

Clinical utility of the combination of lapatinib and letrozole in the management of hormone receptor-positive and HER2-positive advanced breast cancer

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Abstract: Breast cancers that overexpress human epidermal growth factor receptor-2 (HER2-positive [HER2+]) tend to be biologically aggressive and associated with a poor prognosis, even those that coexpress receptors for estrogen and/or progesterone (hormone receptor-positive [HR+]). Optimal therapy for patients with “double-positive” (HR+/HER2+) breast cancers is still being defined. In this subset of patients, the efficacy of targeted endocrine therapies appears to be diminished by cross-activation or “crosstalk” between estrogen receptor-mediated gene transcription and pathways activated by other growth factor receptors, including HER2. Lapatinib is a tyrosine kinase inhibitor which binds reversibly to the intracellular domains of the epidermal growth factor receptor and HER2, interfering with their ability to initiate signal transduction cascades that promote cancer cell proliferation, survival, and metastasis. In a recently published randomized, placebo-controlled Phase III study in postmenopausal HR+ metastatic breast cancer, the addition of lapatinib to the aromatase inhibitor letrozole significantly improved progression-free survival solely in women who were also HER2+. This article reviews the biology of “double-positive” breast cancers and the rationale underlying combining endocrine and HER2-targeted therapies, including the lapatinib/letrozole combination, for these tumors. Results from the Phase III trial are examined, as well as available data on other combinations of HR and HER2-targeted therapies. Ongoing trials and potential future applications of these combinations in both HR+/HER2+ and other subgroups of breast cancer patients are also discussed.

Keywords: breast neoplasm, erbB2, estrogen receptor, letrozole, lapatinib

Introduction

For many years, one of the major goals in the treatment of both early stage and advanced breast cancer has been the identification of markers that predict the behavior of an individual patient's cancer and the development of targeted therapies that improve outcomes in patients whose cancers express that marker. Of the many biologic markers that have been studied, as of 2011, only two – the presence of receptors for the steroid hormones estrogen (ER) and progesterone (PR) and the level of expression of the product of the human epidermal growth factor receptor-2 (HER2) gene – are accepted as reliable indicators of prognosis and response to treatment. Approximately 70% of breast cancers express ER (ER-positive [ER+]) and/or PR (PR-positive [PR+]). While there may be important biologic differences between cancers that are both ER+ and PR+ and those that are ER+ and PR-negative (PR-) or ER-negative (ER-) and PR+, and between cancers

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with differing levels of ER and PR expression, since patients with any level of ER or PR expression are typically eligible for studies of endocrine therapies, for the purposes of this review all of these tumors will be referred to as hormone receptor-positive (HR+). HER2 overexpression (HER2-positive [HER2+]), usually if not always a reflection of amplification of the HER2 gene on chromosome 17, is found in 15%–20% of invasive breast cancers. Of these, approximately half are also HR+, a subset sometimes referred to as “double-positive,” which thus accounts for 7%–10% of all breast cancers.

In general, HER2+ breast cancers exhibit more aggressive biologic behavior than cancers that are both HR+ and HER2-negative (HER2–). The impact of coexpression of the steroid hormone receptors and HER2 in HR+/HER2+ cancers on prognosis and response to treatment is still being explored. When gene expression array is utilized to define breast cancer subtypes, many HR+/HER2+ cancers segregate with the luminal B tumors, exhibiting lower messenger ribonucleic acid (mRNA) expression for ER-associated genes and higher expression for proliferation-associated genes than luminal A tumors, most of which are HR+/HER2–, but also differing from the expression pattern for tumors classified as HER2+, most of which are HR-negative (HR–).¹ Emerging data suggest that HR+/HER2+ cancers respond differently to both endocrine therapies and HER2-targeted treatments, and that blocking activation of pathways linked to both receptors may be necessary to optimize tumor response.² This realization has spurred interest in studying combinations of HR and HER2-targeted therapies. In this review, we will discuss preclinical and clinical data on the impact of HR and HER2 expression on the efficacy of treatments that target only one set of receptors, data that supports the development of regimens that combine HR and HER2-targeted agents. A Phase I study of the lapatinib/letrozole combination will be reviewed, as well as results from a large Phase III trial in patients with HR+ metastatic breast cancer (MBC) that demonstrate its superiority to single agent letrozole in the HR+/HER2+ population. Findings from other studies combining HR and HER2-targeted therapies will also be reviewed and ongoing trials with these combinations will be discussed. Possible future directions for HR and HER2-targeted combinations will be considered, including their potential role in the adjuvant and neoadjuvant settings and in subsets of HER2– patients. Finally, current recommendations for the use of these combinations in HR+/HER2+ MBC will be considered.

Background and rationale

In HR+ breast cancer cells, binding of estrogen to cytoplasmic ER receptors results in receptor dimerization and

translocation to the nucleus. Subsequent binding of this complex to estrogen response elements (ERE) located in the promoter regions of target genes increases transcription of those genes, whose products support cell growth, proliferation, and survival. This is referred to as “classic” or nuclear-initiated steroid signaling. The level of gene transcription induced by the binding of estrogen:ER complex to ERE can be modified by the activity of a variety of coactivators and corepressors.

Activation of pathways linked to the HER2 receptor is more complex. There are no known circulating ligands for the extracellular ligand-binding domain of the transmembrane HER2 receptor. However, while the other members of the HER family require bound ligand to undergo the conformational change that enables dimerization and initiation of signaling via their cytoplasmic domains, HER2 is always present in an open conformation. This allows it to be activated by interacting with another HER2 molecule, which is referred to as homodimerization, especially when there is a high density of HER2 on the cell surface, as in the setting of HER2 gene amplification, or heterodimerization with another member of the HER receptor family. These include HER1, also known as epidermal growth factor receptor (EGFR), HER3, or HER4, each of which has one or more identified ligands. Allosteric interactions between the cytoplasmic domains of HER2 homodimers or heterodimers expose adenosine triphosphate (ATP) binding sites. Bound ATP provides both energy and a phosphate moiety for the tyrosine kinase portion of the HER2 cytoplasmic domain, enabling it to phosphorylate intermediaries that trigger a number of intracellular signal transduction cascades, including the Ras-Raf-mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase-Akt pathways. Activation of these pathways in HER2+ breast cancer cells promotes proliferation, survival, and motility, inhibits differentiation, and supports angiogenesis, all of which contribute to their malignant behavior.

HR+/HER2– breast cancers are typically less aggressive and less frequently metastasize to visceral organs or the brain. Patients with HR+/HER2– MBC often respond, sometimes for years, to therapies designed either to deprive the cancer of estrogen, including surgical or chemical castration in premenopausal women and aromatase inhibition in postmenopausal women, or to prevent binding of estrogen to ER, including selective estrogen receptor modulators such as tamoxifen or toremifene, or the ER downregulator fulvestrant. In many patients with early stage HR+/HER2– cancers, treatment with hormone receptor-targeted (also referred

to as endocrine) therapies alone effectively minimizes the risk of distant disease recurrence. In contrast, HER2+ and triple-negative (ER–, PR–, and HER2–) breast cancers have higher proliferative rates and are much more likely to metastasize and to involve the lungs, liver, brain, and meninges. Once having spread beyond the breast and regional nodes, the prognosis for women with these more aggressive cancers is poor, even with intensive and toxic chemotherapy. While advances in adjuvant chemotherapy over the past 20 years have significantly improved the prognosis for early stage patients with these more aggressive cancers, they continue to have inferior recurrence-free survival (RFS) and overall survival (OS), stage-for-stage, compared to HR+/HER2– patients.³ A major advance for HER2+ patients has been the development of agents that target HER2. The first of these approved for use in patients was the partially humanized monoclonal antibody trastuzumab (Herceptin®). By binding to the juxtamembrane region of HER2, trastuzumab inhibits activation of its cytoplasmic domain, though the mechanism of this inhibition is not well understood. Single agent trastuzumab can induce regression of HER2+ cancers, but also markedly increase their sensitivity to a variety of chemotherapeutic agents. The addition of trastuzumab to chemotherapy in patients with HER2+ MBC has been shown to improve overall response rate (ORR), time to progression (TTP) and OS compared to chemotherapy alone,⁴ as well as to halve the risk of recurrence and thus significantly improve OS in stage I–III HER2+ disease.⁵

