REVIEW

Is the Improved Efficacy of Trastuzumab and Lapatinib Combination Worth the Added Toxicity? A Discussion of Current Evidence, Recommendations, and Ethical Issues Regarding Dual HER2-Targeted Therapy

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Abstract: Following FDA approval of trastuzumab in 1998 and lapatinib in 2007, several clinical studies have addressed the question of whether trastuzumab and lapatinib combination therapy is better than trastuzumab alone in the metastatic breast cancer and neoadjuvant setting. In this review, updated to September 2012, we focus on the relevant clinical trials that address this question and, based on the available data, reach conclusions regarding a rational and reasonably individualized approach to the management of HER2+ breast cancer. With the FDA approval of pertuzumab in June 2012 and the likely approval of T-DM1 approaching, several ethical issues overshadow the excitement oncologists have for these new treatment options. We discuss the potential evolution of highly active anti-HER2 therapy (HAAHT) as an optimal treatment paradigm for HER2+ breast cancer. Additionally, we review lessons learned from the evolution of HAART for HIV treatment.

Keywords: HER2, breast cancer, lapatinib, trastuzumab, dual, T-DM1, pertuzumab

Introduction

Trastuzumab

Trastuzumab is a humanized monoclonal antibody that has been approved by the Food and Drug Administration (FDA) since 1998 for the treatment of HER2-positive breast cancer. It remains the foundation of care for both metastatic and early stage breast cancer. Trastuzumab works by binding to extracellular domain IV of the HER2 receptor[1] and blocks the network of signaling pathways that induce cell division, motility, and adhesion.[2] The monoclonal antibody exerts its effects through various mechanisms such as antibody-dependent cellular cytotoxicity, inhibition of HER2 homodimer signaling, and ligand independent HER2-HER3 heterodimerization, suppression of angiogenesis, and DNA replication.[1–9]

In the metastatic setting, trastuzumab has been proven to be effective as monotherapy, with objective response rates—26% for 1st line and 15% for 2nd or 3rd line—similar to many single agent chemotherapy options with less prominent toxicity.[10,11] The anti-HER2 antibody combined with docetaxel also significantly improves overall survival and progression free survival, with few additional adverse events compared to patients on docetaxel alone.[12,13] However, significant cardiotoxicity has been noted in patients on combined trastuzumab and anthracycline therapy.[13,14]

In the adjuvant setting, when combined with standard chemotherapy regimens, trastuzumab has been shown to markedly improve overall survival in four large randomized controlled trials irrespective of tumor stage, hormone receptor status, or age.[15–18] Three phase III neoadjuvant studies documented efficacy of trastuzumab combined with chemotherapy with essentially a doubling of the pCR rates versus control arms, with two studies showing improved DFS or event free survival.[19–21]

Not all patients respond to trastuzumab. Resistance can exist for a number of reasons, include but not limited to cellular changes which limit trastuzumab binding to HER2 such as an increase of MUC4 expression, a mucin glycopeptide,[22] and the presence of a truncated form of the HER2 receptor.[23] Additionally, resistance can result from activating mutations of PI3K and the loss of PTEN activity, a negative regulator of the PI3K pathway;[24,25] An increase in signaling through alternate dimers, such as ligand dependent HER2:HER3

heterodimers, can also occur.[26] Despite the benefits of trastuzumab, additional agents and strategies targeting the HER2 signaling network are needed.

Lapatinib

Lapatinib is a dual tyrosine kinase inhibitor (TKI) that selectively binds to HER1 and HER2 receptors intracellularly[27] to prevent the phosphorylation of downstream pathways which activate cell proliferation and survival.[28] It also has a long half-life and slowly dissociates from HER1 and HER2 tyrosine kinases,[29] enhancing its inhibition of downstream cellular signals that promote tumor cell survival and proliferation.[28] Whereas trastuzumab has little effect on survivin and apoptosis, lapatinib induces cancer cell susceptibility to apoptosis by down-regulating survivin through post-translational mechanisms.[30,31]

A phase II trial of HER2+ metastatic breast cancer (MBC) patients on lapatinib monotherapy demonstrated modest clinical activity in individuals whose cancer was refractory to trastuzumab, demonstrating a clinical benefit rate (CBR or objective response or stable disease > 6 months) of 6%.[32] When combined with other chemotherapeutics, lapatinib exhibits increased efficacy. In combination with capecitabine, Lapatinib is FDA-approved at a dose of 1250 mg/d for the treatment of HER2-positive MBC in patients who have progressed on prior therapy, including an anthracycline, a taxane, and trastuzumab.[33,34] In the pivotal trial EGF100151, enrollment was prematurely terminated due to a successful interim analysis of median time to progression (TTP). TTP for lapatinib and capecitabine was 8.4 months, while TTP for capecitabine monotherapy was 4.4 months (HR 0.49; 95% CI 0.34 to 0.71; $P > 0.001$). Subsequent follow-up and analysis showed a median OS of 75.0 and 64.7 weeks for combination and monotherapy respectively, a difference that did not achieve statistical significance. However, using Cox regression analysis to account for crossover as a time-dependent covariate (36 of 201 patients on capecitabine alone crossed over to combination), significance was attained ($P = 0.043$).

Lapatinib is also FDA-approved in combination with letrozole as first-line therapy in patients with estrogen receptor (ER) positive and HER2+ MBC.[35] In the pivotal study EGF3008, patients were still eligible even if they received adjuvant tamoxifen, aromatase

inhibitor, or trastuzumab, provided it was completed less than 1 year prior to enrollment. The primary endpoint, progression free survival, was 8.2 months for patients on lapatinib and letrozole and 3 months for those on letrozole alone (HR 0.71; 95% CI 0.53 to 0.96; $P = 0.19$). CBR was 48% for the combination and 29% for the monotherapy ($P = 0.003$).

HER2+ breast cancer has an increased tendency to metastasize to the brain. The incidence of CNS metastases in patients with HER2+ MBC ranges from 25%–34%.[36,37] Unlike trastuzumab, the small molecular size of lapatinib allows it to easily diffuse through the blood brain barrier.[38,39] In a phase II study evaluating the benefits of lapatinib and capecitabine on HER2 positive metastatic brain lesions,[40] 6% of patients who received lapatinib alone had objective responses and 21% had more or greater than a 20% volumetric reduction in CNS lesions. Of patients who received both lapatinib and capecitabine, 20% had an objective response and 40% had a more or greater than 20% volumetric reduction in their lesions. Lapatinib is therefore considered as an alternative HER2-targeted therapy to trastuzumab or as an important partner in dual HER2-targeted therapy for its potential to reduce the incidence or delay the onset of CNS disease.[41]

Lapatinib, as a monotherapy or in combination with other chemotherapeutics, also elicited low cardiotoxicity rates.[42] In a pooled study of 3689 patients from 44 clinical trials, only 1.6% of patients on the TKI experienced cardiac events and in those cases decrease in LVEF was rarely severe (mean nadir was 43%). The mean duration of the decrease in LVEF was 7.3 weeks and 88% of the patients had a full or partial recovery. The most frequently reported adverse effects with lapatinib alone, in order of frequency, are diarrhea, a rash consisting of occasionally pustular papules typical of EGFR-inhibitors, nausea, and fatigue.[43]

Three large phase III studies have identified trastuzumab to have a better therapeutic index than lapatinib. A neoadjuvant trial, GeparQuinto, evaluated the safety and efficacy of lapatinib in comparison to trastuzumab. 615 individuals were randomly assigned 1:1 to receive chemotherapy (four cycles of EC, epirubicin and cyclophosphamide, and four cycles of docetaxel) either with trastuzumab or with lapatinib.[44] The main study endpoint was pathological complete response (pCR) rate, defined as no microscopic—invasive and noninvasive—evidence of residual viable tumor in any resected specimen of the breast and axillary nodes. In the trial, 30.3% of patients on chemotherapy with trastuzumab and 22.7% of those on chemotherapy with lapatinib had complete pCR (odds ratio 0.68 with 95% CI 0.47–0.97 and $P = 0.04$). Additionally, the lapatinib arm produced more significant adverse events (87 versus 70 events) resulting in more treatment discontinuations (33.1% versus 14.0%) when compared to the trastuzumab arm. In the ongoing adjuvant trial, ALLTO, an independent data monitoring committee determined that the lapatinib alone arm was unlikely to meet the pre-specified criteria to demonstrate non-inferiority to trastuzumab alone in terms of DFS.[45]

Lastly, results from MA-31,[46] a phase III trial that randomized 656 women to either lapatinib (1250 mg/d titrated up to 1500 mg/d) and a taxane or trastuzumab and a taxane for first line therapy of HER2+ MBC were announced at the ASCO 2012 meeting. The primary endpoint, PFS, was 8.8 months for the lapatinib arm and 11.4 months for the trastuzumab arm (HR 1.33, $P = 0.01$). Patients were allowed to receive trastuzumab as (neo)adjuvant treatment if it was received more than 12 months prior to enrollment. Of note, only 18% of patients had prior trastuzumab therapy. The correlation of inferior PFS for lapatinib versus trastuzumab in the metastatic setting to inferior pCR in the neoadjuvant setting confirmed the wisdom of testing new targeted biologics head to head, with the standard of care in the first line metastatic setting, prior to testing them in the (neo)adjuvant setting.

