in all patients, and in patients with metastatic disease, tumors inevitably progress. However, trastuzumab provides benefit even after progression. This was first shown in a study1 in which patients with metastatic disease that had progressed with a trastuzumab-based regimen were randomly assigned to receive capecitabine alone or capcitabine plus trastuzumab. Trastuzumab continuation significantly improved time to progression compared with capecitabine alone.

An alternative approach to HER2-targeting is the use of small molecule tyrosine kinase inhibitors such as lapatinib (which has been approved by the US Food and Drug Administration), and the investigational drugs afatinib, neratinib, and ONT-380. Lapatinib was approved on the basis of a study1 showing that capecitabine and lapatinib improved progression-free survival compared with capecitabine alone in patients who had previously progressed on trastuzumab. Lapatinib was also directly compared with trastuzumab in MA.31, a trial of predominantly trastuzumab-naive patients (82%) randomly assigned to first-line treatment with a taxane and either lapatinib or trastuzumab; the lapatinib group had inferior progression-free survival and more toxic effects compared with the trastuzumab group.3

An unanswered question is how lapatinib or any other tyrosine kinase inhibitor compares with trastuzumab in patients after progression with trastuzumab. Nadia Harbeck and colleagues4 report the results of the first study that addresses this question. The LUX-Breast 1 trial compared afatinib plus vinorelbine versus trastuzumab plus vinorelbine in patients whose cancer had progressed on one line of trastuzumab. The data monitoring committee stopped the study because it had a low likelihood of showing superiority of afatinib for progression-free survival, and overall survival was greater in the trastuzumab group than in the afatinib group (hazard ratio 1·48 [95% CI 1·13–1·95]; p=0·0048).4 In addition, the afatinib regimen was associated with greater toxic effects.

Superficially, the LUX-Breast 1 trial seems to be just another study showing that a tyrosine kinase inhibitor has inferior outcomes and greater toxic effects compared with trastuzumab. But one could argue that the results of this trial were unexpected. Unlike lapatinib, which reversibly inhibits EGFR and HER2, afatinib is a highly potent and irreversible inhibitor of all kinase-competent HER proteins (EGFR, HER2, and HER4).5 In addition, afatinib blocks all heterodimers and homodimers of the HER family.6 Preclinical studies suggest that signalling through heterodimers, most notably HER2–HER3, is an important mechanism of trastuzumab resistance.6 Thus, the LUX-Breast 1 investigators had a strong rationale for comparing afatinib with trastuzumab. Finally, one could argue that the study design favoured afatinib because the patient population had all previously progressed on trastuzumab. Despite these points favouring afatinib, the study was negative. Faced with these surprising data, it is useful to take a step back and ask what broader lesson can be learned from these results.

One potential explanation for the consistent superiority of trastuzumab over tyrosine kinase inhibitors is trastuzumab’s ability to act through mechanisms affecting immunity, rather than solely as a HER2 signalling inhibitor. Evidence to support this contention includes preclinical studies showing that the ability of trastuzumab to activate antibody-dependent cell-mediated cytotoxicity is crucial for its efficacy in vivo.7 Several clinical studies also suggest an immunomodulatory component to trastuzumab activity. Patients with tumours enriched for gene signatures of immunity benefit more from adjuvant trastuzumab than do patients who have tumors without such signatures.8 The presence of many tumour-infiltrating lymphocytes also predicts benefit of trastuzumab,9 although not all studies are concordant. Trastuzumab’s ability to act via immune-related mechanisms could explain its unique benefit across multiple lines of treatment.

These data do not rule out a potential role for tyrosine kinase inhibitors for treating breast cancer. Combinations of tyrosine kinase inhibitors with trastuzumab, as well as other targeted drugs, are being explored. In addition, a phase 3 study10 has shown that 1 year of treatment with the irreversible
tyrosine kinase inhibitor neratinib after completion of adjuvant trastuzumab significantly improved invasive disease-free survival compared with placebo.

The consistently negative results from the LUX-Breast 1 trial, and other studies comparing tyrosine kinase inhibitors to trastuzumab, strongly suggest that further attempts to improve outcomes by substituting a tyrosine kinase inhibitor for trastuzumab are unlikely to be successful. Instead, research should focus on alternative strategies to exploit the activity of tyrosine kinase inhibitors in the clinic, either in combination with other drugs, or in specific niche indications. In addition, a better understanding of why trastuzumab repeatedly outperforms even the most potent tyrosine kinase inhibitors might provide important insights into the biology and resistance mechanisms of HER2-positive breast cancer.

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10 Chan A, Delaforge S, Holmes F, et al. Neratinib after trastuzumab-based adjuvant therapy in early-stage HER2+ breast cancer: 3-year analysis from a phase 3 randomized, placebo-controlled, double-blind trial (ExteNET). San Antonio Breast Cancer Symposium; Dec 8–12, 2015; San Antonio, TX, USA.