Letrozole and lapatinib

In postmenopausal women, estrogens are synthesized by peripheral conversion of adrenally-produced androgens by the enzyme aromatase. Letrozole is a highly selective, third generation nonsteroidal aromatase inhibitor (AI) that has well-documented activity in postmenopausal patients with advanced HR+ breast cancer, and is, along with its fellow nonsteroidal AI anastrozole and the steroidal AI exemestane, generally accepted as first-line therapy for postmenopausal HR+ MBC, having demonstrated superiority to tamoxifen in that setting.⁶

Lapatinib is a 4-anilinoquinazoline tyrosine kinase inhibitor that binds reversibly to ATP-binding sites on the cytoplasmic domains of both EGFR and HER2, thereby blocking phosphorylation of intermediaries responsible for activating the MAPK and Akt signaling pathways.⁷ Given its mechanism and site of action, lapatinib should retain antitumor activity against HER2+ breast cancer cells that have become resistant to suppression by trastuzumab due

to the presence of a truncated HER2 receptor referred to as p95^{erbB2}, which has lost the receptor's extracellular domain (ECD) but retains the intracellular ATP binding sites and tyrosine kinase.⁸ It may also be able to overcome intrinsic or acquired resistance to trastuzumab related to the formation of heterodimers between HER2 and other members of the HER family. Lapatinib has demonstrated clinical activity in some trastuzumab-resistant HER2+ cancers, though there are other mechanisms of resistance to trastuzumab that also render the cells resistant to lapatinib.⁹ Whether lapatinib's ability to inhibit the EGFR tyrosine kinase contributes to its antitumor efficacy is unclear (discussed below).

In Phase II trials in trastuzumab-refractory HER2+ MBC, single agent lapatinib exhibited ORR of 4%–8%, and clinical benefit rates (CBR) of 5.7%–33.3%, where clinical benefit combines patients who achieve an objective response with those with stable disease lasting at least 24 weeks.^{8,10,11} As first-line therapy for HER2+ MBC, single agent lapatinib demonstrated an ORR of 24%, a CBR of 31%, and median progression-free survival (PFS) of 6 months.¹²

Endocrine therapies in HR+/HER2+ breast cancer

In patients with HR+ breast cancers, overexpression of HER2 is associated with more aggressive biology and a much poorer prognosis. While results from individual studies vary, a meta-analysis of 12 studies encompassing 2379 patients with HR+ MBC demonstrated that PFS for HR+/HER2+ patients on endocrine therapy was inferior by 42% ($P < 0.00001$) compared to HR+/HER2– patients, whether patients were treated with tamoxifen or some other form of endocrine therapy.¹³ Elevated serum levels of the HER2/neu ECD, considered a surrogate for HER2 overexpression, was associated with inferior PFS (5.7 months vs 9.4 months, hazard ratio [HR]: 0.56, $P < 0.0001$) as well as lower ORR and CBR in patients receiving first-line endocrine therapy for HR+ MBC.¹⁴ In patients with early stage HR+ cancers, HER2 positivity is associated with a significantly higher risk of disease recurrence and a relative lack of efficacy of adjuvant endocrine therapies. This explains the heavy weighting for HER2-associated gene expression in the calculation of Recurrence Score by the Oncotype Dx assay (Genomic Health, Redwood City, CA).¹⁵ Subgroup analyses of postmenopausal HR+ patients treated with either tamoxifen or an AI on the Arimidex, Tamoxifen, Alone or in Combination (ATAC) and Breast International Group 1–98 (BIG 1–98) trials demonstrate that HER2+ patients have a poorer prognosis than HER2– patients.^{16,17} However, data suggest that these cancers retain

some degree of endocrine responsiveness. Retrospective analysis of patients with node-positive, HR+/HER2+ cancers who received cyclophosphamide, doxorubicin, and fluorouracil as adjuvant chemotherapy on the Cancer and Leukemia Group B (CALGB) 8541 trial revealed that those patients who subsequently received tamoxifen had a 32% reduction in disease recurrence or death compared to patients not receiving tamoxifen, a benefit not substantially less than that seen in HR+/HER2- patients (39%).¹⁸

Data as to whether antitumor efficacy is influenced by choice of endocrine therapy in HR+/HER2+ cancers are suggestive but not conclusive. In HR+ patients receiving first-line endocrine therapy for MBC, patients with elevated serum levels of HER2/neu ECD had similar ORR and CBR whether assigned to letrozole or tamoxifen, but patients treated with the AI enjoyed a significant prolongation of median time to treatment failure (6.0 months vs 3.2 months; $P = 0.0418$).¹³ In a subset analysis from a Phase III trial of neoadjuvant endocrine therapy in postmenopausal patients with stage II–III HR+ cancer, HER2+ patients had a much higher clinical response rate to letrozole (11/16, 69%) than to tamoxifen (4/23, 17%).¹⁹ In the adjuvant setting, HER2+ patients treated on the ATAC and BIG 1–98 trials received the same incremental benefit from an AI compared to tamoxifen as seen in the overall study populations.^{16,17} These findings support the hypothesized biology of endocrine resistance in HR+/HER2+ breast cancer cells discussed below, and suggest that in postmenopausal patients an AI should be the endocrine treatment of choice. The role of fulvestrant in HR+/HER2+ patients is being explored in clinical trials. The Fulvestrant First-Line Study Comparing Endocrine Treatments (FIRST) trial demonstrated superior TTP for fulvestrant 500 mg compared to anastrozole as first-line therapy in HR+ MBC.²⁰ While this study did not exclude patients with HER2+ tumors, results for this cohort have not been reported.

Preclinical data on mechanisms of resistance in HR+/HER2+ cancers

The presumed etiology of the observed relative endocrine resistance in HR+/HER2+ patients is “crosstalk” between the ER and HER2 signaling pathways. This hypothesis is supported by a number of observations. Transfection of multiple copies of the HER2 gene (mimicking amplification of the HER2 gene) into ER-responsive breast cancer cell lines has been shown to reduce expression of both ER and PR and to induce tamoxifen resistance.^{21–23} Postulated mechanisms for this resistance include HER2-mediated activation of the MAPK and Akt signaling pathways and tyrosine

kinase-mediated phosphorylation of ER, all of which can upregulate ER-mediated gene transcription in the presence of small or even negligible amounts of ER, mimicking the clinical situation in patients being treated with tamoxifen or an AI.²⁴ This may relate to increased levels of the ER coactivator Amplified in Breast 1 (AIB1). Supporting this hypothesis are observations that acquired resistance to tamoxifen in HER2- tumors is often associated with increased expression of EGFR and/or HER2, and that treatment with trastuzumab or lapatinib may suppress the growth of breast cancer cell lines and xenografts with acquired endocrine resistance.^{2,25} These observations suggest that blocking HER2 might prolong or restore endocrine sensitivity.