To date, trastuzumab has therefore remained the standard of care and foundation for HER2+ breast cancer interventions. We will now focus on the relevant clinical trials which address the question of whether trastuzumab and lapatinib combination is better than trastuzumab alone.

Is Trastuzumab and Lapatinib Combination better than Trastuzumab Alone in the Metastatic Setting?

Clinical interest in trastuzumab and lapatinib combination therapy began with laboratory evidence both that lapatinib had significant in vitro activity against HER2-overexpressing breast cancer cell lines resistant to trastuzumab-containing media, and that trastuzumab and lapatinib dual therapy had synergistic

in vitro activity against four HER2-overexpressing cell lines.[27] There have been several mechanisms suggested as an explanation for the combination's effectiveness. As described earlier, a preclinical study identified that trastuzumab had little effect on survivin protein expression and apoptosis in HER2 overexpressing breast cancer cell lines, whereas the effect of lapatinib upon survivin expression and apoptosis was enhanced with combination therapy.[47] Since in vitro studies have demonstrated that trastuzumab combined with gefitinib, a selective EGFR inhibitor, also induces apoptosis seen with lapatinib alone, the apoptotic effects of lapatinib appear to be due to its ability to inhibit both EGFR and HER2.[48] Another possible mechanism for synergy with combination therapy is that lapatinib enhances immune-mediated trastuzumab-dependent cytotoxicity by inducing inactive HER2 homo- and heterodimers.[49] Based on the preclinical data, clinical studies evaluating the effectiveness of trastuzumab and lapatinib combination therapy were initiated.

A phase I clinical trial explored the safety, clinical feasibility, optimally tolerated regimen, pharmacokinetics, and preliminary clinical activity of the lapatinib plus trastuzumab treatment in HER2+ MBC.[50] Half of the 54 individuals that participated in the study were enrolled in the dose escalation group to define the optimally tolerated regimen and the other half to evaluate the pharmacokinetic profile. The dose escalation group consisted of 3 patient cohorts who were administered increasing doses of lapatinib (750 to 1500 mg/d) with weekly trastuzumab (4 mg/kg loading dose, then 2 mg/kg). It is worth emphasizing that while the optimally tolerated regimen (OTR) was determined to be a lapatinib dose of 1000 mg/d, responses were seen at 750 mg/d with no dose limiting toxicity (DLT). The 1000 mg/d does was chosen in part due to only one DLT (fatigue) observed in 11 patients in that cohort, whereas 2 DLTs were observed in the 1250 mg/d cohort. Subsequently, patients were treated at the OTR dose of 1000 mg/d to determine the overall safety and efficacy of the combination therapy, as well as the pharmacokinetic profile. For patients on the combination, the overall response rate (CR + PR) was 15%, making it a candidate treatment for HER2+ MBC. Patients on dual therapy had mild to moderate adverse events with no

grade 4 toxicities. The most common adverse events included diarrhea, rash, fatigue, nausea, anorexia, and vomiting. Diarrhea, fatigue, and rash were the most common of the grade 3 drug-related events. Low levels of cardiotoxicity were also reported. Lastly, the lapatinib and trastuzumab combination demonstrated the same pharmacokinetic profile as the two drugs individually, showing maximum concentration in plasma and area under the curve.

EGF104900, a phase III trial, investigated the possibility of a non-chemotherapy approach to treating HER2+ MBC in 291 patients.[51,52] Patients were required to have had prior treatment with an anthracycline, taxane, and a recent trastuzumab regimen, and were randomized to either lapatinib monotherapy (1500 mg/d) or lapatinib (1000 mg/d) and trastuzumab combination. The primary endpoint of the study was PFS and one secondary endpoint was OS. Final PFS and OS analysis published in 2012 confirmed trends seen in an earlier analysis—combination therapy had better median PFS (11.1 weeks versus 8.1 weeks; HR 0.74; 95% CI 0.58 to 0.94; $P = 0.011$) and median OS (14 months versus 9.5 months; HR 0.74; 95% CI 0.57 to 0.97; $P = 0.026$) than monotherapy. These numbers were similar in intention-to-treat analysis. The results were impressive for a chemotherapy-free approach in patients who had already become rather chemotherapy-experienced, even more so because the study allowed for crossover. Patients in the monotherapy arm who had disease progression after at least 4 weeks of lapatinib were allowed to receive combination therapy and more than half (77/148) did so. If the crossover patients were excluded from data analysis, the OS difference between combination and monotherapy increased slightly (14 months versus 8.3 months; HR 0.65; 95% CI 0.46–0.94; $P = 0.009$).

Not every participant benefitted from the dual treatment. Patients with ER+ HER2+ disease experienced no difference in median OS with dual therapy (12 versus 11.2 months; HR 0.85; 95% CI 0.57 to 1.26; $P = 0.404$), but those with ER− HER2+ disease did (16.5 versus 8.9 months; HR 0.68; 95% CI 0.47 to 0.98; $P = 0.012$). A likely explanation is that significant cross-talk between the ER and HER2 signaling pathways confounds sensitivity to HER2-targeted therapy.[53] The relevance of ER expression in HER2+ disease to the probability of treatment response with

HER2-targeted therapy is a theme that repeats itself in neoadjuvant trials, which will be reviewed later.

This trial has produced the first clinical data that suggests a favorable relationship between earlier initiation of dual HER2-targeted therapy and improvement in overall survival, despite allowance of crossover after progression. The OS benefit is also striking considering the relatively long post-progression survival, which has been considered by some to be an unfair scenario in which to expect OS to benefit from such a novel intervention.[54] The reason for this finding is likely complex. Subgroup univariate analysis which examined baseline covariates showed that the subgroups which most benefited from combination therapy were patients with better overall prognosis [ie, ECOG PS 0 versus ≥ 1 (HR 0.44; 95% CI 0.34 to 0.58; $P < 0.001$)], greater time from diagnosis to random assignment (HR 0.95; 95% CI 0.91 to 0.99, $P = 0.0285$), less metastatic sites [ie, <3 versus ≥ 3 (HR 0.44; 95% CI 0.33 to 0.57; $P < 0.001$)], non-visceral versus visceral metastases (HR 0.59; 95% CI 0.43 to 0.81; $P = 0.001$) and absence of brain metastasis (HR 0.64; 95% CI 0.44 to 0.92; $P = 0.0175$). It is possible that a more timely intervention with combination therapy is of greater importance in the metastatic setting when patients have HER2+ breast cancer biology that is not as aggressive or has more favorable prognostic features. It is likely that with a greater burden of metastatic disease, a greater complexity of mutations and diversity of cancer clones and a less favorable host environment limits efficacy of a chemotherapy-free, HER2+ targeted approach. The correlation between OS benefit and earlier initiation of combination therapy may also be related to the fact that the overall response rate in this study was relatively small (10.3% in combination versus 6.9% with lapatinib alone $P = 0.46$) and the improved clinical benefit rate (CBR or CR + SD + SD > 24 weeks) from combination therapy was derived mostly from stable disease (CBR 24.7% versus 12.4% with lapatinib alone, $P = 0.01$).

The EGF104900 study raised some safety concerns, particularly those of a cardiac nature. While most adverse events with an incidence of 10% or more were grade 1 or 2 events such as diarrhea, nausea, rash, fatigue, and vomiting or similar, in both treatment arms, 26% of patients in the combination arm and 16% in the lapatinib arm experienced serious cardiac events (defined as >20% decrease in left ventricular ejection fraction relative to baseline value and below the lower limit of normal for the institution). Diarrhea was more frequent in the combination arm (62% versus 48%) although grade 3 diarrhea was similar (7% versus 7%). Rash was more frequent in the monotherapy arm (29% versus 23%).

In summary, the EGF104900 study supports an important role for trastuzumab/lapatinib combination therapy for HER2+ MBC. While lapatinib is FDA approved for use in conjunction with capecitabine for HER2+ MBC that has progressed through chemotherapy with anthracyclines, taxanes and trastuzumab, the EGF104900 study validates consideration of a chemotherapy-free approach with trastuzumab and lapatinib in the same clinical setting. It might be tempting to offer trastuzumab and lapatinib as a chemotherapy free approach to patients who already have significant declines in their ECOG performance score either from their disease, comorbid conditions, or prior chemotherapy, but on this point it is worth emphasizing that subset analyses in EGF104900 did not identify benefit from trastuzumab and lapatinib combination in patients with ECOG PS ≥ 1 or those with visceral or brain metastases. Additionally, the trastuzumab and lapatinib combination was found to have low overall response rates. Therefore, lapatinib/capecitabine is preferable over lapatinib/trastuzumab if a patient has symptoms from metastatic disease or has visceral/brain metastases with trastuzumab-refractory HER2+ MBC.

