First, it's important to note that HER2 gene amplification is a significant factor in both early-stage and advanced breast cancer. The development of trastuzumab, a HER2-targeted monoclonal antibody, has led to significant improvements in patient outcomes. However, it's important to recognize that innate or acquired resistance to trastuzumab is common, even when combined with chemotherapy, and can severely limit its effectiveness. This resistance can manifest in various ways, including the formation of heterodimers between HER2 and other members of the HER-gene family, particularly HER3, the presence of a truncated form of the HER2 receptor that cannot be inhibited by trastuzumab, cross-activation of HER2-associated signaling pathways such as the phosphoinositide kinase-3 (PI3K)/AKT/mTOR pathway by HER1 (EGFR), and cross-talk between estrogen receptor (ER) and HER2-associated pathways in HER2+ patients whose cancer cells co-express ER.

The second generation HER2-targeted therapies, such as lapatinib and pertuzumab, have the potential to counteract some of these resistance mechanisms. TBCRC006 was a phase II neoadjuvant trial that studied the efficacy of the combination of lapatinib and trastuzumab without concurrent chemotherapy in HER2+ patients. In 65 patients with T2-3 HER2+ cancers, the overall pathologic complete response (pCR) rate was 27%, including 36% in ER+ tumors. A total of 54% of ER+/HER2+ patients had either a pCR or were downstaged to T <1 cm. Correlative studies on tissue obtained prior to and during neoadjuvant therapy are ongoing. These results suggest that a significant fraction of HER2+ patients may respond to dual HER2-targeted therapy without cytotoxic chemotherapy, and that antihormonal therapy to block ER/HER2 'crosstalk' may be necessary to achieve optimal responses in ER+/HER2+ patients.

**Keywords:** HER2-positive breast cancer; neoadjuvant therapy; lapatinib; trastuzumab

**Abstract:** Trastuzumab has had a major impact on outcomes in HER2-positive breast cancer, but innate or acquired resistance to it is recognized as a problem that can limit its effectiveness. Given its locus of action, the oral tyrosine kinase inhibitor lapatinib would be expected to counteract many of the mechanisms of trastuzumab resistance. It has demonstrated activity in trastuzumab-resistant patients, and studies in HER2+ patients have demonstrated higher pathologic complete response (pCR) rates with the addition of lapatinib to trastuzumab and chemotherapy. TBCRC006 was a phase II neoadjuvant trial that studied the efficacy of the lapatinib and trastuzumab combination without concurrent chemotherapy, but with estrogen deprivation therapy in ER+ patients. In 65 patients with T2-3 HER2+ cancers, the overall pCR rate was 27%, including 36% in ER+ tumors. A total of 54% of ER+/HER2+ patients had either a pCR or were downstaged to T <1 cm. Correlative studies on tissue obtained prior to and during neoadjuvant therapy are underway. These results suggest that a significant fraction of HER2+ patients will respond to dual HER2-targeted therapy without cytotoxic chemotherapy, and that antihormonal therapy to block ER/HER2 'crosstalk' may be necessary to achieve optimal responses in ER+/HER2+ patients.
enhanced antitumor efficacy, particularly in more aggressive cancers such as HER2+ breast cancer. In such cancers, achievement of a pathologic complete response (pCR), as a surrogate for eradication of occult metastatic disease, correlates with significant improvements in recurrence-free and overall survival (10). While not well studied in this patient subset, achievement of minimal residual disease is likely also predictive of a favorable prognosis compared to patients with gross residual disease in the breast and axillary nodes, sometimes referred to as Residual Cancer Burden (RCB) (11). Single agent trastuzumab rarely induces pCR in HER2+ patients, but a much larger impact is seen with the addition of trastuzumab to neoadjuvant chemotherapy (12-14). However, even with this combination, only about half of HER2+ patients achieve a pCR, with lower pCR rates typically reported for the ER+/HER2+ cohort; for example, in the recently reported ACOSOG Z1041 trial, the overall pCR (breast) rate was 55%, but only 41% in ER+ patients compared to 75% in ER- patients (15).

TBCRC 006, as reported by Rimawi and colleagues in the May 10, 2013 edition of the Journal of Clinical Oncology, was a single-arm, phase II study that tested the combination of lapatinib and trastuzumab over 12 weeks as neoadjuvant therapy in HER2+ patients with tumors \( \geq 3 \) cm in diameter, or \( \geq 2 \) cm in patients with clinical nodal involvement (16). It is distinguished by the absence of concurrent chemotherapy and the addition of estrogen deprivation therapy in the form of the aromatase inhibitor letrozole, as well as the LHRH analog goserelin in premenopausal women, in patients with ER+/HER2+ tumors. By binding to the tyrosine kinase site in the intracellular domains of both HER1 (EGFR) and HER2 lapatinib blocks their ability to initiate the signal transduction cascade associated with the malignant phenotype; it could also be expected to block constitutive signaling by the truncated p95 HER2 receptor, if present. Among the 65 patients who initiated therapy, 62% had tumors \( \geq 5 \) cm, 62% were ER+, 64% were premenopausal, and 54% were either African-American or Hispanic. The authors do not report the percentage of patients who were clinically node-positive, nor whether any of the patients had fixed (T4) or inflammatory cancers. As might be expected in patients not receiving standard cytotoxic therapy, treatment was well tolerated; common toxicities included grade 1-2 diarrhea, rash and fatigue, all likely due to lapatinib, but grade 3-4 toxicities were essentially limited to a few patients with transaminase elevations. The study's primary endpoint was pCR, defined as the absence of residual invasive disease in the breast. A total of 27% of patients achieved this endpoint—36% in ER- and 21% in ER+—with another 33% of the ER+ and just 4% of the ER- patients found to have residual invasive tumors \( \leq 1 \) cm. Applying the more widely used criteria for pCR—the absence of invasive disease in both the breast and the axilla—reduced the rate to 22%. They do not break down the pCR or T1a/b rates in the ER+ cohort by menopausal status.