This “crosstalk” also impacts the biologic actions of HER2 and the antitumor efficacy of HER2-targeted therapies. Transcriptional activation by ER has been shown to reduce levels of HER2, while increasing the expression of ligands such as transforming growth factor α and amphiregulin and receptors like the insulin-like growth factor-1 receptor (IGF-1R), which can activate signaling pathways independent of HER2 activation, and thus might render cells less susceptible to growth inhibition by HER2-blockade.²⁶ Both in the lab and in the clinic, resistance to HER2-targeted therapies has been associated with increased ER expression, while ER blockade upregulates expression of both EGFR and HER2.^{27,28} In addition, separate from their “classic” influence on transcription of target genes in the nucleus (nuclear initiated steroid signaling), it is now recognized that estrogen:ER complexes adjacent or bound to the cell membrane can interact directly with signal transduction mediators associated with the intracellular domains of EGFR, HER2, and IGF-1R. These interactions can activate the MAPK and Akt pathways and trigger cell growth and proliferation by what is referred to as nongenomic, or “nonclassic,” or membrane-initiated steroid signaling. In addition, while binding of tamoxifen to ER inhibits its genomic activities, it may potentiate these nongenomic mechanisms. This mechanism may play a significant role in tamoxifen resistance, especially in HR+/HER2+ tumors, which would support the preferential use of alternative endocrine therapies, such as an AI or fulvestrant, in these patients.

Clinical data on the effects of HR expression on response in HER2+ breast cancer

The impact of HR expression on tumor response in HER2+ patients is reflected in results from neoadjuvant trials in which the pathologic complete response (pCR) rates

achieved with chemotherapy administered with one or more HER2-targeted agents are consistently lower in HR+/HER2+ patients compared to HR-/HER2+ patients.^{29,30} While this might raise concerns regarding the activity of chemotherapy/HER2-targeted combinations in these patients, a retrospective analysis of three clinical trials of first-line therapy for MBC with trastuzumab, given either as a single agent or in combination with chemotherapy, failed to show any decrement in ORR or TTP for HR+/HER2+ patients compared to those with HR-/HER2+ tumors, and median OS was actually longer for the HR+ patients.³¹ Moreover, there is no evidence that being HR+ reduces the benefits of the addition of trastuzumab to adjuvant chemotherapy in early stage HER2+ patients. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) and North Central Cancer Treatment Group (NCCTG) HER2+ adjuvant trials, at a median follow-up of 4 years, RFS for HR+/HER2+ patients, who received adjuvant endocrine therapy after completing adjuvant chemotherapy and trastuzumab, was superior to that for HR-/HER2+ patients.³²

In vitro data on patterns of resistance to trastuzumab or lapatinib may be instructive as to the choice of HER2 targeted therapy in HR+/HER2+ cancers. ER+/HER2+ fulvestrant-resistant cell lines selected for resistance to trastuzumab demonstrated reactivation of the HER2 signaling pathway and sensitivity to inhibition by lapatinib, but did not demonstrate increased levels of ER activity or restored sensitivity to fulvestrant.³³ On the other hand, when these cell lines were selected for resistance to either lapatinib or the combination of lapatinib and trastuzumab, they did not demonstrate HER2 reactivation but instead exhibited high levels of ER activity and phosphorylated Akt, and had regained sensitivity to fulvestrant. In aggregate, these data suggest that combining lapatinib with either an AI or fulvestrant may be the preferred approach to blocking both ER and HER2 mediated signaling.

Phase I study of the lapatinib/letrozole combination

Chu and colleagues conducted a Phase I trial of lapatinib and letrozole in patients with either advanced HR+ breast cancer or any other malignancy that the treating physician believed might benefit from this combination.³⁴ The study was designed to determine if the lapatinib dose could be escalated from 1250 mg to 1500 mg daily with the standard daily dose of letrozole (2.5 mg), then to enroll sufficient patients to assess the efficacy of the combination and the frequency and severity of adverse events and to perform

pharmacokinetic analyses. A total of 39 patients were enrolled, of whom nearly half had advanced breast cancer. The investigators were able to escalate the lapatinib dose to 1500 mg without difficulty and saw no unanticipated toxicities. Diarrhea (77%), rash (62%), nausea (46%), and fatigue (26%) were the most common side effects, with grade 3 diarrhea in six patients and grade 3 rash, anemia, or infection (*Clostridium difficile* colitis) in one each. Reductions in the left ventricular ejection fraction (LVEF) of $\geq 20\%$ from baseline were seen in four patients, but the LVEF fell below the lower limit of normal in only one, who was asymptomatic. Among the heavily pretreated breast cancer patients, one had a transient partial response and two maintained stable disease for approximately 9 months. However, none of the three patients classified as HER2+ by immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH) had evidence of clinical benefit.

Phase III study of letrozole with or without lapatinib (EGF30008 trial)

In 2003, Johnston and colleagues initiated a randomized, double-blind Phase III study of letrozole 2.5 mg daily with lapatinib 1500 mg daily or a matching placebo in patients with histologically-confirmed stage IIIB/C or IV HR+ invasive breast cancer.³⁵ For patients randomized to placebo, no crossover to lapatinib at disease progression was planned. No prior treatment for locally advanced or metastatic disease was permitted, but patients were allowed to have received prior neoadjuvant or adjuvant endocrine therapy or chemotherapy. They were also allowed to have received prior therapy with an AI or trastuzumab, provided these were discontinued at least a year before study entry. Patients were stratified by sites of disease and prior adjuvant antiestrogen therapy (< 6 months since discontinuation of tamoxifen vs ≥ 6 months or no prior endocrine therapy). The primary endpoint for the study was investigator-assessed PFS in patients with HER2+ tumors, and the study was designed to have 80% power to detect improvement in PFS in this cohort. Analysis of PFS in the overall study population was planned only if a positive result was achieved in the HER2+ subgroup.

Of the 1286 patients enrolled in the study, 219 were considered HER2+ based on available assays from their primary tumor or a metastatic site, 952 were HER2-, and 115 had no available HER2 testing results and did not meet study criteria for HER2 positivity. Of the HER2+ patients, median age was 60, and 51% had received adjuvant or neoadjuvant chemotherapy. Adjuvant antiestrogen therapy had been discontinued less than 6 months before enrolling

on the study in 36% of the HER2+ patients, while 64% either had received no prior antiestrogen therapy (45%) or had discontinued it more than 6 months prior to registration (19%). Only two had received prior trastuzumab. Most (85%) had visceral and/or soft tissue metastases. After a median follow-up of 1.8 years, median PFS in HR+/HER2+ patients was 8.2 months for the lapatinib/letrozole combination compared to 3.0 months for letrozole plus placebo (HR: 0.71, 95% confidence interval: 0.53–0.96, $P = 0.019$). The addition of lapatinib improved the ORR from 15% to 28% (odds ratio: 0.4, $P = 0.021$) and the CBR from 29% to 48% (odds ratio: 0.4, $P = 0.003$). No difference in median OS was reported (32.3 months for single agent letrozole compared to 33.3 months for the combination, $P = 0.113$), but less than half of the HER2+ patients had succumbed to their disease at the time the data were censored for publication. To what extent treatment received following removal from the study affected the OS results is not known.