The greater arsenal of HER2+ targeted therapies will raise questions more quickly than can be satisfactorily answered with clinical trials. An unanswered question is whether patients with HER2+ MBC would benefit from a trastuzumab/lapatinib +/− capecitabine combination as first line therapy. Likewise, clinical trials have yet to determine optimal sequential single-agent HER2 therapy (SSHT) or what the optimal regimen would be after progression through a chemotherapy free approach with lapatinib/trastuzumab combination. Several retrospective studies have now demonstrated that continuing trastuzumab beyond progression appears to be beneficial,[36,37,55–57] and most relevant to our current discussion, a randomized controlled study showed that in patients with HER2+ MBC

refractory to trastuzumab, continuing trastuzumab with the initiation of capecitabine was superior to capecitabine alone in median time to progression (TTP 8.2 months in capecitabine and trastuzumab versus 5.6 months in capecitabine alone; HR 0.69; 95% CI 0.48–8.97; $P = 0.0338$).[36,37,58] A phase III randomized controlled study is currently randomizing patients with HER2+ MBC to either trastuzumab and capecitabine or lapatinib and capecitabine, and will help fill in one of the many blanks regarding optimal SSHT.[59]

To optimize treatment of HER2+ MBC, accurate tests to predict which HER2-targeted therapy would be most effective for an individual patient would be ideal. However, such tests will be confounded by the phenomena of tumor heterogeneity within the primary tumor itself,[60,61] as well as the evolution of diverse clones in the course of MBC treatment[62] and the logistics of repeated biopsies. In the interim, rather than asking whether trastuzumab and lapatinib is better than trastuzumab alone in the metastatic setting, perhaps a better global question to ask for the future would be whether the consistent use of highly active anti-HER2 therapy (HAAHT) using two agents is superior to sequential single-agent HER2 therapy (SSHT) over the lifetime course of HER2+ MBC treatment. Between the June 2012 FDA approval of pertuzumab (a monoclonal antibody that blocks ligand-dependent HER2-HER3 heterodimerization) for combination with trastuzumab and docetaxel as first line therapy for HER2+ MBC, and the pending approval of T-DM1 (trastuzumab linked to cytotoxic agent emtansine), trastuzumab and lapatinib combination looks to be one of only three validated "two in one" or HAAHT strategies. We review this question further and the potential ethical dilemmas in the conclusions section.

We have not addressed the question of whether trastuzumab and lapatinib is better than trastuzumab alone when used in combination with anti-estrogen therapy in HR+ HER2+ MBC. This is due mainly to the relative lack of sufficient clinical evidence to answer this question for the metastatic setting. A clinical study is accruing data to help address this question and will be reviewed in the future studies section.[63] Until such data is available, the improved PFS documented with lapatinib and letrozole in the EGF3008 trial and trastuzumab and anastrazole in the TAnDEM study[64] (both compared to endocrine therapy alone) has established the importance of combining HER2-targeted therapy with endocrine therapy.[65]

Is Trastuzumab and Lapatinib Combination better than Trastuzumab Alone in the Neoadjuvant Setting?

Although neoadjuvant chemotherapy has not been shown to be superior or inferior to adjuvant chemotherapy in improving overall survival with locally advanced breast cancer,[66] neoadjuvant studies have generally been preferred in the investigation of new HER2-targeted agents for HER2+ breast cancer for reasons beyond the known benefits to the patient and physician. Reasons for this preference include additional prognostic information and the improved probability of breast conserving surgery. Neoadjuvant studies allow tumor snapshots before and after therapy and, in some cases, in-study, opening possibilities for new insights into biomarkers that either predict response to treatment and/or actually drive the therapeutic outcome and become new drug targets. Neoadjuvant studies also allow gradual introduction of more paradigm shifting or controversial approaches to breast cancer ie, dual HER2-targeted therapy without chemotherapy via integration of the study protocol with current standards of care neoadjuvantly and/ or adjuvantly. Additionally, since chemotherapy and trastuzumab is standard of care for any tumor larger than 1 cm (NCCN guidelines), there is less ambiguity without definitive pathological staging of lymph nodes as to whether a patient with a HER2+ breast cancer needs chemotherapy. Lastly, comparative effects from neoadjuvant studies give more immediate data compared to DFS and OS from adjuvant studies, and more rapidly informs development of novel trial concepts.

Prior to a discussion of the neoadjuvant trials, it is worthwhile to consider the significance of pCR in locally advanced HER2+ breast cancer. Although several smaller scale studies suggested pCR was prognostic for DFS and OS,[67–69] a recent analysis strongly validates the significance of pCR for HR− HER2+ breast cancer. In a highly powered review of more than 6377 patients enrolled in 7 neoadjuvant anthracycline-taxane based chemotherapy clinical trials, Von Minckwitz et al demonstrated that both the specific definition of pCR and the subtype of breast cancer were important in terms of the reliability of pCR as

a surrogate for DFS and OS.[70] The optimal definition to this end was evidence that there was neither residual invasive cancer nor in situ disease in the breast and lymph nodes. The most commonly reported pCR definition in the neoadjuvant trials to be discussed in this review was no evidence of residual invasive cancer in the breast and lymph nodes (allowance of in situ disease), which was the second best definition in this analysis. Compared to luminal A/B (HR+) breast cancer subtypes, patients with non-luminal (HR−) HER2+ breast cancer were not only more likely to achieve pCR using this definition (27.6% without trastuzumab and 32.9% with trastuzumab) but the pCR was also found to have significant prognostic value for DFS and OS. Importantly, pCR in luminal B (HR+) HER2+ breast cancer did not have prognostic value for DFS and OS (nor luminal A). Significance of pCR was also found with luminal B HER2− and triple negative breast cancer subtypes. Whether pCR has similar value when HER2-targeted therapy is given without chemotherapy remains unknown, since this analysis was limited to patients receiving chemotherapy, predominantly anthracycline-taxane containing regimens.

As of September 2012, five neoadjuvant studies with a treatment arm that included trastuzumab and lapatinib combination have reported results on pCR rate (See Table 1 for overview). The international phase III NeoALTTO study[57,71] randomized 455 patients with locally advanced (>2 cm) HER2+ breast cancer to 3 treatments arms: oral lapatinib (1500 mg/d), trastuzumab (4 mg/kg loading dose, 2 mg/kg subsequent doses), or lapatinib (1000 mg/d) plus trastuzumab, the same doses as the EGF104900 study. The HER2-targeted therapy was given alone for 6 weeks and then with weekly paclitaxel for 12 weeks until surgery. After surgery, patients were treated with 4 cycles of FEC (5-fluorouracil, epirubicin, and cyclophosphamide without concurrent HER2-targeted therapy), followed by 34 weeks on the same HER2-targeted treatment given prior to surgery. In this study, the primary endpoint, pCR, was defined by NSABP criteria ie, as no invasive cancer in the breast. The pCR for the combination group was 51.3%, almost double the pCR of the trastuzumab and lapatinib alone groups, 29.5% and 21.1% respectively. When using a definition of no invasive disease in the breast and lymph nodes, pCR was 46.8% for combination

and 27.6% and 20.0% for trastuzumab and lapatinib respectively. Hormone receptor negative (HR−) tumors had an overall higher pCR compared to HR+ tumors for all treatment arms. Regardless, combination therapy produced the highest pCR rates in both HR+ (42% for combination versus 16.3% for lapatinib and 22.7% for trastuzumab) and HR− (61.3% for combination versus 33.8% for lapatinib and 36% for trastuzumab) breast cancer. All of these differences in pCR were significant when comparing the combination arm to trastuzumab alone.

Toxicities such as diarrhea, neutropenia, and elevation of liver enzymes were more common in the two arms containing lapatinib versus trastuzumab alone and such toxicities contributed to the higher rates of discontinuation in these treatment groups (18.8% of the patients discontinued due to adverse events in the lapatinib arm, 1.3% in the trastuzumab arm, and 21% in the combination). The frequency of treatment discontinuation and adverse events might have been due to pharmacokinetics of lapatinib and paclitaxel concurrent therapy. This combination has been shown to cause an increase of more than 20% in systemic exposure to both drugs.[72] Another study noted more adverse events—specifically grade 3 diarrhea causing lapatinib dose reductions—when lapatinib 1000 mg/d was added to paclitaxel and trastuzumab.[73] In fact, the NeoALLTO protocol was later modified and the lapatinib dose was amended and reduced from 1000 mg to 750 mg in the combination group. However, due to fast accrual, only about a third of patients in the combination arm actually started at the lower dose. One patient with diabetes in the combination group died immediately after the end of treatment, from complications related to hypoglycemia. Only one patient in each treatment arm had a left ventricular ejection fraction (LVEF) of less than 50% and a decrease of more than 10% from baseline. One patient in the combination group developed class III congestive heart failure and showed a LVEF decrease from 66% to 55%, but recovered after therapy was stopped. Overall, this study showed that dual therapy is more effective at achieving pCR in the treatment of HER2+ breast cancer in the neoadjuvant/adjuvant setting, albeit with significantly greater toxicity.

Similar findings were observed in a phase II study, CHERLOB, where 121 preoperative HER2+

BC patients were randomized to three treatment arms where HER2-targeted therapy was given throughout an anthracycline and taxane based neo-adjuvant chemotherapy: arm A of trastuzumab; arm B of lapatinib (1500 mg); and arm C of trastuzumab and lapatinib (1000 mg) combined.[74] Chemotherapy included 12 weeks of weekly paclitaxel (80 mg/m²) followed by 4 courses of fluorouracil, epirubicin, and cyclophosphamide (FEC75) every 3 weeks. The primary endpoint, pCR, defined as absence of invasive tumor in the breast and axillary lymph nodes (ie, allowance of residual DCIS) was 25% in arm A, 26.3% in arm B, and 46.7% in arm C. Just as in the NeoALLTO study, a near doubling of the pCR rate was observed with combination therapy (risk ratio 1.81; $P = 0.019$ in exploratory analysis versus the pooled two single-agent arms A and B). Consistent also with NeoALLTO, pCR was higher in ER− cases (41.3% versus 28.8%).

