Breast Cancer

Neoadjuvant Dual HER2-Targeted Therapy With Lapatinib and Trastuzumab Improves Pathologic Complete Response in Patients With Early Stage HER2-Positive Breast Cancer: A Meta-Analysis of Randomized Prospective Clinical Trials

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Neoadjuvant chemotherapy • Meta-analysis • Breast cancer • HER2 • Lapatinib • Trastuzumab

ABSTRACT

Background. Randomized clinical trials (RCT) that evaluated the addition of lapatinib to trastuzumab plus neoadjuvant chemotherapy (NAC) in patients with HER2-positive, operable breast cancer revealed a questionable improvement in pathologic complete response (pCR) rate. We performed a meta-analysis of prospective RCTs that examined the effect of adding lapatinib to trastuzumab and NAC on pCR rate.

Methods. PubMed databases and abstracts from the proceedings of the American Society of Clinical Oncology and the San Antonio Breast Cancer Symposium were searched for RCTs that compared lapatinib plus trastuzumab and NAC with trastuzumab in combination with NAC that included pCR as the primary outcome. Our main objective was to estimate the effect of adding lapatinib to trastuzumab plus NAC on pCR rate.

Results. In total, 1,017 patients with early stage breast cancer from 5 trials were included. Four trials examined the addition of lapatinib to trastuzumab plus NAC; this resulted in statistically significant improvement in pCR, defined as no residual carcinoma in breast and lymph nodes. The pCR rate was 55.76% and 38.36% in the lapatinib plus trastuzumab and the trastuzumab plus NAC arms, respectively (odds ratio [OR]: 1.94; 95% confidence interval [CI]: 1.44–2.60). In three trials, the rates of pCR, defined as no residual invasive carcinoma in breast only, for the lapatinib plus trastuzumab and trastuzumab-alone groups were 55.01% and 40.70%, respectively, also resulting in significant improvement (OR: 1.78; 95% CI: 1.27–2.50).

Conclusion. The addition of lapatinib to trastuzumab in combination with neoadjuvant chemotherapy significantly improves pCR rates in patients with HER2-positive breast cancer.

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Implications for Practice: This meta-analysis reports that the addition of lapatinib to trastuzumab and neoadjuvant chemotherapy improves pathologic complete response (pCR) rates in patients with HER2-positive breast cancer, regardless of the pCR definition or hormone receptor status.

INTRODUCTION

The outcomes of patients with HER2-amplified breast cancer have been dramatically improved by the development of trastuzumab, a chimeric monoclonal antibody to the extracellular region of the HER2 protein [1]. In recent years, many other inhibitors of the HER2 protein have become available, including small molecule tyrosine kinase inhibitors, other monoclonal antibodies, and antibody-drug conjugates [2]. Lapatinib is an orally bioavailable dual inhibitor of the intracellular portion of the HER2 protein and epidermal growth factor receptor, and aside from trastuzumab, it has been best studied in clinical trials to date. Given the promising results of trials that evaluated the addition of lapatinib to trastuzumab in metastatic disease [3], multiple studies have been conducted to evaluate the clinical benefit of adding...
lapatinib to standard trastuzumab plus chemotherapy for operable HER2-positive (HER2+) breast cancer in both neoadjuvant and adjuvant settings; results have been conflicting.

The NeoALTTO trial tested the addition of lapatinib to standard neoadjuvant chemotherapy (NAC) with weekly paclitaxel and trastuzumab. This trial reported a near doubling of the pCR rate from 29.5% to 51.3% (p < .0001) [4]. However, other large randomized neoadjuvant trials showed a trend toward improvement in pCR rates when trastuzumab and lapatinib were combined with NAC compared with standard NAC with trastuzumab alone, but that trend was not statistically significant [5, 6]. Given that multiple trials and a meta-analysis suggest improvement in disease-specific survival in patients who achieve pCR following neoadjuvant anti-cancer therapy [7], it is vital to understand the full impact of dual HER2-targeted therapy on pCR rates when lapatinib is combined with trastuzumab. In this report, we investigate the pCR rate when lapatinib is added to trastuzumab and NAC in early stage HER2+ breast cancer in an up-to-date, comprehensive meta-analysis of randomized clinical trials.