Within the HR+/HER2+ population, patients with liver metastases or more than three sites of metastatic disease at baseline tended to benefit more from combination therapy.³⁶ Elevated baseline serum levels of the HER2/neu ECD, detected in 42% of HER2+ patients, were associated with greater relative benefit from the addition of lapatinib (PFS 24.1 weeks vs 11.7 weeks for single agent letrozole, HR: 0.44, $P = 0.0002$), though changes in serum levels of the HER2/neu ECD during treatment did not correlate with response.³⁷

In the overall study population, the addition of lapatinib to letrozole prolonged median PFS from 10.8 to 11.9 months (HR: 0.86, $P = 0.026$), but this improvement was due solely to its impact on the HER2+ cohort. The addition of lapatinib did not improve ORR or CBR (31% and 56% for single agent letrozole compared to 33% and 59% for the combination). In patients with HER2– cancers, there was no improvement in median PFS with the addition of lapatinib (13.4 months vs 13.7 months, HR: 0.90, $P = 0.188$). Consistent with prior data on the impact of HER2 positivity on the efficacy of endocrine therapy, HER2+ patients assigned to single agent letrozole had significantly shorter median PFS (3.0 months) than HER2– patients (10.8 months). Patients classified as HER2– with either a borderline FISH value, 2+ IHC staining for HER2, or unknown HER2 status did not have a demonstrable benefit from the addition of lapatinib, nor did the subset of patients who were treatment naïve.³⁸ The investigators did note a trend favoring combination therapy in HER2– patients who enrolled on the study within 6 months of discontinuing antiestrogen therapy ($n = 200$), many of whom had recurred while still on adjuvant

endocrine therapy, with a median PFS of 8.3 months vs 3.1 months for single agent letrozole (HR: 0.78, $P = 0.117$) and CBR of 44% vs 32%.³⁵ Another subgroup of interest was HER2– patients whose tumors had the lowest levels of ER expression by quantitative analysis, in whom PFS was 13.6 months with the combination vs 6.6 months with letrozole alone (HR: 0.65, $P < 0.005$).³⁹ These findings are consistent with in vitro evidence that intrinsic or acquired resistance to endocrine therapy may be associated with increased signaling mediated by growth factor receptors such as EGFR and HER2.

Patients continued treatment on the combination arm for a median of 40 weeks vs 38 weeks on the letrozole/placebo arm, with about 12% of all patients and 7% of HER2+ patients still on treatment after 2 years. Side effects of the lapatinib/letrozole combination were consistent with those seen in the Phase I trial as well as what had been reported for a group of HR+/HER– women who received this combination therapy in the neoadjuvant setting.⁴⁰ Diarrhea (64% vs 20%), rash (44% vs 13%), nausea (31% vs 21%), and fatigue (21% vs 18%) were more common in patients treated with combination therapy compared to single agent letrozole, but most adverse events in both groups were grade 1–2. Grade 3–4 diarrhea occurred in 10% of patients treated with letrozole and lapatinib, compared to <1% of patients taking letrozole alone, but most cases could be managed with treatment interruption, dose reduction, or symptomatic management. Only 1.5% of patients randomized to the combination arm discontinued treatment due to diarrhea. No other grade 3 side effect occurred in more than 2% of patients on either arm. AI-attributed arthralgias were reported in 23% of patients on letrozole/placebo compared to 21% on lapatinib/letrozole. Treatment-related declines in LVEF were reported in five patients (0.8%) given lapatinib compared to two patients (0.3%) on placebo. Serious adverse events related to the study drugs were reported in 8% of patients on combination therapy compared to 4% on letrozole/placebo, but of 16 fatalities reported as serious adverse events, only three – one patient on combination therapy and two patients on letrozole/placebo – were attributed to the study drugs.^{35,36,41,42}

Quality of life was assessed using the Functional Assessment of Cancer Therapy (FACT)-Breast and FACT-General survey tools. In the HER2+ subpopulation, quality of life scores were equivalent in the letrozole plus lapatinib and the letrozole plus placebo arms, demonstrating that improvement in PFS with combination therapy did not come at the expense of a significant decrement in quality

of life.^{43,44} Costs associated with the study treatments were evaluated from the standpoint of the United Kingdom National Health Service. Although pharmacy costs would be increased with the administration of two oral medications (letrozole and lapatinib), overall health system costs would be expected to be less with this combination than with a regimen that requires administration of an intravenous drug like trastuzumab.⁴⁵

Other studies combining endocrine and HER2-targeted agents in HER2+ patients

Other combinations of endocrine therapies and HER2-targeted agents have been studied in various patient populations. Marcom and colleagues reported a Phase II study of letrozole and trastuzumab as first-line or second-line therapy in 31 evaluable patients with HR+ MBC, of whom 25 were HER2+ by IHC or FISH, and most of whom had previously received tamoxifen. Treatment was well tolerated except for one patient who developed grade 3 congestive heart failure that improved with discontinuation of trastuzumab. In the HER2+ patients, ORR was 24%, CBR 44%, median TTP 5.5 months, and median duration of response exceeded 17 months. While these results appeared to be better than what would be expected for either agent alone, the fact that over half of the patients failed to benefit led the authors to hypothesize that downstream mutations might have resulted in constitutive activation of pathways common to ER and HER2 signaling that were not inhibited by their combination regimen.⁴⁶

The Trastuzumab in Dual HER2 ER-Positive Metastatic Breast Cancer (TAnDEM) study randomized 207 patients with HR+/HER2+ MBC to first-line therapy with either single agent anastrozole or the combination of anastrozole and trastuzumab. The median age of patients enrolled on the study was 55, and 63% of patients had received prior antiestrogen therapy. Patients treated with combination therapy had significant prolongation of PFS (4.8 months vs 2.4 months, HR: 0.63, $P = 0.0016$). At 2 years, approximately 15% of patients on the combination had not progressed, compared to 5% on single agent anastrozole. ORR (20.3% vs 6.8%, $P = 0.018$) and CBR (42.7% vs 27.9%, $P = 0.026$) were significantly higher with the addition of trastuzumab. Median OS was 28.5 months for the combination vs 23.5 months for single agent anastrozole. While the OS difference was not statistically significant ($P = 0.325$), this may have been influenced by the large proportion of patients (70%) assigned to single agent anastrozole who received trastuzumab at some point

following disease progression. The addition of trastuzumab to anastrozole was associated with an increase in grade 3–4 adverse events (23.3% vs 15.4%), although no specific grade 3–4 adverse event was reported in >3% of patients on the combination. Five patients on the combination arm discontinued treatment due to a cardiac adverse event, including three patients with asymptomatic declines in LVEF and one who developed symptomatic congestive heart failure.⁴⁷

The Study of the Efficacy and Safety of Letrozole Combined with Trastuzumab in Patients with Metastatic Breast Cancer (eLEcTRA) trial was designed to address whether the addition of trastuzumab to letrozole would improve TTP in HR+/HER2+ MBC, and also to compare results achieved with single agent letrozole in HR+/HER2+ and HR+/HER2– patients. Unfortunately, the study was closed after enrolling only 92 of a planned 370 patients. In 57 HR+/HER2+ patients, the addition of trastuzumab to letrozole improved CBR from 39% to 65% and median TTP from 3.3 months to 14.1 months (HR: 0.67), but due to the small size of the study this difference was not statistically significant ($P = 0.23$). In addition, results could have been influenced by imbalances in study characteristics, including the proportion of patients who had received any prior adjuvant therapy (71% for single agent letrozole vs 42% for combination therapy) and the percentage of patients with liver metastases (39% for single agent letrozole vs 19% for the combination). In contrast, HR+/HER2– patients treated with letrozole had a CBR of 77% and median TTP of 15.2 months.⁴⁸ While underpowered to make any firm conclusions, these results suggest that the addition of trastuzumab at least partially reversed resistance to single agent letrozole in the HR+/HER2+ cohort.