The improved pCR with combination therapy also came with increased adverse events (primarily due to the lapatinib component) such as diarrhea (grade 3: 2.7% in arm A, 33% in arm B, 34.8% in arm C), dermatologic toxicities (grade 3: 5.5% in arm A, 12.8% in arm B, 10.8% in arm C), and hepatic toxicities (grade 3: 2.7% in arm A, 12.8% in arm B, 4.3% in arm C). The protocol starting doses of lapatinib were amended for arm B and C, where lapatinib was reduced from 1500 mg to 1250 mg and from 1000 mg to 750 mg respectively, in order to address a high occurrence of grade 3 diarrhea in arm B (20%) and arm C (41%). Even though the majority of patients enrolled to lapatinib containing arms received the amended dose reduction, 30% of patients from arm B and 17% from arm C discontinued the trial due to adverse reactions, and 43.6% in arm B and 54% in arm C had to schedule breaks in their treatment. For patients enrolled before and after the protocol amendment, a lapatinib dose reduction was required in 80% and 54% respectively for arm B and 55% and 34% for arm C. There were no significant cardiac toxicities (1 patient in Arm A had an asymptomatic decrease in LVEF below limit of normal) even though trastuzumab and lapatinib were given concurrently with an anthracycline. Similar to the NeoALLTO study, even with the high rate of dose reductions and treatment discontinuations, CHERLOB demonstrated nearly a doubling of pCR

rate with combination therapy versus single agent HER2-targeted therapy.

Like CHERLOB, NSABP protocol B-41 also examined the impact of trastuzumab and lapatinib combination on pCR when given with an anthracycline and taxane based neoadjuvant chemotherapy regimen. However, unlike CHERLOB, HER2-targeted therapy was not given concurrently with an anthracycline. The results were recently announced at the ASCO 2012 annual meeting. A total of 529 women with HER2+ operable breast cancer received neoadjuvant 4 cycles of AC followed by 12 doses of "weekly paclitaxel" (3 treatments given every 4 weeks), and were randomized to receive the paclitaxel with either weekly trastuzumab, lapatinib (1250 mg/d) or trastuzumab and lapatinib (750 mg/d) combined. Of 519 evaluable patients, pCR defined by NSABP criteria (no invasive disease in the breast) was 52.5% for the trastuzumab arm, 53.2% for the lapatinib arm, and 62% for the combination arm, with the combination arm not quite obtaining statistical significance ($P = 0.075$). For HR+ subtypes (63% of the study population), pCR was 46.7%, 48% and 55.6% respectively and for HR− subtypes pCR was 65.5%, 60.6% and 73% respectively. When pCR was more tightly defined as no invasive disease in the breast or lymph nodes, percentages of 49.1%, 47.4% and 60.4% were observed, with the latter achieving statistical significance ($P = 0.04$). Grade 3 and 4 toxicities, particularly diarrhea, were 2%, 20%, and 27% respectively. Symptomatic grade 3 and 4 left ventricular systolic dysfunction in 4%, 4%, and 2% respectively.

At ASCO 2011,[75] Holmes et al presented results from a phase II trial where 100 patients with operable HER2+ breast cancer were randomized to neoadjuvant trastuzumab, lapatinib (1250 mg/d), or trastuzumab and lapatinib combination (1250 mg/d) for 2 weeks, a repeat biopsy, then the same HER2-targeted therapy concurrently with FEC75 for 4 cycles and paclitaxel weekly for 12 weeks. Both lapatinib arms used 750 mg/d during FEC, 1000 mg/d during paclitaxel. In addition to taking molecular profiles of the index tumor before and after HER2-targeted therapy, the study also documented pCR (defined as absence of invasive cancer in the breast and lymph nodes) rates of 54%, 45% and 74% respectively. Permanent treatment discontinuations due to adverse events were 9.4% (3/32) in the trastuzumab arm, 11.7% (4/34) in the lapatinib arm,

and 25.8% (8/31) in the combination arm (personal communication). The reasons 97 and not 100 patients were included in this analysis were early discovery of metastatic disease in the liver, metastatic disease in the lung, and patient choice to withdraw from study before initiation of therapy.

Lastly, a phase II trial TBCRC 006 evaluated the efficacy of neoadjuvant weekly trastuzumab and lapatinib (1000 mg/d) without chemotherapy for 12 weeks amongst 66 patients with operable HER2+ breast cancer.[76] Patients with HR+ breast cancer were also given letrozole and goserelin if premenopausal. Biopsies were obtained prior to the intervention, as well as during weeks 2, 8, and 12, in order to evaluate responses. Approximately 65% of the tumors were HR+. This treatment protocol generated a pCR rate of 28%, with pCR defined as absence of invasive cancer in the breast. Median size of index tumors was 6 cm and 62% had lesions larger than 5 cm in diameter, 54% were pre-menopausal, and 65% of the tumors were HR+. Similar to the findings of NeoALLTO and CHERLOB, pCR was higher for HR− breast cancer (40%) versus HR+ breast cancer (21%). Approximately 56% of the HR+ breast cancers had less than 1 cm of residual disease, generating a hypothesis that longer treatment would have induced a higher pCR rate. Toxicities were mostly composed of grade 1 and 2 diarrhea (66%), nausea (31%), rash (46%), and abnormal LFTs (25%), with 18% of participants experiencing grade 3 metabolic, gastrointestinal, and hepatic toxicities, and 1 patient having grade 4 hepatotoxicity. 8% of patients had to discontinue treatment. Overall, the TBCRC 006 trial demonstrated that the combination of trastuzumab and lapatinib with anti-estrogen therapy can be effective in HR+ HER2+ breast cancer.

A meta-analysis that included four of the five neoadjuvant studies discussed here, excluding TBCRC 006, pooled a total of 779 patients who received neoadjuvant chemotherapy with either trastuzumab and lapatinib combination or trastuzumab alone, and calculated an average pCR (defined as invasive disease in breast and axilla) of 53% (209/392) for combination compared to 39% (150/387) for trastuzumab alone.[77] The probability of pCR was significantly higher for the combination (RR 1.39, 95% CI 1.20–0.63; $P < 0.001$). However, combination therapy did not result in a higher breast conserving surgery rate

(RR 0.98, 95% CI 0.85–1.14, 3 trials 734 patients). Adverse events pooled from the studies reporting sufficient information were reported in terms of events/total number of patients in the combination arms, and relative risk was reported relative to the trastuzumab arms. Grade 3 or 4 diarrhea had a frequency of 25.6% (95/371, RR 11.54, 95% CI 5.69–93.41, $P < 0.001$) and while other adverse events did not have RR of statistical significance, discontinuation of treatment was 29.6% (94/317, RR 5.89, 95% CI 0.56–61.69 $P = 0.14$) and grade 3–4 dermatologic toxicity was 7.6% (15/198, RR 2.27, 95% CI 0.90–0.72, $P = 0.08$). Of note, cardiac toxicity was rare with only 1 of 198 patients (NeoALLTO and CHERLOB) having an LVEF of less than 50% or a decline greater than 10% from baseline in the combination arms. The low rate is surprising, given that 46 patients were from the CHERLOB study and received anthracycline concurrent with combination therapy (none of which had cardiac toxicity). Excluded from those totals, patients in NSABP B-41 who received anthracycline chemotherapy without dual HER2-targeted therapy had a 2% incidence of symptomatic grade 3 or 4 LV systolic dysfunction.

Table 1 provides an overview of the five neoadjuvant trials discussed. It is interesting to note that even though NSABP B-41 utilized one of the shortest durations of HER2-targeted therapy neoadjuvantly (16 weeks), the pCR rate of 60.4% was among the highest for trastuzumab and lapatinib combination therapy. NSABP B-41 was the only study that utilized an AC/T backbone and had rather strict criteria for continuation of HER2-targeted therapy within 1–7 days prior to surgery. Unlike CHERLOB and Holmes et al, where patients got FEC75x4 and weekly paclitaxel × 12, NSABP B-41 did not give concurrent HER2-targeted therapy with the anthracycline and used the lowest protocol dose of lapatinib (750 mg/d). The average pCR of patients receiving combination HER2-targeted therapy from the CHERLOB and Holmes et al studies was 58.1%, essentially similar to NSABP B-41. The numbers, while inconclusive, are a reminder that a definitive randomized head to head clinical trial is needed before concluding that the longer courses of HER2-targeted therapy given concurrently with a regimen like FEC75/P are indeed superior.

Although not specifically testing the trastuzumab and lapatinib combination, phase II TRYPHAENA

Table 1. Overview of neoadjuvant trials looking at pCR for trastuzumab and lapatinib combination.