**Methods**

**Literature Search Strategy and Study Criteria**

PubMed citations were reviewed from January 1998 to January 2014. Clinical trials published in English were searched with the keywords HER2, breast cancer, and neoadjuvant. Abstracts from the San Antonio Breast Cancer Symposium and the American Society of Clinical Oncology annual meetings between 2009 and 2014 were also queried. Subsequently, studies were reviewed for eligibility, defined as randomized clinical trials of NAC with trastuzumab or NAC with trastuzumab and lapatinib for HER2+ operable breast cancer, with a primary endpoint of pCR rate. The eligible studies were carefully reviewed and screened for duplication or incomplete data. Efforts were made to contact investigators when relevant data were unclear.

**Data Extraction, Quality Control, and Risk of Bias**

Data extraction from eligible studies was conducted independently by three investigators (M.A.-R., M.H., E.R.M.) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement [8], and any discrepancies were resolved by consensus. The following information was collected for each study: first author’s name, year of publication, trial phase, definition of pCR (no invasive cancer in the breast only vs. no invasive breast cancer in breast and axillary lymph nodes), hormone receptor (HR) status, stage of breast cancer included, number of enrolled patients, chemotherapy backbone, treatment arms, and duration and schedule of NAC plus trastuzumab with or without lapatinib. To assess the validity of the included studies, we examined the randomization procedure, sample size, blinding procedure, loss to follow-up, dropout, and intention to treat. Jadad scores were used to assess the quality of each study [9].

**Outcome Definition**

The primary objective of our study was to compare the rates of pCR following NAC plus trastuzumab with or without lapatinib. Treatment with lapatinib alone was excluded from the analysis because of toxicities and sufficient evidence that single-agent lapatinib plus NAC has inferior efficacy compared with NAC with trastuzumab or with trastuzumab and lapatinib [4–6]. The definition of pCR varied among studies. Some studies defined pCR as no invasive disease in breast alone, whereas others defined pCR as no residual invasive disease in both breast and axillary lymph nodes. For the purpose of our analysis, we used pCR in the breast and lymph nodes as our primary endpoint and the definition of no invasive breast cancer in the breast as a secondary endpoint. As a subgroup analysis, we examined the difference in pCR rates for patients with HR+ versus HR− breast cancer.

**Statistical Analysis**

For the calculation of pCR incidence, the number of patients achieving pCR and the total number of patients in each treatment group were extracted from the selected studies for both definitions of pCR. The proportions of patients achieving pCR and the 95% confidence intervals (CIs) were derived for each treatment group for both definitions of pCR from each trial. We calculated summary pCR incidence rates and confidence intervals for each treatment group and pCR definition using random-effects meta-analysis modeling with the DerSimonian and Laird method, which considers both within-study and between-study variations [10].

The pooled estimates for the main effect of adding lapatinib to trastuzumab plus NAC for both definitions of pCR and the subgroup analysis were calculated from random-effects meta-analysis models using the DerSimonian and Laird method. Results were reported as pooled odds ratios and 95% CIs, with the patients receiving trastuzumab alone as the control group. Hypothesis tests comparing the differences between treatment groups for each definition of the outcome were conducted, and two-tailed p values < .05 were considered statistically significant. We assessed statistical heterogeneity among trials included in the meta-analysis using the I² statistic [11], which estimates the percentage of total variation across studies due to heterogeneity rather than chance. We considered an I² value of > 50% as indicative of substantial heterogeneity. A prespecified subgroup analysis was performed to determine whether the effect of adding lapatinib to trastuzumab plus NAC differed between HR+ and HR− patients. The difference in the odds ratios for the two subgroups was tested, and a two-tailed p value < .05 was considered statistically significant.

Publication bias was evaluated through funnel plots and with Begg’s and Egger’s tests [12, 13]. Statistical analyses were performed using RevMan 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, https://tech.cochrane.org) and Stata/SE version 11.0 (StataCorp, College Station, TX, http://www.stata.com).