These studies demonstrate that while patients with HR+/HER2+ MBC may respond to endocrine therapy alone, the addition of a HER2-targeted agent markedly improves treatment results. Whether the addition of endocrine therapy would improve outcomes in HR+/HER2+ MBC patients being treated with a HER2-targeted agent, either alone or in combination with chemotherapy, has not been studied, nor is it known whether the superior RFS for HR+/HER2+ patients (compared to HR–/HER2+) reported from the adjuvant trastuzumab studies is due to the impact of adjuvant endocrine therapy, differences in tumor biology, or both.³²

Koerberle and colleagues planned a study in which patients with HR+/HER2+ MBC recurring or progressing on a nonsteroidal AI were to receive single agent trastuzumab, with the addition of letrozole when they progressed on trastuzumab. They theorized that AI resistance, if due to increased

HER2 activation, might enhance sensitivity to trastuzumab and that treatment with trastuzumab while off endocrine therapy might lead to enhanced ER signaling, thereby possibly restoring endocrine sensitivity. Unfortunately, the study closed early due to poor accrual. In 13 patients started on trastuzumab, six (48%) either responded or had stable disease lasting at least 6 months with median TTP of 161 days. Of greater interest, in eleven patients who progressed on trastuzumab, CBR for the addition of letrozole was 73% with median TTP (from initiation of letrozole) of 188 days. These limited results suggest the dynamic nature of HR and HER2 mediated signaling and sensitivity to targeted therapies in these tumors.⁴⁹

Other studies of lapatinib in HR+ patients unselected for HER2 status

Schwartz and colleagues studied whether adding lapatinib 1500 mg daily could restore endocrine sensitivity in patients with HR+ MBC who had progressed after an initial response to either an AI or antiestrogen. Seven of 16 evaluable patients (only one of whom was HER2+) had stable disease at 26 weeks (CBR 43.8%) with median TTP of 179 days (results were not stratified by class of endocrine agent). The addition of lapatinib resulted in four instances of grade 3 diarrhea.⁵⁰

Burstein and colleagues reported results from CALGB 40302, on which 267 patients with HR+ MBC who had progressed on an AI were treated with fulvestrant (500 mg day 1, 250 mg days 15 and 28, then every 28 days) and randomized to the addition of lapatinib 1500 mg daily or placebo. Overall, no differences were seen in median PFS (5.2 months for fulvestrant/letrozole vs 4.0 months for fulvestrant/placebo, $P = 0.94$) or OS (22.3 months vs 21.9 months). However, in 59 HER2+ patients, a trend favored the lapatinib arm (PFS 5.9 months vs 2.8 months, $P = 0.29$). Treatment with lapatinib was associated with an increase in grade 3 diarrhea (9%), fatigue (4%), and rash (4%).⁵¹

Targeting EGFR expression

Since lapatinib targets the tyrosine kinase associated with EGFR as well as that of HER2, is there any evidence that this plays a role in its clinical activity? The significance of EGFR expression, and thus the value of blocking its activation, on the prognosis and treatment of breast cancer is unclear. Depending on patient group and the technique used to assess EGFR expression, EGFR positivity has been reported in 14%–91% of breast cancers. EGFR is approximately twice as likely to be expressed in HR– cancers as HR+ cancers, and

most studies have suggested higher rates of EGFR positivity in higher grade tumors and those with nodal involvement. However, aside from its association with poorer prognosis triple-negative cancers, studies have failed to demonstrate a correlation between EGFR expression and OS. As discussed above, increased EGFR activity has been associated with the development of endocrine resistance in HR+ breast cancer through many of the same “crosstalk” mechanisms implicated for HER2+ activation.⁵² However, while breast cancer cell lines with acquired tamoxifen resistance may demonstrate EGFR as well as HER2 expression, clinical data regarding the significance of EGFR expression are scant.⁵³ In contrast to other solid tumors like nonsmall cell lung cancer, activating mutations of EGFR as a potential therapeutic target have not been identified in breast cancer tumors. Still, the possibility that EGFR activation could trigger signal transduction pathways that promote tumor cell survival, proliferation, and metastasis has made EGFR an attractive target. Phase I and II studies with gefitinib, a small molecule inhibitor of the EGFR tyrosine kinase, in heavily pretreated MBC patients, typically unselected for EGFR expression, demonstrated few objective responses and disease stabilization in only a modest proportion of patients. In a recently reported trial, 28 patients with tamoxifen-resistant HR+ MBC treated with single agent gefitinib had CBR of 53.6% with median PFS of 8.74 months, compared to CBR of 11.5% and median PFS of only 1.84 months in 26 patients with HR– MBC not thought to be good candidates for chemotherapy.⁵⁴ A small randomized Phase II study of anastrozole/gefitinib vs anastrozole/placebo in HR+ women who had either received no prior endocrine therapy or had recurred during or after adjuvant tamoxifen demonstrated a trend favoring the combination in terms of median PFS (14.7 months vs 8.4 months, HR: 0.55) and CBR (49% vs 34%) despite a higher ORR for single agent anastrozole (12% vs 2%). This suggests that gefitinib might act not by sensitizing cancer cells to endocrine therapies but perhaps by delaying the development of endocrine resistance. However, EGFR expression was not predictive of greater benefit for the combination.⁵⁵ A sizable ($n = 206$) randomized neoadjuvant trial of 16 weeks of anastrozole with or without gefitinib in postmenopausal HR+ women failed to demonstrate improvement in response rate or suppression of proliferation, as measured by Ki67 levels, with the addition of gefitinib.⁵⁶

Ongoing trials and future directions

Promising results from the EGF30008 and TAnDEM trials have stimulated interest in further study of combinations of

Table 1 Ongoing or planned trials of lapatinib and endocrine therapies in breast cancer

Designation	Patient population	Phase	Study design	Accrual goal
NCT01160211	HR+, HER2+ MBC following adjuvant trastuzumab + endocrine therapy	III	Lapatinib + AI vs trastuzumab + AI vs lapatinib + trastuzumab + AI	525
NCT00688194	HR+, HER2+/- MBC, progressed or relapsed on AI	III	Fulvestrant + lapatinib +/- AI vs fulvestrant + placebo +/- AI (four arms)	396
NCT00118157	HR+, HER2+/- MBC, tamoxifen-resistant	II	Lapatinib + tamoxifen	41
NCT00225758	HR+, HER2+/- MBC, progressing on endocrine Rx	II	Lapatinib + continue current endocrine Rx	50
NCT01005641	HR+, HER2+/- MBC, no prior hormonal Rx for MBC	II	Lapatinib + exemestane	104
NCT00422903	HR+, HER2- stage II-IIIa, neoadjuvant	II	Letrozole + lapatinib vs letrozole + placebo	91
NCT00548184	HER2+, HR+/-, stage II-III, neoadjuvant	II	Lapatinib + trastuzumab (+ endocrine therapy if HR+)	64

Abbreviations: HR+, hormone receptor-positive; HER2+, human epidermal growth factor receptor positive; MBC, metastatic breast cancer; AI, aromatase inhibitor; Rx, prescription; vs, versus.

endocrine therapy and HER2-targeted therapies. Ongoing and planned trials combining lapatinib with various endocrine therapies are listed in Table 1. In patients with MBC, the most relevant to the data reviewed here is a Phase III study planned by GlaxoSmithKline (NCT01160211) in which postmenopausal HR+/HER2+ patients who relapse following adjuvant or neoadjuvant chemotherapy and trastuzumab and subsequent endocrine therapy will be given an AI and randomized to single agent lapatinib vs trastuzumab vs the combination of lapatinib and trastuzumab. The basis for this trial is a randomized study which demonstrated improved results for the combination of lapatinib and trastuzumab over single agent lapatinib in patients with HER2+ MBC who had progressed on trastuzumab.⁵⁷ The study is powered to compare PFS, OS, ORR, and CBR for each of the single agents vs the combination, as well as the incidence and severity of adverse events and impact on quality of life. An attempt will also be made to assess the predictive value of biomarkers associated with sensitivity or resistance to lapatinib and trastuzumab, including the presence of mutations affecting the Akt pathway and the p95^{erbB2} truncated HER2 receptor. Given higher pCR rates achieved with combinations of two HER2-targeted therapies and chemotherapy in the neoadjuvant setting,^{29,30} it seems likely that combining endocrine therapy and dual HER2 blockade will improve results in HR+/HER2+ patients.