	Neoadjuvant treatment arms	Lapatinib dose (mg)	Duration of neoadjuvant HER2-targeted therapy	Number of patients	pCR (no invasive dz in breast and lymph nodes)	Treatment discontinuation rates
NeoALLTO	T × 6w, Pw + T × 12w	0	18	154	27.6%	1.3%
	L × 6w, Pw + L × 12w	1500	18	159	20.0%	18.8%
	TL × 6w, Pw + TL × 12w	750–1000	18	152	46.8%	21.0%
CHERLOB	(Pw × 12w, FEC75 × 4 over 12w) + T	0	26	39	25.0%	0%
	(Pw × 12w, FEC75 × 4 over 12w) + L	1250–1500	26	36	26.3%	17%
	(Pw × 12w, FEC75 × 4 over 12w) + TL	750–1000	26	46	46.7%	30%
NSABP B-41	AC × 4 over 12w, (Pw × 12w) + T	0	16*	173	49.1%	18%
	AC × 4 over 12w, (Pw × 12w) + L	1250	16*	178	47.4%	27%
	AC × 4 over 12w, (Pw × 12w) + TL	750	16*	173	60.4%	28%
Holmes et al	T × 2w, (FEC75 × 4 over 12w, Pw × 12w) + T	0	26	34	54.0%	9.4%
	L × 2w, (FEC75 × 4 over 12w, Pw × 12w) + L	750–1250	26	33	45.0%	11.7%
	TL × 2w, (FEC75 × 4 over 12w, Pw × 12w) + TL	750–1250	26	33	74.0%	25.8%
TBCRC 006	TL × 12w (no chemo, letrozole +/– goserelin if ER+)	1000	12	66	NR (28%, no invasive dz in breast)	8%

Notes: *NSABP B-41 required continuation of HER2-targeted therapy until 1–7 days before surgery, though the protocol defined 16 weeks minimum.
Abbreviations: T, trastuzumab; L, lapatinib; TL, combination; Pw, paclitaxel weekly.

results presented at SABCS 2011 shed more light on the relative importance of initiating dual HER2-targeted therapy—specifically trastuzumab and pertuzumab—concurrently with anthracyclines. In this study, 225 women with HER2+ operable breast cancer larder than 2 cm were randomized to arm A (FEC100 for 3 cycles), arm B (docetaxel for 3 cycles) or arm C [TCHP × 6 cycles (HP = trastuzumab and pertuzumab)]. In arm A, HP was started with cycle 1 of FEC. In arm B HP, was started with cycle 1 of docetaxel. Arm A had a pCR of 61.6%, arm B 57.3%, and arm C 66.2% using a definition of no invasive disease in the breast. Using a definition of no invasive or non-invasive disease in the breast and lymph nodes, arm A had a pCR of 50.7%, arm B 45.3% and arm C 51.9%. It is worth emphasizing that the study was not powered to detect differences in pCR between the treatment arms, and the primary endpoint was cardiac safety. Greater differences for arm A and B were seen when looking at the HR− subset, a subset where, again, pCR has more prognostic value for DFS and OS, whereas pCR in HR+ HER2+ breast cancer does not.[70] For the HR− subset, arm A had a pCR of 79.4%, arm B 65.0%, and arm C 83.8% using a definition of no invasive disease in the breast. In this subset, pCR using no invasive disease in the breast and axilla as a definition was not included in the SABCS oral presentation. Of note, a higher dose of epirubicin was used in TRYPHAENA versus the dose used in the CHERLOB, NSABP B41, and Holmes et al studies. The pCR rates show a numerical advantage for dual HER2-targeted therapy given concurrently throughout FEC/docetaxel compared to concurrently with docetaxel only, which is more pronounced in the HR− HER2+ breast cancer subset, although TCHP was slightly higher and avoids the concern of synergistic cardiotoxicity with HER2-targeted therapy and anthracyclines. Symptomatic LV systolic dysfunction was only seen in 2 patients in Arm B (2.7%). LV systolic dysfunction of all grades were 4 (5.6%) in Arm A, 3 (4.0%) in Arm B and 2 (2.6%).

Also unexplained in the five neoadjuvant trials summarized in Table 1 is the relatively low pCR rate seen with trastuzumab and FEC75/P in the CHERLOB study (25.0%). The initial study, which generated interest in FEC75/P with trastuzumab in HER2+ locally advanced breast cancer, was a small study of 34 patients wherein 18 received the trastuzumab concurrent with chemotherapy and 16 received chemotherapy alone. The trastuzumab group had a pCR rate (no invasive disease in breast and axilla) of 65.2% compared to the chemotherapy alone group 26.0% ($P = 0.016$).[21] The treatment schema of this study included an uncommonly used 24 hour paclitaxel infusion every 3 weeks and was closed prematurely due to the surprising efficacy. Pernas et al prospectively monitored 51 patients getting the same trastuzumab based chemotherapy regimen, but using the more common paclitaxel weekly dosing schema, and still observed a pCR of 61.4%.[78] Additionally, a retrospective chart review of patients treated at MD Anderson showed that 235 patients who received trastuzumab with FEC75/P had a pCR of 60.6% (versus 43.3% for 65 patients who received TCH; $P = 0.016$).[79] In this study, no significant difference in LVEF declines were seen between the two treatment protocols; however, patients treated with FEC75/P and trastuzumab had fewer cardiac morbidities at baseline ($P = 0.002$), suggesting an understandable selection bias.

Proponents of trastuzumab integrated throughout an FEC/P regimen cite data showing the relative importance of anthracyclines in HER2+ breast cancer. A pooled analysis of 5354 patients who received anthracycline and non-anthracycline curative intent chemotherapy regimens highlights this concern.[80] The study showed that patients with HER2+ breast cancer were more likely to benefit in terms of OS from anthracycline versus non-anthracycline regimens (HR of death from any cause 0.73; 95% CI 0.62–2.85; $P < 0.001$) compared to those with HER2− tumors (HR 1.03; 95% CI 0.92–2.16; $P = 0.6$). However, none of the trials included in this analysis gave HER2-targeted therapy. The pCR rates observed with dual-inhibition of HER2 and a taxane were 39.3% and 46.9% in NeoSphere and NeoALLTO respectively.[19,71] These were also similar to the pCR rates seen with anthracycline/taxane chemotherapy with concurrent trastuzumab throughout, at 38.0% and 45.0% with NOAH and GeparQuinto respectively.[19,44] These trends beg the question whether more patients can be spared anthracyclines and attain similar pCR and OS to current standard of care by employing more effective HER2-targeted therapy and whether dual-inhibition of HER2 concurrent throughout anthracycline/taxane chemotherapy can push pCR and OS higher in patients that have the highest risk of recurrence.

No neoadjuvant study has yet been completed that looks at trastuzumab and lapatinib combination with a TCH chemotherapy backbone, though one is in accrual (see next section). BCIRG 006, a study of 3222 patients, provides several insights into the risks and benefits of trastuzumab combined with an anthracycline/taxane regimen, compared to a non-anthracycline regimen, TCH. In this study, patients were randomized to receive adjuvant ACx4-docetaxel × 4 (AC-T), ACx4-docetaxel × 4 with 1 year of trastuzumab beginning with docetaxel (AC-TH), or TCH with 1 year total of trastuzumab. In a third planned efficacy analysis reported at SABCS 2009, 5 year DFS with AC-TH was 84%, TCH 81%, and AC-T 75%. Though numerically higher, AC-TH did not achieve statistical significance compared to TCH, although the study was not powered to detect equivalence between the two arms. However, both AC-TH and TCH attained significant improvement compared to AC-T for DFS and OS. The slightly numerical improvement in DFS and OS with AC-TH versus TCH came with the cost of higher rate of cardiac toxicity (21 versus 4 cases), and a small but awful risk of secondary leukemia.

Adding more granularity to the anthracycline question, Press et al found co-amplification of *TOP2A*, a target of anthracycline activity, and not HER2 amplification, is the more clinically useful predictor of benefit from anthracycline chemotherapy. This finding was achieved using a dataset of nearly 5000 breast cancers, including those from BCIRG 006.[81] Of note, 35% of HER2+ breast cancers had *TOP2A* co-amplification, whereas none were seen in HER2– cases, a finding that correlates with *TOP2A*'s close localization to HER2 on chromosome 17q. In another study of 373 patients with high-risk breast cancer, defined as cancer larger than 3 cm or inflammatory in nature, 46% of 94 HER2+ tumors also had TOP2A co-amplification, whereas no TOP2A co-amplification was found in the HER2– tumors. TOP2A co-amplification with HER2 was also associated with higher rate of pCR to an anthracycline-based neoadjuvant chemotherapy (30% versus 11% $P = 0.002$).[82]

Without mature data on DFS and OS from the neoadjuvant studies reviewed here, trastuzumab and lapatinib combination therapy is not ready to be incorporated into standard of care even though the aggregate pCR of five available neoadjuvant studies document that combination therapy results in superior pCR rates. In addition to DFS and OS data, several modifications are needed to improve the therapeutic index of lapatinib and trastuzumab combination, if it is to gain traction in the neoadjuvant setting, given the better therapeutic index of other combinations like pertuzumab and trastuzumab. Subpopulation treatment effect pattern plot analysis in the GeparQuinto study showed that patients who received neoadjuvant lapatinib have a generous therapeutic window—for example, patients who received lapatinib in a dose range of 700–1250 mg/d had no difference in pCR rates.[44] Additionally, despite the high rate of treatment delays and discontinuations seen in the reviewed neoadjuvant studies, pCR rates remained impressive for combination therapy in NeoALLTO and CHERLOB. Preclinical data also shows that reducing the dose of lapatinib and trastuzumab by half, either by reducing the daily dose by half or by using an intermittent treatment schedule, did not lead to significant differences in rates of complete regression and tumor recurrence in a xenograft mouse model.[83]

Taken altogether the data suggest that future studies should attempt to validate a lower dose of lapatinib for dual HER2-inhibition with trastuzumab, in all treatment settings. Reliable biomarkers are needed that will help identify which patients are most likely to benefit from trastuzumab and lapatinib combination and which patients are candidates for a chemotherapy free approach. TOP2A co-amplification in HER2+ breast cancer might help identify patients more likely to benefit from anthracycline chemotherapy. A chemotherapy-free approach using dual-inhibition of the HER2 pathway may be particularly desirable for treatment of the controversial T1aT1b (<1 cm) HER2+ operable breast cancer, where no standard of care has yet been established with a prospective, randomized clinical trial.