**Results**

**Population Characteristics**

The original search yielded a total of 1,806 potentially relevant HER2 neoadjuvant breast cancer studies: 706 abstracts from PubMed and 1,100 from ASCO and SABCS meetings. The detailed selection process is presented in Figure 1. After evaluating each study for eligibility, we initially excluded 1,774 studies. The remaining 32 studies were carefully screened, and an additional 17 were excluded as duplicates. Two studies were...
excluded because they did not report pCR as the primary endpoint [14, 15], two studies were excluded because they are ongoing [16, 17], and six studies were excluded because they did not contain a combination lapatinib and trastuzumab arm [18–23]. Of the final five eligible randomized trials, four were peer-reviewed published reports [4, 6, 24, 25] and one was an abstract [5]. Two trials were phase II trials [24, 25], and three were phase III trials [4, 6, 25].

Among the five trials, two used a pCR definition of no invasive disease in the breast and lymph nodes (our primary objective) [24, 25], one included a pCR definition of no invasive breast cancer in the breast alone (our secondary objective) [5], and two included both definitions of pCR [4, 6]. In total, 1,017 patients were available for the meta-analysis. For the primary outcome of pCR in the breast and lymph nodes, 767 patients were evaluated, and 887 patients were available for the secondary outcome of pCR in the breast only. Baseline characteristics of each trial are presented in Table 1. All trials included patients with HER2+ breast cancer and a diagnosis of operable stage II–III breast cancer. Participants were randomly assigned to a control group (NAC plus trastuzumab) or to the treatment group (NAC plus trastuzumab and lapatinib). Treatments arms within trials were similar in terms of mean and median patient ages, HR status, nodal status, and stage of breast cancer. Patients were required to have adequate baseline organ function, good performance status, and normal systolic heart function at entry for all studies. Chemotherapy agents given with lapatinib and trastuzumab included taxanes [4–6, 24, 25], anthracyclines [6, 24, 25], cyclophosphamide [24, 25], and fluorouracil [24, 25].

Trastuzumab was administered at a 4-mg/kg loading dose followed by 2 mg/kg in every study. When lapatinib was used in combination with trastuzumab, it was initially administered at 1,000 mg and then reduced to 750 mg because of unacceptable toxicities in 4 studies [4, 6, 24, 25]. One study used 750 mg lapatinib in combination with trastuzumab from the time of study onset [5]. Two studies reported the intent-to-treat population in the analysis [4, 5], whereas two studies reported different populations as a result of some patients not having breast surgery [6, 25], protocol violations [25], or withdrawal of consent [6, 25]. In one study, analysis of pCR rates was performed only on participants who underwent the surgery and received at least 75% of chemotherapy [24].

Primary Outcome: Incidence of pCR in Breast and Lymph Nodes
A total of 767 patients (n = 384 in the lapatinib plus trastuzumab arm and n = 383 in the trastuzumab arm) from 4 studies [4, 6, 24, 25] were analyzed for the effect of adding lapatinib to trastuzumab plus NAC on pCR rate in both breast and axillary lymph nodes. The absolute pCR rate was estimated to be 38.36% (95% CI: 23.85%–52.88%) in the trastuzumab

Figure 1. Selection process for the randomized controlled trials included in the meta-analysis.
Abbreviations: AHT, anti-HER2 therapy; ASCO, American Society of Clinical Oncology; pCR, pathological complete response; SABCS, San Antonio Breast Cancer Symposium.
Table 1. Characteristics of the randomized controlled trials included in the meta-analysis