Other studies in HR+ MBC permit enrollment of HER2- as well as HER2+ patients despite uncertainty as to the value of lapatinib in the absence of HER2 overexpression. These include a four-arm study of fulvestrant with lapatinib or placebo, with or without continuation of AI, in HR+ patients progressing or relapsing on an AI (NCT00688194). At least two Phase II studies are designed to investigate the ability of lapatinib to reverse resistance to endocrine agents. In the

neoadjuvant setting, a stratified Phase II study in HER2+ patients investigates the activity of the combination of lapatinib and trastuzumab, without concurrent chemotherapy, with the addition of an endocrine agent if the cancer is HR+ (NCT00548184), and a randomized Phase II study (NCT00422903) explores the benefit of adding lapatinib to letrozole in HR+/HER2- patients.

Studies not specifically designed to address the interaction of endocrine and HER2-targeted therapies may yet yield interesting data. The Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO) trial evaluates the benefits of substituting lapatinib for or adding lapatinib to trastuzumab given with adjuvant chemotherapy in patients with stage I-III HER2+ cancers. Patients with HR+ cancers would be expected to receive adjuvant endocrine therapy concurrent with HER2-targeted treatment for 7-9 months after completing chemotherapy. While not powered for this comparison, it will be of interest to see if there are differences in outcomes for HR+/HER2+ patients related to the assigned HER2-targeted treatment or to the use of tamoxifen in premenopausal and perimenopausal women compared to an AI in postmenopausal women. The Suppression of Ovarian Function trial (SOFT) randomized premenopausal, early stage, HR+ patients to tamoxifen, ovarian suppression or ablation with tamoxifen, or ovarian suppression or ablation with exemestane, with or without prior adjuvant/neoadjuvant chemotherapy. While HER2 status was not used to stratify patients, its impact on the efficacy of the various endocrine therapy strategies will be examined, and may yield interesting insights for the HR+/HER2+ population.

There are other clinical settings where combinations of endocrine therapies and HER2-targeted therapies may be of interest. This could include adjuvant therapy for patients with low-risk (T1a/b, possibly T1c, N0) HR+/HER2+ cancers.

These patients were not included in the first generation of adjuvant chemotherapy with or without trastuzumab trials, such as the NSABP and NCCTG studies mentioned above, but many oncologists extrapolate results achieved in the node-positive and high-risk node-negative HER2+ populations and recommend chemotherapy with trastuzumab as standard treatment. While patients with small HER2+ cancers are clearly at greater risk of distant recurrence than patients with T1 N0 HR+/HER2- tumors, it is not yet clear that the benefits of these regimens in these lower risk patients justify their toxicities and costs. In lower risk postmenopausal patients, an all-oral regimen such as lapatinib/letrozole could be worth studying to determine if it might be as effective as adjuvant chemotherapy with trastuzumab with fewer short- and long-term toxicities and reduced treatment costs and inconvenience. In the neoadjuvant setting, the impact of a therapeutic trial or “window” treatment with combined endocrine and HER2-targeted therapies in older patients with larger HR+/HER2+ cancers may also be worth investigating. Patients would be switched to a standard chemotherapy/HER2-targeted regimen either at treatment failure (disease progression or lack of clinical response at a designated time point) or after a set interval. Obtaining pretreatment and posttreatment tissue biopsies could shed light on the biologic effects of this treatment approach and possibly identify markers associated with response. It would also be interesting to see if the addition of endocrine therapy could improve pCR rates achieved with HER2-targeted neoadjuvant therapies in HR+/HER2+ tumors. In addition, given the ability of lapatinib to penetrate the central nervous system⁵⁸ combined with the ability of letrozole to suppress residual ER production in postmenopausal patients, a trial of this combination in patients with unresectable HR+/HER2+ brain metastases may be warranted.

The benefit of adding endocrine therapy to novel HER2-targeted agents such as the HER2:HER3 heterodimer blocker pertuzumab, irreversible inhibitors of the HER2 and EGFR tyrosine kinases such as neratinib and afatinib, or the monoclonal-cytotoxic conjugate trastuzumab-DM-1, should be studied in HR+/HER2+ patients as the efficacy and toxicities of these novel agents are better defined. Similarly, if the promising results with combinations of HER2-targeted agents in the neoadjuvant setting are confirmed in subsequent studies in early stage and/or advanced HER2+ breast cancer, the benefit of adding an endocrine agent in the HR+ subpopulation should be investigated. Unless results from the FIRST trial in the HER2+ cohort are conclusive, studies in HR+/HER2+ MBC that compare the efficacy and toxicity of endocrine therapies, such as an AI vs fulvestrant, with a common HER2-targeted therapy, should also be considered.

Analysis of biopsies taken from metastatic sites compared to baseline tissue samples in 52 HR+/HER2- patients who relapsed on tamoxifen demonstrated upregulation of HER2 expression in 20%, including two who became HER2+ by FISH.³³ Based on the subsets of patients who appeared to benefit from the addition of lapatinib to letrozole in the EGF30008 trial,^{34,38} HER2- patients with clinically relevant HER2 activation may be more prevalent among those who relapse while still on endocrine therapy or those who had lower levels of ER expression in their breast primary. Trials performed specifically in this subset of HR+/HER2- patients to assess the benefit of adding a targeted agent like lapatinib, as opposed to studies that permit any HR+ patient who recurs on or after adjuvant endocrine therapy, may be more likely to determine if such treatment is beneficial. The feasibility of such studies is enhanced by the increasing interest in biopsying metastatic sites to determine if there has been a change in HR or HER2 expression compared to the breast primary.

Summary and treatment recommendations

Where does the lapatinib/letrozole combination, or other combinations of endocrine and HER2-targeted therapies, fit into the treatment algorithm for HR+/HER2+ MBC? Given that response rates to chemotherapy/HER2-targeted therapy combinations typically exceed the 28% reported for the combination in EGF30008, such an approach cannot be recommended in young patients or those with life-threatening or symptomatic disease. However, given the encouraging survival results from the EGF30008 study, and understanding that no treatment is curative in this setting, a therapeutic trial of this generally well tolerated oral regimen, with appropriate dose reductions for diarrhea or any other significant toxicities, could be considered in postmenopausal HR+/HER2+ patients with less extensive or asymptomatic metastatic disease. Such an approach offers the possibility of delaying initiation of a more toxic chemotherapy-based HER2-targeted combination for 6–12 months, and occasionally longer. In addition, while the value of this approach has not been tested in a randomized trial, it seems reasonable to offer patients with HR+/HER2+ MBC who have responded to a chemotherapy/HER2-targeted regimen a trial of combined endocrine and HER2-targeted “maintenance” therapy, in the hope of delaying disease progression once chemotherapy is discontinued due to toxicity or plateau of response.