Future Studies

There are several studies currently in accrual that will answer more questions regarding the therapeutic index of using a trastuzumab and lapatinib combination. CALGB 40601 will compare the primary endpoint of pCR in the breast using neoadjuvant weekly paclitaxel for 16 weeks combined with three HER2-targeted regimens—weekly trastuzumab, lapatinib 1500 mg/d, or combination therapy with lapatinib

750 mg/d.[84] Of note, the lapatinib arm has been discontinued as of June 15 2011 due to the higher toxicity and lower pCR rates already documented in NeoALTTO and GeparQuinto results. Patients will also receive additional adjuvant treatment such as radiation, hormone therapy, and chemotherapy, if deemed necessary by the treating physician. In addition to the primary endpoint of pCR, patients will be followed for 10 years to document RFS and OS.

ICORG 10-05 (TCHL) is a phase II neoadjuvant study that compares the efficacy of TCH (docetaxel, carboplatin, trastuzumab), TCHL (docetaxel, carboplatin, trastuzumab, lapatinib at 1000 mg/d) and TCL (docetaxel, carboplatin, lapatinib at 1000 mg/d) based on pCR, the primary endpoint.[85] The secondary endpoints of the study include disease free survival, overall survival, clinical response rate, and overall response rate. After surgery, all treatment arms will receive trastuzumab to complete a total of one year of trastuzumab therapy.

EORTC 10054, also known as LAPATAX, is a phase II trial that will offer a neoadjuvant chemotherapy backbone of 3 cycles of FEC100 followed by 3 cycles of docetaxel and will randomize 150 patients to receive either trastuzumab, lapatinib, or both, starting only with the docetaxel.[86] Stage 1 of the study is completed and confirmed that G-CSF and docetaxel at 100 mg/m^2 can be given safely with lapatinib at 1250 mg/d. Patients in all treatment arms will receive adjuvant trastuzumab and hormone therapy as per local guidelines.

The largest adjuvant study looking at trastuzumab and lapatinib combination, ALTTO, closed to accrual in 2011, successfully enrolled 8000 patients in 50 countries and anticipates results for DFS by July 2013. The complex design includes patients receiving anthracycline/taxane chemotherapy as well as non-anthracycline chemotherapy (TCH), both neoadjuvantly and adjuvantly, and randomizes patients to receive HER2-targeted therapy either as trastuzumab, lapatinib, trastuzumab followed by lapatinib, or trastuzumab concurrent with lapatinib, for a total of 52 weeks. The doses used for combination therapy will be lapatinib 750 mg/d and trastuzumab 2 mg/kg weekly when given concurrent with a taxane, and then 1000 mg/d and 6 mg/kg every 3 weeks during maintenance therapy. The lapatinib alone arms will receive 750 mg/d during taxanes and then 1500 mg/d during maintenance.

Meanwhile, the role of lapatinib and trastuzumab dual therapy in the first line treatment of HR+ HER2+ MBC will be better defined by an ongoing III clinical trial that randomizes postmenopausal women with HR+ HER2+ MBC to treatment with an aromatase inhibitor (AI: letrozole, anastrazole or exemestane) with either trastuzumab, lapatinib (1500 mg/d), or dual therapy with lapatinib 1000 mg/d.[63] Eligible patients are required to have received trastuzumab and endocrine therapy in the (neo)adjuvant setting and may not have received prior treatment for metastatic disease. The primary endpoint is comparing the overall survival of trastuzumab/lapatinib/AI versus trastuzumab/AI. The secondary endpoint looks at overall survival, progression free survival, overall response rate, clinical benefit rate, and safety and tolerability of the three treatment arms.

Conclusion and Ethical Concerns

Lapatinib and trastuzumab combination therapy has better efficacy than single agent HER2-targeted therapy in both the metastatic and (neo)adjuvant setting, but at the cost of greater toxicity. In patients with trastuzumab refractory HER2+ MBC, improved PFS and OS with combination therapy has been documented compared to lapatinib therapy alone, despite allowance of crossover to combination therapy. The impact of combination therapy when utilizing concurrent chemotherapy or hormone therapy for HR+ HER2+ MBC remains unclear; however, a study actively accruing will help answer this question. Combination therapy in the neoadjuvant setting likewise has better efficacy in terms of pCR, but data from neoadjuvant studies are not yet mature enough to answer whether it improves DFS and OS. Although the pCR rate has been shown to be a reliable proxy for DFS and OS in HR− HER2+ breast cancer, due to the greater toxicity, financial cost, and nearly 30% average discontinuation rate, it is too early to declare that the standard of care for operable HER2+ breast cancer larger than 1.0 cm has changed.

Optimal sequence and use of combination therapy will be even more complex as the number of available HER2-targeted agents increase. As we have reviewed elsewhere,[87] clinical trials such as CLEOPATRA (metastatic) and NEOSPHERE (neoadjuvant) have

documented impressive efficacy, as well as superior tolerability with a trastuzumab and pertuzumab combination. Additionally, the FDA will likely approve T-DM1 as 2nd line therapy for HER2+ MBC,[88] and ongoing clinical trials might identify improved efficacy of T-DM1 combined with pertuzumab.

Unfortunately the real world question for most clinicians and patients in the United States is not only whether dual-HER2 therapy is better than HER2 monotherapy, but whether insurances and third-party payers will cover dual-HER2 therapy outside of the FDA approved indications. In the United States oncologists are already reporting difficulty in using pertuzumab and trastuzumab combination for patients with HER2+ MBC beyond first line therapy, despite clinical trials that support its efficacy and safety beyond first line. At the time of this publication, pertuzumab costs $2830 for 420 mg and trastuzumab $2009 for 440 mg and a 52 week course of both would start at $107,298 for a Veterans Hospital facility.

We anticipate that a probable theme that will develop over the next decade is that patients with HER2+ metastatic breast cancer will benefit most from an up-front strategy of highly active anti-HER2 therapy (HAAHT) and that similar lessons learned from the optimal treatment of HIV and chronic myeloid leukemia (CML) will cross-apply.[89,90] For example, the recommended approach to treatment of HIV or CML is to select a highly active anti-retroviral therapy (HAART) or a BCR-ABL targeting agent respectively, with the goals of reducing active viral copies to undetectable levels or obtaining a complete cytogenetic response within a preferred timeframe.[89,91] Thanks to improved HAART strategies and options, HIV seroconversion has now become a chronic illness with a reduction of death rates from 29.4/100 person-years in 1995 to 8.8 per 100 in 1997.[92] In fact, one study projects that a 30 year old man who seroconverts and is compliant with HAART is estimated to have a mean reduction of life expectancy of only 7 years.[93]

Although it is premature to extrapolate the HIV story to HER2+ metastatic breast cancer, HIV history foreshadows an important ethical lesson. One of the key innovations to HAART was the development of protease inhibitors, and patients with HIV who had private insurance were more likely to get a protease inhibitor as part of their HAART compared to those covered by Medicare or Medicaid. This discrepancy was identified as a key reason for the higher mortality seen in the Medicare/Medicaid population between 1994 and 1997.[92] To minimize a repeat of the socioeconomic prejudices observed in the evolution of HAART, in the treatment of HER2+ MBC, collaboration between academia and pharmaceutical companies will be needed to develop clinical studies that test whether persistent use of HAAHT (ie, trastuzumab and lapatinib, trastuzumab and pertuzumab, and TDM-1 +/− pertuzumab) through the course of HER2+ MBC indeed leads to improved overall survival and manageable toxicity, particularly when compared to their use only for FDA-approved indications (ie, current practice realities).

Author Contributions

Conceived and designed the experiments: N/A. Analyzed the data: EA. Wrote the first draft of the manuscript: EA, EW. Contributed to the writing of the manuscript: EA, EW. Agree with manuscript results and conclusions: EA, EW, SG. Jointly developed the structure and arguments for the paper: EA. Made critical revisions and approved final version: EA, EW, SG. All authors reviewed and approved of the final manuscript.

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SG has received grants and consulting fees from Genetech and GSK, and is also a board member for both organizations. ERA has received consulting fees from Amgen. EW discloses no competing interests.