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Chemotherapy backbone</th>
<th>Duration (weeks)</th>
<th>Anthracycline containing</th>
<th>Arm</th>
<th>Participants enrolled (n)</th>
<th>Participants for analysis (n)</th>
<th>Quality of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carey et al., 2013 [5] (CALGB 40601)</td>
<td>III</td>
<td>P (80 mg/m²)</td>
<td>16</td>
<td>No</td>
<td>Trastuzumab, 4 mg/kg loading, then 2 mg/kg</td>
<td>120</td>
<td>120</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lapatinib plus trastuzumab, 750 mg/day</td>
<td>118</td>
<td>118</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lapatinib, 1,500 mg/day</td>
<td>67</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>Robidoux et al., 2013 [6] (NSABP B-41)</td>
<td>III</td>
<td>AC (60 mg/m², 600 mg/m²); P (80 mg/m²)</td>
<td>4 cycles chemotherapy, then 4 cycles P and AHT</td>
<td>Yes</td>
<td>Trastuzumab, 4 mg/kg loading, then 2 mg/kg</td>
<td>181</td>
<td>177c</td>
<td>3</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Lapatinib plus trastuzumab, 1,000 mg/day, then 750 mg/day</td>
<td>174</td>
<td>171</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lapatinib, 1,500 mg/day, then 1,250 mg/day</td>
<td>174</td>
<td>171</td>
<td></td>
</tr>
<tr>
<td>Guarneri et al., 2008 [25] (CHERLOB)</td>
<td>II</td>
<td>P (80 mg/m²), then FEC (600 mg/m², 75 mg/m², and 600 mg/m²)</td>
<td>12 weeks, then 4 courses</td>
<td>Yes</td>
<td>Trastuzumab, 4 mg/kg loading, then 2 mg/kg</td>
<td>36</td>
<td>36f</td>
<td>2</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lapatinib plus trastuzumab, 1,000 mg/day, then 750 mg/day</td>
<td>46</td>
<td>45</td>
<td></td>
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<td>Lapatinib, 1,500 mg/day, then 1,250 mg/day</td>
<td>39</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Baselga et al., 2012 [4] (NeoALTTO)</td>
<td>III</td>
<td>P (80 mg/m²)</td>
<td>6-week run-in, then 12 weeks AHT and P</td>
<td>No</td>
<td>Trastuzumab, 4 mg/kg loading, then 2 mg/kg</td>
<td>149</td>
<td>149</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lapatinib plus trastuzumab, 1,000 mg/day, then 750 mg/day</td>
<td>152</td>
<td>152</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td>Lapatinib, 1,500 mg/day</td>
<td>154</td>
<td>154</td>
<td></td>
</tr>
<tr>
<td>Holmes et al., 2013 [24]</td>
<td>II</td>
<td>FEC75 (500 mg/m², 75 mg/m², 500 mg/m²), then P (80 mg/m²)</td>
<td>AHT 2-week run-in, then with 4 courses, then P 12 courses</td>
<td>Yes</td>
<td>Trastuzumab, 4 mg/kg loading, then 2 mg/kg</td>
<td>33</td>
<td>26j</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lapatinib plus trastuzumab, 1,000 mg/day, then 750 mg/day</td>
<td>33</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lapatinib, 1,500 mg/day, then 1,250 mg/day</td>
<td>34</td>
<td>29</td>
<td></td>
</tr>
</tbody>
</table>

aStudy quality was assessed on the 7-item Jadad score, with a score range of 0–5 [9].
bThe lapatinib arm was closed when negative efficacy and toxicity data emerged from preliminary analysis of ALTTO.
Patients analyzed differed from intent to treat because they either withdrew consent from the study or did not have surgery.
On June 10, 2008, the starting dose of lapatinib was reduced to 1,250 mg in the lapatinib group and 750 mg in the combination group because of the excessive diarrhea reported in other trials using the initial doses.
Lapatinib doses were reduced because of the occurrence of grade 2 diarrhea in 20% of patients in the lapatinib-alone group and 41% of patients in the combination group.
Patients analyzed differed from intent to treat because of protocol violations or they withdrew consent.
Lapatinib dose was reduced from 1,000 to 750 mg when P was added to reduce the occurrence of diarrhea.
Lapatinib dose was reduced to reduce diarrhea after a safety review of the first 45 patients enrolled.
Patients analyzed differed from the intention-to-treat population because of selection of patients who received surgery and >75% chemotherapy.
Abbreviations: AC, doxorubicin and cyclophosphamide; AHT, anti-HER2 therapy; FEC, 5-fluourouracil, epirubicin, and cyclophosphamide; P, weekly paclitaxel.

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alone arm and 55.76% (95% CI: 45.19%–66.33%) in the combination arm using random-effects meta-analysis modeling. The odds of pCR in the breast and lymph nodes were 1.94 times higher for the combination arm (95% CI: 1.44–2.60; \( p < .0001 \); heterogeneity test: \( p = .55 \); \( I^2 = 0% \)) (Fig. 2A).