Without a head-to-head comparison, arguments favoring the choice of lapatinib over trastuzumab as the HER2-targeted agent in any combination are largely theoretical, though

supported by in vitro data. Further study of endocrine/HER2-targeted combinations is warranted, as discussed above. Laboratory and correlative studies should help to further elucidate the mechanisms of “crosstalk” between the signaling pathways linked to ER and HER2, its influence on the biologic behavior of these cancers, and how best to block it to enhance or restore sensitivity to endocrine and HER2-targeted therapies. Such advances should help us to improve outcomes for patients with “double-positive” HR+/HER2+ cancers.

Disclosure

The authors report no conflicts of interest in this work.

References

- Prat A, Perou CM. Deconstructing the molecular portraits of breast cancer. *Mol Oncol*. 2011;5(1):5–23.
- Witters L, Engle L, Lipton A. Restoration of estrogen responsiveness by blocking the HER-2/neu pathway. *Oncol Rep*. 2002;9(6):1163–1166.
- Berry DA, Cirincione CC, Henderson IC, et al. Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer. *JAMA*. 2006;295(14):1658–1667.
- Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*. 2001;344(11):783–792.
- Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med*. 2005;353(16):1673–1684.
- Mouridsen H, Gershonovich M, Sun Y, et al. Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. *J Clin Oncol*. 2003;21(11):2101–2109.
- Spector NL, Xia W, Burris H 3rd, et al. Study of the biologic effects of lapatinib, a reversible inhibitor of ErbB1 and ErbB2 tyrosine kinases, on tumor growth and survival pathways in patients with advanced malignancies. *J Clin Oncol*. 2005;23(11):2502–2512.
- Scaltriti M, Rojo F, Ocana A, et al. Expression of p95HER2, a truncated form of the HER2 receptor, and response to anti-HER2 therapies in breast cancer. *J Natl Cancer Inst*. 2007;99(8):628–638.
- Burstein HJ, Storniolo AM, Franco S, et al. A phase II study of lapatinib monotherapy in chemotherapy-refractory HER2-positive and HER2-negative advanced or metastatic breast cancer. *Ann Oncol*. 2008;19(6):1068–1074.
- Blackwell KL, Pegram MD, Tan-Chiu E, et al. Single-agent lapatinib for HER2-overexpressing advanced or metastatic breast cancer that progressed on first- or second-line trastuzumab-containing regimens. *Ann Oncol*. 2009;20(6):1026–1031.
- Iwata H, Toi M, Fujiwara Y, et al. Phase II clinical study of lapatinib (GW57206) in patients with advanced or metastatic breast cancer [abstract]. *Breast Cancer Res Treat*. 2006;100 Suppl 1:S68.
- Gomez HL, Doval DC, Chavez MA, et al. Efficacy and safety of lapatinib as first-line therapy for ErbB2-amplified locally advanced or metastatic breast cancer. *J Clin Oncol*. 2008;26(18):2999–3005.
- De Laurentiis M, Arpino G, Massarelli E, et al. A meta-analysis on the interaction between HER-2 expression and response to endocrine treatment in advanced breast cancer. *Clin Cancer Res*. 2005;11(13):4741–4748.
- Lipton A, Ali SM, Leitzel K, et al. Elevated serum Her-2/neu level predicts decreased response to hormone therapy in metastatic breast cancer. *J Clin Oncol*. 2002;20(6):1467–1472.
- Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol*. 2006;24(23):3726–3734.
- Rasmussen BB, Regan MM, Lykkesfeldt AE, et al. Adjuvant letrozole versus tamoxifen according to centrally assessed ERBB2 status for postmenopausal women with endocrine-responsive early breast cancer: supplementary results from the BIG 1–98 randomised trial. *Lancet Oncol*. 2008;9(1):23–28.
- Dowsett M, Allred C, Knox J, et al. Relationship between quantitative estrogen and progesterone receptor expression and human epidermal growth factor receptor 2 (HER-2) status with recurrence in the ATAC trial. *J Clin Oncol*. 2008;26(7):1059–1065.
- Berry DA, Muss HB, Thor AD, et al. HER-2/neu and p53 expression versus tamoxifen resistance in estrogen receptor–positive, node-positive breast cancer. *J Clin Oncol*. 2000;18(20):3471–3479.
- Ellis MJ, Coop A, Singh B, et al. Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: evidence from a phase III randomized trial. *J Clin Oncol*. 2001;19(18):3808–3816.
- Robertson JFR, Lindemann JPO, Llombart-Cussac A, et al. A comparison of fulvestrant 500 mg with anastrozole as first-line treatment for advanced breast cancer: follow-up analysis from the ‘FIRST’ study. *Cancer Res*. 2010;70(24 Suppl):S1–3.
- Benz CC, Scott GK, Sarup JC, et al. Estrogen-dependent, tamoxifen-resistant tumorigenic growth of MCF-7 cells transfected with HER2/neu. *Breast Cancer Res Treat*. 1992;24(2):85–95.
- Pietras RJ, Arboleda J, Reese DM, et al. HER-2 tyrosine kinase pathway targets estrogen receptor and promotes hormone-independent growth in human breast cancer cells. *Oncogene*. 1995;10(12):2435–2446.
- Liu Y, el-Ashry D, Chen D, Ding IY, Kern FG. MCF-7 breast cancer cells overexpressing transfected c-erbB-2 have an *in vitro* growth advantage in estrogen-depleted conditions and reduced estrogen-dependence and tamoxifen sensitivity in vivo. *Breast Cancer Res Treat*. 1995;34(2):97–117.
- Konecny G, Pauletti G, Pegram M, et al. Quantitative association between HER-2/neu and steroid hormone receptors in hormone receptor-positive primary breast cancer. *J Natl Cancer Inst*. 2003;95(2):142–153.
- Kurokawa H, Lenferink AE, Simpson JF, et al. Inhibition of HER2/neu (erbB-2) and mitogen-activated protein kinases enhances tamoxifen action against HER2-overexpressing, tamoxifen-resistant breast cancer cells. *Cancer Res*. 2000;60(20):5887–5894.
- Weinstein-Oppenheim CR, Burrows C, Steelman LS, McCubrey JA. The effects of beta-estradiol on Raf activity, cell cycle progression, and growth factor synthesis in the MCF-7 breast cancer cell line. *Cancer Biol Ther*. 2002;1(3):256–262.
- Yarden RI, Wilson MA, Chrysogelos SA. Estrogen suppression of EGFR expression in breast cancer cells: a possible mechanism to modulate growth. *J Cell Biochem Suppl*. 2001;Suppl 36:232–246.
- Newman SP, Bates NP, Vernimmen D, Parker MG, Hurst HC. Cofactor competition between the ligand-bound oestrogen receptor and an intron 1 enhancer leads to oestrogen repression of ERBB2 expression in breast cancer. *Oncogene*. 2000;19(4):490–497.
- Baselga J, Bradbury I, Eidtmann H, et al. First results of the NeoALTTO trial (BIG 01–06 / EGF 106903): a phase III, randomized, open label, neoadjuvant study of lapatinib, trastuzumab, and their combination plus paclitaxel in women with HER2-positive primary breast cancer [abstract]. *Cancer Res*. 2010;70(24 Suppl):S3–3.
- Gianni L, Pienkowski T, Im YH, et al. Neoadjuvant pertuzumab (P) and trastuzumab (H): antitumor and safety analysis of a randomized phase II study (‘NeoSphere’) [abstract]. *Cancer Res*. 2010;70(24 Suppl):S3–2.
- Brufsky A, Lembersky B, Schiffman K, Lieberman G, Paton VE. Hormone receptor status does not affect the clinical benefit of trastuzumab therapy for patients with metastatic breast cancer. *Clin Breast Cancer*. 2005;6(3):247–252.
- Perez EA, Romond EH, Suman VJ, et al. Updated results of the combined analysis of NCCTG N9831 and NSABP B-31 adjuvant chemotherapy with/without trastuzumab in patients with HER2-positive breast cancer. *J Clin Oncol*. 2007;25(18S):512.
- Leary AF, Drury S, Detre S, et al. Lapatinib restores hormone sensitivity with differential effects on estrogen receptor signaling in cell models of human epidermal growth factor receptor 2-negative breast cancer with acquired endocrine resistance. *Clin Cancer Res*. 2010;16(15):1486–1497.