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The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest. Provenance: the authors were invited to submit this paper.

References

1. Cho HS, Mason K, Ramyar KX, et al. Structure of the extracellular region of HER2 alone and in complex with the Herceptin Fab. *Nature*. 2003;421:756–60.
2. Yarden Y, Sliwkowski MX. Untangling the ErbB signaling network. *Nat Rev Mol Cell Biol*. 2001;2:127–37.
3. Barok M, Isola J, Palyi-Krekk Z, et al. Trastuzumab causes antibody-dependent cellular cytotoxicity-mediated growth inhibition of submacroscopic JIMT-1 breast cancer xenografts despite intrinsic drug resistance. *Mol Cancer Ther*. 2007:2065–72.
4. Clynes RA, Towers TL, Presta LG, Ravetch JV. Inhibitory Fc receptors modulate in vivo cytotoxicity against tumor targets. *Nat Med*. 2000;2000:443–6.
5. Fendly BM, Winget M, Hudziak RM, Lipari MT, Napier MA, Ullrich A. Characterization of murine monoclonal antibodies reactive to either the human epidermal growth factor receptor or HER2/neu gene product. *Cancer Res*. 1990;50:1550–8.
6. Ghosh R, Narasanna A, Wang SE, et al. Trastuzumab has preferential activity against breast cancers driven by HER2 homodimers. *Cancer Res*. 2011;71:1871–82.
7. Junttila TT, Akita RW, Parsons K, et al. Ligand-independent HER2/HER3/PI3K complex is disrupted by trastuzumab and is effectively inhibited by the PI3K inhibitor GDC-0941. *Cancer Cell*. 2009;15:429–40.
8. Sliwkowski MX, Lofgren JA, Lewis GD, Hotaling TE, Fendly BM, Fox JA. Nonclinical studies addressing the mechanism of action of trastuzumab (Herceptin). *Semin Oncol*. 1999;26:60–70.
9. Spector NL, Blackwell KL. Understanding the mechanisms behind trastuzumab therapy for human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol*. 2009;27:5838–47.
10. Cobleigh MA, Vogel CL, Tripathy D, et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. *J Clin Oncol*. 1999;17: 2639–48.
11. Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. *J Clin Oncol*. 2002;20:719–26.
12. Marty M, Cognetti F, Maraninchi D, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *J Clin Oncol*. 2005;23:4265–74.
13. 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;344:783–92.
14. Seidman A, Hudis C, Pierri MK, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. *J Clin Oncol*. 2002;20:1215–21.
15. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med*. 2005;353:1659–72.
16. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med*. 2011;365:1273–83.
17. Smith I, Procter M, Gelber RD, et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet*. 2007;369:29–36.
18. Perez EA, Romond EH, Suman VJ, et al. Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. *J Clin Oncol*. 2011;29:3366–73.
19. Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. *Lancet*. 2010;375:377–84.
20. Untch M, Rezai M, Loibl S, et al. Neoadjuvant treatment with trastuzumab in HER2-positive breast cancer: results from the GeparQuattro study. *J Clin Oncol*. 2010;28:2024–31.
21. Buzdar AU, Ibrahim NK, Francis D, et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. *J Clin Oncol*. 2005;23:3676–85.
22. Nagy P, Friedlander E, Tanner M, et al. Decreased accessibility and lack of activation of ErbB2 in JIMT-1, a herceptin-resistant, MUC4-expressing breast cancer cell line. *Cancer Res*. 2005;65:473–82.
23. 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;99:628–38.
24. Berns K, Horlings HM, Hennessy BT, et al. A functional genetic approach identifies the PI3K pathway as a major determinant of trastuzumab resistance in breast cancer. *Cancer Cell*. 2007;12:395–402.
25. Nagata Y, Lan KH, Zhou X, et al. PTEN activation contributes to tumor inhibition by trastuzumab, and loss of PTEN predicts trastuzumab resistance in patients. *Cancer Cell*. 2004;6:117–27.
26. Sergina NV, Rausch M, Wang D, et al. Escape from HER-family tyrosine kinase inhibitor therapy by the kinase-inactive HER3. *Nature*. 2007;445:437–41.
27. Konecny GE, Pegram MD, Venkatesan N, et al. Activity of the dual kinase inhibitor lapatinib (GW572016) against HER-2-overexpressing and trastuzumab-treated breast cancer cells. *Cancer Res*. 2006;66:1630–9.
28. Xia W, Mullin RJ, Keith BR, et al. Anti-tumor activity of GW572016: a dual tyrosine kinase inhibitor blocks EGF activation of EGFR/erbB2 and downstream Erk1/2 and AKT pathways. *Oncogene*. 2002;21:6255–63.
29. Wood ER, Truesdale AT, McDonald OB, et al. A unique structure for epidermal growth factor receptor bound to GW572016 (Lapatinib): relationships among protein conformation, inhibitor off-rate, and receptor activity in tumor cells. *Cancer Res*. 2004;64:6652–9.
30. Xia W, Bisi J, Strum J, et al. Regulation of survivin by ErbB2 signaling: therapeutic implications for ErbB2-overexpressing breast cancers. *Cancer Res*. 2006;66:1640–7.
31. Xia W, Bacus S, Hegde P, et al. A model of acquired autoresistance to a potent ErbB2 tyrosine kinase inhibitor and a therapeutic strategy to prevent its onset in breast cancer. *Proc Natl Acad Sci*. 2006;103:7795–800.
32. 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;19:1068–74.
33. Cameron D, Casey M, Oliva C, Newstat B, Imwalle B, Geyer CE. Lapatinib plus capecitabine in women with HER-2-positive advanced breast cancer: final survival analysis of a phase III randomized trial. *Oncologist*. 2010;15:924–34.
34. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med*. 2006;355:2733–43.
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*. Nov 20, 2009;27(33):5538–46.
36. Bendell JC, Domchek SM, Burstein HJ, et al. Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. *Cancer*. 2003;97:2972–7.
37. Clayton AJ, Danson S, Jolly S, et al. Incidence of cerebral metastases in patients treated with trastuzumab for metastatic breast cancer. *Br J Cancer*. 2004;91:639–43.
38. Dhillon S, Wagstaff AJ. Lapatinib. *Drugs*. 2007;67:2101–8.

39. Gril B, Palmieri D, Bronder JL, et al. Effect of lapatinib on the outgrowth of metastatic breast cancer cells to the brain. *J Natl Cancer Inst*. 2008;100:1092–103.

40. Lin NU, Dieras V, Paul D, et al. Multicenter phase II study of lapatinib in patients with brain metastases from HER2-positive breast cancer. *Clin Cancer Res*. 2008;15:1452–9.

41. Gluck S, Castrellon A. Lapatinib plus capecitabine resolved human epidermal growth factor receptor 2-positive brain metastases. *Am J Ther*. 2009;16:585–90.

42. Perez EA, Koehler M, Byrne J, Preston AJ, Rappold E, Ewer MS. Cardiac safety of lapatinib: pooled analysis of 3689 patients enrolled in clinical trials. *Mayo Clin Proc*. 2008;83:679–86.

43. Burris HA III. Dual kinase inhibition in the treatment of breast cancer: initial experience with the EGFR/ErbB-2 inhibitor lapatinib. *Oncologist*. 2004;9 Suppl 3:10–5.

44. Untch M, Loibl S, Bischoff J, et al. Lapatinib versus trastuzumab in combination with neoadjuvant anthracycline-taxane-based chemotherapy (GeparQuinto, GBG 44): a randomised phase 3 trial. *Lancet Oncol*. 2012;13:135–44.

45. Lapatinib Clinical Trial Update. http://us.gsk.com/html/media-news/pressreleases/2011/2011-pressrelease-614856.htm. 2011.

46. Gelmon KA, Boyle F, Kaufman B, et al. Open-label phase III randomized controlled trial comparing taxane-based chemotherapy (Tax) with lapatinib (L) or trastuzumab (T) as first-line therapy for women with HER2+ metastatic breast cancer: Interim analysis (IA) of NCIC CTG MA.31/GSK EGF 108919. *J Clin Oncol*. 2012:LBA671.

47. Xia W, Gerard CM, Liu L, Baudson NM, Ory TL, Spector NL. Combining lapatinib (GW572016), a small molecule inhibitor of ErbB1 and ErbB2 tyrosine kinases, with therapeutic anti-ErbB2 antibodies enhances apoptosis of ErbB2-overexpressing breast cancer cells. *Oncogene*. 2005;24:6213–21.

48. O'Donovan N, Byrne AT, O'Connor AE, McGee S, Gallagher WM, Crown J. Synergistic interaction between trastuzumab and EGFR/HER-2 tyrosine kinase inhibitors in HER-2 positive breast cancer cells. *Invest New Drugs*. 2011;29:752–9.

49. Scaltriti M, Verma C, Guzman M, et al. Lapatinib, a HER2 tyrosine kinase inhibitor, induces stabilization and accumulation of HER2 and potentiates trastuzumab-dependent cell cytotoxicity. *Oncogene*. 2009;28:803–14.