While the pCR rates reported from this study are low compared to those from studies in which patients received concurrent chemotherapy and HER2-targeted therapy, they raise hopes that, with dual HER2-targeted therapy, and the addition of estrogen deprivation therapy in ER+/HER2+ patients a subset of HER2+ patients who could have an excellent prognosis without being exposed to the short-term toxicities and long-term risks of cytotoxic therapy. A number of randomized studies have investigated the impact of adding either lapatinib (NeoALTTO, NSABP B-41, CALGB 40601) (17-19) or pertuzumab (NeoSphere) (20) to combinations of neoadjuvant chemotherapy and trastuzumab. All demonstrated an increase in the pCR rate with dual HER2-targeted therapy, though only in NeoALTTO and NeoSphere did the difference reach statistical significance. None of these studies administered estrogen deprivation therapy to ER+/HER2+ patients, and all displayed inferior pCR rates in their ER+ cohort. Also, only TBCRC006 and one arm of NeoSphere evaluated dual HER2-targeted therapy without concurrent chemotherapy; in NeoSphere, 17% of 107 patients treated with trastuzumab and pertuzumab alone for 12 weeks achieved pCR in the breast, but only 6% of ER+ compared to 27% of ER-.

Studies in patients with advanced ER+/HER2+ cancer have demonstrated the benefit of adding HER2-targeted therapy to endocrine therapies as measured by response and clinical benefit rates, time to progression and even survival (21,22). While there have been no randomized studies of the addition of endocrine therapy to HER2-targeted therapy without chemotherapy in ER+/HER2+ (sometimes called ‘double-positive’) patients, higher response rates in the combination arms of these studies than those reported from studies of single agent trastuzumab or lapatinib suggest a benefit to blocking ER/HER2 ‘crosstalk’.

In the TCBRC 006 study, while the discrepancy in pCR rates between ER+ and ER- persisted, the percentage of ER+ who patients either achieved a pCR or were downstaged to T1a-b is much higher. This supports the hypothesis that blocking the ER pathway may be important for achieving optimal response in double-positive patients.
This hypothesis will be tested in a planned NSABP neoadjuvant study, NSABP B-52, in which ER+/HER2+ patients will receive docetaxel, carboplatin, trastuzumab and pertuzumab, and be randomized as to whether they also receive estrogen deprivation therapy. However, even with dual HER2-blockade and chemotherapy or endocrine therapy many HER2+ patients, ER- or ER+, do not achieve a pCR with neoadjuvant therapy. Part of the problem is the heterogeneity of tumors currently classified as HER2+, which likely includes cancers that are truly HER2-dependent and others with overexpression of HER2 but in which blocking HER2-associated pathways may be unnecessary; a more consistent and biologically accurate definition of HER2-positivity needs to be developed. This is illustrated by the preliminary results of intrinsic subtype analysis of pretreatment tumor samples from patients enrolled on CALGB 40601 (19). Thus far, only 33% of the study’s HER2+ tumors would be classified as HER2-enriched; in contrast 55% were either luminal A or luminal B, 7% basal-like and 5% ‘normal-like’. In the ER+ cohort only 18% were classified as HER2-enriched, while 77% were luminal. Preliminary analysis of pCR rates by subtype suggest that HER2-enriched cancers were much more likely to achieve a pCR with the combination of HER2-targeted therapy (either lapatinib, trastuzumab or both) with weekly paclitaxel than the non-HER2-enriched subtypes. Fortunately, the TBCRC006 researchers had the foresight to collect tissue samples at baseline, week 2, week 8 and at surgery (when residual tumor was present); we await their analysis of predictive factors for optimal response to their biologics-only (including estrogen deprivation therapy for ER+ tumors) regimen. The treatment of HER2+ breast cancer has advanced considerably over the last 20 years, and it is certain that treatment will continue to evolve as new agents, such as ado-trastuzumab, more potent tyrosine kinase inhibitors, and agents that target the signaling pathways activated by HER2 and other members of its family, are studied, and our understanding of what determines response or resistance to HER2 blockade advances. Along with the other studies of dual HER2-targeted therapies in the neoadjuvant setting, the TCBRC 006 study suggests a way forward, particularly for ER+/HER2+ patients. It must be pointed out that none of these studies have yet demonstrated improvements in recurrence-free or overall survival, and thus cannot be considered to have changed the standard of care for HER2+ patients treated in the neoadjuvant or adjuvant settings. They will have much greater impact on the treatment of HER2+ cancers if correlative studies can identify biologically meaningful subsets and these results translated into larger, more definitive trials.

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