34. Chu QS, Cianfrocca ME, Goldstein LJ, et al. A phase I and pharmacokinetic study of lapatinib in combination with letrozole in patients with advanced cancer. *Clin Cancer Res*. 2008;14(14):4484–4490.
35. Johnston S, Pippen J Jr, Pivot X, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. *J Clin Oncol*. 2009;27(33):5538–5546.
36. Schwartzberg LS, Franco SX, Florance A, O'Rourke L, Maltzman J, Johnston S. Lapatinib plus letrozole as first-line therapy for HER-2+ hormone receptor-positive metastatic breast cancer. *Oncologist*. 2010;15(2):122–129.
37. Platek GT, Koehler M, Gagnon R, et al. Relevance of serum HER2 extracellular domain (sECD) in EGF30008, a study of letrozole ± lapatinib in patients (pts) with hormone-receptor positive (HR+) metastatic breast cancer (MBC) [abstract]. *J Clin Oncol*. 2009;27(15S):1019.
38. O'Rourke L, Pegram M, Press M, et al. First-line lapatinib combined with letrozole versus letrozole alone for hormone receptor positive (HR+) metastatic breast cancer (MBC): subgroup analyses of borderline FISH+, IHC 2+, HER2 unknown (UNK), and treatment-naïve (TN) populations from EGF30008 [abstract]. *J Clin Oncol*. 2009;27(15S):1062.
39. Finn RS, Press M, Dering J, et al. Progression-free survival (PFS) of patients with HER2-negative, estrogen-receptor (ER)-low metastatic breast cancer (MBC) with the addition of lapatinib to letrozole: Biomarker results of EGF30008 [abstract]. *J Clin Oncol*. 2009;27(15S):1018.
40. Frassoldati A, Guarneri V, Bottini A, et al. Preplanned first-step analysis of LET-LOB neoadjuvant study: a double-blind randomized phase IIb trial of letrozole (L) plus lapatinib (Lp) or placebo (P) in postmenopausal HER2-ve, HR+ve operable breast cancer [abstract]. *J Clin Oncol*. 2009;27(15S):570.
41. Ro J, Pippen J, Pivot X, et al. Safety of first-line letrozole compared with lapatinib plus letrozole in patients with postmenopausal hormone receptor positive metastatic breast cancer: EGF30008 Study [abstract]. *Cancer Res*. 2009;69(24 Suppl 3):5094.
42. Zembryki D, Gomez H, Koehler M, et al. Cardiac safety of the lapatinib/letrozole combination as first-line therapy in patients (pts) with metastatic breast cancer (MBC) [abstract]. *J Clin Oncol*. 2009;27(15S):1095.
43. Sherrill B, Amonkar MM, Sherif B, Maltzman J, O'Rourke L, Johnston S. Quality of life in hormone receptor-positive HER-2+ metastatic breast cancer patients during treatment with letrozole alone or in combination with lapatinib. *Oncologist*. 2010;15(9):944–953.
44. Sherif BN, Sherrill B, Amonkar M, et al. Lapatinib plus letrozole compared with letrozole alone as first-line therapy in hormone receptor positive HER2+ metastatic breast cancer (MBC): a quality-of-life (QOL) analysis [abstract]. *J Clin Oncol*. 2009;27(15S):1039.
45. Hastings V, Delea TE, Amonkar M, Lykopoulos K, Diaz J, Johnston S. Indirect comparison of the cost-effectiveness of letrozole plus lapatinib (LET+LAP) versus anastrozole plus trastuzumab (ANA+TZ) as first-line treatment for postmenopausal women with HER2+ and HR+ metastatic breast cancer (MBC) from the U.K. National Health Service (NHS) perspective [abstract]. *J Clin Oncol*. 2010;28(15S):1035.
46. Marcom PK, Isaacs C, Harris L, et al. The combination of letrozole and trastuzumab as first or second-line biological therapy produces durable responses in a subset of HER2 positive and ER positive advanced breast cancers. *Breast Cancer Res Treat*. 2007;102(1):43–49.
47. Kaufman B, Mackey JR, Clemens MR, et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. *J Clin Oncol*. 2009;27(33):5529–5537.
48. Huober J, Fasching P, Paepke S, et al. Letrozole in combination with trastuzumab is superior to letrozole monotherapy as first line treatment in patients with hormone-receptor-positive, HER2-positive metastatic breast cancer – results of the eLEcTRA trial [abstract]. *Cancer Res*. 2009;69(24 Suppl 3):4094.
49. Koeberle D, Ruhstaller T, Jost L, et al. Can resistance to trastuzumab be reversed by endocrine therapy? Results from a proof-of-principle trial in postmenopausal patients with hormonal receptor (HR) positive, HER-2 positive advanced breast cancer (SAKK 23/03) [abstract]. *Cancer Res*. 2010;70(24 Suppl):P3–14–16.
50. Schwartz G, Borges V, Weiselberg L, Elias A, Budman D. Lapatinib restores endocrine sensitivity in selected patients with estrogen receptor (ER) positive metastatic breast cancer [abstract]. *Cancer Res*. 2009;69(24 Suppl 3):3089.
51. Burstein HJ, Barry WT, Cirincione C, et al. CALGB 40302: Fulvestrant with or without lapatinib as therapy for hormone receptor positive advanced breast cancer: a double-blinded, placebo-controlled, randomized phase III study [abstract]. *Cancer Res*. 2011;71:PD05–01.
52. Giltinan JM, Rydén L, Cregger M, Bendahl PO, Jirstrom K, Rimm DL. Quantitative measurement of epidermal growth factor receptor is a negative predictive factor for tamoxifen response in hormone receptor positive premenopausal breast cancer. *J Clin Oncol*. 2007;25(21):3001–3014.
53. Chan SK, Hill ME, Gullick WJ. The role of the epidermal growth factor receptor in breast cancer. *J Mammary Gland Biol Neoplasia*. 2006;11(1):3–11.
54. Gutteridge E, Agrawal A, Nicholson R, Leung Cheung K, Robertson J, Gee J. The effects of gefitinib in tamoxifen-resistant and hormone-insensitive breast cancer: a phase II study. *Int J Cancer*. 2010;126(8):1806–1816.
55. Cristofanilli M, Valero V, Mangalik A, et al. Phase II, randomized trial to compare anastrozole combined with gefitinib or placebo in postmenopausal women with hormone receptor-positive metastatic breast cancer. *Clin Cancer Res*. 2010;16(6):1904–1914.
56. Smith IE, Walsh G, Skene A, et al. A phase II placebo-controlled trial of neoadjuvant anastrozole alone or with gefitinib in early breast cancer. *J Clin Oncol*. 2007;25(25):3816–3822.
57. O'Shaughnessy J, Blackwell KL, Burstein H. A randomized study of lapatinib alone or in combination with trastuzumab in heavily pretreated HER2+ metastatic breast cancer progressing on trastuzumab therapy [abstract]. *J Clin Oncol*. 2008;26(15S):1015.
58. Lin NU, Carey LA, Liu MC, et al. Phase II trial of lapatinib for brain metastases in patients with human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol*. 2008;26(12):1993–1999.

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