50. Storniolo AM, Pegram MD, Overmoyer B, et al. Phase I dose escalation and pharmacokinetic study of lapatinib in combination with trastuzumab in patients with advanced ErbB2-positive breast cancer. *J Clin Oncol*. 2008;26:3317–23.

51. Blackwell KL, Burstein HJ, Storniolo AM, et al. Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: final results from the EGF104900 study. *J Clin Oncol*. 2012;30:2585–92.

52. Blackwell KL, Burstein HJ, Storniolo AM, et al. Randomized study of Lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. *J Clin Oncol*. 2010;28:1124–30.

53. Arpino G, Wiechmann L, Osborne CK, Schiff R. Crosstalk between the estrogen receptor and the HER tyrosine kinase receptor family: molecular mechanism and clinical implications for endocrine therapy resistance. *Endocr Rev*. 2008;29:217–33.

54. Saad ED, Buyse M. Overall survival: patient outcome, therapeutic objective, clinical trial end point, or public health measure? *J Clin Oncol*. 2012;30:1750–4.

55. Garcia-Saenz JA, Martin M, Puente J, et al. Trastuzumab associated with successive cytotoxic therapies beyond disease progression in metastatic breast cancer. *Clin Breast Cancer*. 2005;6:325–9.

56. Gelmon KA, Mackey J, Verma S, et al. Use of trastuzumab beyond disease progression: observations from a retrospective review of case histories. *Clin Breast Cancer*. 2004;5:52–8.

57. Stemmler HJ, Kahlert S, Siekiera W, Untch M, Heinrich B, Heinemann V. Prolonged survival of patients receiving trastuzumab beyond disease progression for HER2 overexpressing metastatic breast cancer (MBC). *Onkologie*. 2005;28:582–6.

58. von Minckwitz G, du Bois A, Schmidt M, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a german breast group 26/breast international group 03–05 study. *J Clin Oncol*. 2009;27:1999–2006.

59. Lapatinib plus capecitabine versus trastuzumab plus capecitabine in ErbB2 (HER2) positive metastatic breast cancer. http://clinicaltrials.gov/ct2/show/NCT00820222. 2012.

60. Durrett R, Foo J, Leder K, Mayberry J, Michor F. Intratumor heterogeneity in evolutionary models of tumor progression. *Genetics*. 2011;188:461–77.

61. Potts SJ, Krueger JS, Landis ND, et al. Evaluating tumor heterogeneity in immunohistochemistry-stained breast cancer tissue. *Lab Invest*. 2012;92:1342–57.

62. Nik-Zainal S, Van LP, Wedge DC, et al. The life history of 21 breast cancers. *Cell*. 2012;149:994–1007.

63. A study to compare the safety and efficacy of an aromatase inhibitor in combination with lapatinib, trastuzumab or both for the treatment of hormone receptor positive, HER2+ metastatic breast cancer. http://clinicaltrials.gov/ct2/show/NCT01160211. 2012.

64. 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;27:5529–37.

65. Gluck S, Arteaga CL, Osborne CK. Optimizing chemotherapy-free survival for the ER/HER2-positive metastatic breast cancer patient. *Clin Cancer Res*. 2011;17:5559–61.

66. Mauri D, Pavlidis N, Ioannidis JP. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. *J Natl Cancer Inst*. 2005;97:188–94.

67. Chollet P, Amat S, Cure H, et al. Prognostic significance of a complete pathological response after induction chemotherapy in operable breast cancer. *Br J Cancer*. 2002;86:1041–6.

68. Kuerer HM, Newman LA, Smith TL, et al. Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. *J Clin Oncol*. Feb 1999;17(2):460–9.

69. Shimizu C, Masuda N, Yoshimura K, et al. Long-term outcome and pattern of relapse after neoadjuvant chemotherapy in patients with human epidermal growth factor receptor 2-positive primary breast cancer. *Jpn J Clin Oncol*. 2009;39:484–90.

70. von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J Clin Oncol*. 2012;30:1796–804.

71. Baselga J, Bradbury I, Eidtmann H, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. *Lancet*. 2012;379:633–40.

72. Crown JP, Burris HA, Jones S, et al. Safety and tolerability of lapatinib in combination with taxanes (T) in patients with breast cancer (BC). *J Clin Oncol*. 2007;25:1027.

73. Dang C, Lin N, Moy B, et al. Dose-dense doxorubicin and cyclophosphamide followed by weekly paclitaxel with trastuzumab and lapatinib in HER2/neu-overexpressed/amplified breast cancer is not feasible because of excessive diarrhea. *J Clin Oncol*. 2010;28:2982–8.

74. Guarneri V, Frassoldati A, Bottini A, et al. Preoperative chemotherapy plus trastuzumab, lapatinib, or both in human epidermal growth factor receptor 2-positive operable breast cancer: results of the randomized phase II CHER-LOB study. *J Clin Oncol*. 2012;28:2982–8.

75. Holmes FA, Nagarwala YM, Espina VA, et al. Correlation of molecular effects and pathologic complete response to preoperative lapatinib and trastuzumab, separately and combined prior to neoadjuvant breast cancer chemotherapy. *J Clin Oncol*. 2011;29:A506.

76. Chang JCN, Mayer IA, Forero-Torres A, et al. TBCRC 006: A multicenter phase II study of neoadjuvant lapatinib and trastuzumab in patients with HER2-overexpressing breast cancer [abstract]. *J Clin Oncol*. 2011;29:505.

77. Valachis A, Nearchou A, Lind P, Mauri D. Lapatinib, trastuzumab or the combination added to preoperative chemotherapy for breast cancer: a meta-analysis of randomized evidence. *Breast Cancer Res Treat*. 2012;135:655–62.

78. Pernas S, Gil-Gil M, de Olza MO, et al. Efficacy and safety of concurrent trastuzumab plus weekly paclitaxel-FEC as primary therapy for HER2-positive breast cancer in everyday clinical practice. *Breast Cancer Res Treat*. 2012;134:1161–8.

79. Bayraktar S, Gonzalez-Angulo AM, Lei X, et al. Efficacy of neoadjuvant therapy with trastuzumab concurrent with anthracycline- and nonanthracycline-based regimens for HER2-positive breast cancer. *Cancer*. 2012;118:2385–93.

80. Gennari A, Sormani MP, Pronzato P, et al. HER2 status and efficacy of adjuvant anthracyclines in early breast cancer: a pooled analysis of randomized trials. *J Natl* Cancer *Inst*. 2008;100:14–20.

81. Press MF, Sauter G, Buyse M, et al. Alteration of topoisomerase II-alpha gene in human breast cancer: association with responsiveness to anthracycline-based chemotherapy. *J Clin Oncol*. 2011;29:859–67.

82. Konecny GE, Pauletti G, Untch M, et al. Association between HER2, TOP2 A, and response to anthracycline-based preoperative chemotherapy in high-risk primary breast cancer. *Breast Cancer Res Treat*. 2010;120:481–9.

83. Rimawi MF, Wiechmann LS, Wang YC, et al. Reduced dose and intermittent treatment with lapatinib and trastuzumab for potent blockade of the HER pathway in HER2/neu-overexpressing breast tumor xenografts. *Clin Cancer Res*. 2011;17:1351–61.

84. Phase III randomized study of neoadjuvant paclitaxel in combination with trastuzumab (herceptin) with or without lapatinib ditosylate in patients with HER2-positive resectable stage II or III breast cancer. http://clinicaltrials.gov/ct2/show/NCT00770809. 2012.

85. A phase II neo-adjuvant study assessing TCH (docetaxel, carboplatin and trastuzumab), TCL (docetaxel, carboplatin and lapatinib) and the combination of TCHL (docetaxel, carboplatin, trastuzumab and lapatinib) in HER-2 positive breast cancer patients. (TCHL Phase II). http://clinicaltrials.gov/ct2/show/NCT01485926. 2011.

86. Cameron DA, Marreaud S, Zaman K, et al. LAPATAX: A randomized phase II trial of FEC-docetaxel combined with lapatinib and/or trastuzumab as neoadjuvant therapy of HER2-positive breast cancer—EORTC 10054 trial. *J Clin Oncol*. 2010;28:TPS116.

87. Ahn ER, Vogel CL. Dual HER2-targeted approaches in HER2-positive breast cancer. *Breast Cancer Res Treat*. 2012;131:371–83.

88. Blackwell KL, Miles D, Gianni L, et al. Primary results from EMILIA, a phase III study of trastuzumab emtansine (T-DM1) versus capecitabine (X) and lapatinib (L) in HER2-positive locally advanced or metastatic breast cancer (MBC) previously treated with trastuzumab (T) and a taxane. *J Clin Oncol*. 2012;30:LBA1.

89. Bock C, Lengauer T. Managing drug resistance in cancer: lessons from HIV therapy. *Nat Rev Cancer*. 2012;12:494–501.

90. Glickman MS, Sawyers CL. Converting cancer therapies into cures: lessons from infectious diseases. *Cell*. 2012;148:1089–98.

91. Cortes J, Kantarjian H. How I treat newly diagnosed chronic phase CML. *Blood*. 2012;120:1390–7.

92. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med*. 1998;338:853–60.

93. Nakagawa F, Lodwick RK, Smith CJ, et al. Projected life expectancy of people with HIV according to timing of diagnosis. *AIDS*. 2012;26:335–43.