Secondary Outcome: Incidence of pCR in Breast Only

Data were available for the pCR definition of no invasive disease in the breast only for the comparison of trastuzumab versus the combination of trastuzumab and lapatinib in 3 trials (887 patients; 446 patients treated with trastuzumab and 441 patients treated with lapatinib plus trastuzumab) [4–6]. Two studies were excluded because pCR in the breast only was not evaluated [24, 25]. The absolute pCR rate was 40.70% (95% CI: 26.87%–54.53%) in the trastuzumab arm in comparison to 55.01% (95% CI: 47.55%–62.46%) in the combination arm. The odds of achieving pCR in the breast was statistically higher for the dual HER2-targeted combination arm (OR: 1.78; 95% CI: 1.27–2.50; \( p = .0007 \); heterogeneity test: \( p = .22 \); \( I^2 = 35\% \)) (Fig. 2B).

Influence of Hormone Receptor Status on pCR Rate

Two trials [4, 6] (\( n = 649; n = 326 \) in the trastuzumab arm and \( n = 323 \) in the lapatinib plus trastuzumab arm) reported the effect of HR status on pCR rates (defined as no residual invasive cancer in breast only) for the comparison of trastuzumab versus the combination of trastuzumab and lapatinib. One study was excluded because it did not examine HR status [25], and two studies were excluded because they reported HR+ and HR− subgroups as pCR percentages without providing the total numbers of patients analyzed [5, 24]. The pCR rates for HR+ patients were 34.76% (95% CI: 11.18%–58.33%) in the trastuzumab arm compared with 48.87% (95% CI: 35.16%–62.57%) in the combination arm. The absolute pCR rates for HR− patients were 50.80% (95% CI: 22.42%–79.19%) in the trastuzumab arm compared with 67.19% (95% CI: 55.74%–78.64%) in the combination arm. The odds of achieving pCR in the breast were 1.76 times higher for the combination arm in the HR+ subgroup (OR: 1.76; 95% CI: 1.06%–2.93%; \( p = .03 \); heterogeneity test: \( p = .23 \); \( I^2 = 29\% \)) (Table 2). The odds of achieving pCR in the breast were 2.06 times higher for the combination arm in the HR− subgroup (OR: 2.06; 95% CI: 1.08%–3.91%; \( p = .03 \); heterogeneity test: \( p = .21 \); \( I^2 = 37\% \)) (Table 2). The odds ratios for the HR+ and HR− subgroups did not differ significantly (\( p = .71 \)).

Study Quality and Publication Bias

All trials included in this meta-analysis were randomized, multicenter, open-label, phase II/III trials. No evidence of publication bias was detected for the odds of pCR in breast and lymph nodes by treatment regimen using Egger’s test (\( p = .365 \)) and Begg’s test (\( p = .99 \)). In addition, no evidence of publication bias was detected for the odds of pCR in breast only by treatment regimen using Egger’s test (\( p = .856 \)) and Begg’s test (\( p = .99 \)).

**Discussion**

To our knowledge, this report is the largest and most current to show a significant increase in the pCR rate with the use of dual HER2-targeted therapy with lapatinib in combination with trastuzumab in early stage HER2-amplified breast cancer. The incidence of pCR in breast and lymph nodes in the lapatinib plus trastuzumab arm was 55.76% (95% CI: 45.19%–66.33%) compared with 38.36% (95% CI: 23.85%–52.88%) in the trastuzumab-only arm. Comparable efficacy was seen in studies examining the pCR rate in breast only, for which the pCR rate was 55.01% (95% CI: 47.55%–62.46%) in the lapatinib plus trastuzumab arm compared with 40.70% (95% CI: 26.87%–54.53%) in the trastuzumab-only arm. Patients receiving lapatinib plus trastuzumab have an almost twofold increase in pCR compared with trastuzumab alone.
Table 2. Incidence and odds ratios of pCR stratified by definition of pCR and hormonal status

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of trials</th>
<th>Patients achieved pCR (n)</th>
<th>Total patients (N)</th>
<th>pCR (%)</th>
<th>95% CI</th>
<th>OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast and lymph nodes</td>
<td>4 [4, 6, 24, 25]</td>
<td>209</td>
<td>384</td>
<td>55.76</td>
<td>45.19–66.33</td>
<td>150</td>
</tr>
<tr>
<td>Breast only</td>
<td>3 [4–6]</td>
<td>244</td>
<td>441</td>
<td>55.01</td>
<td>47.55–62.46</td>
<td>185</td>
</tr>
</tbody>
</table>

Hormonal status

| Hormone receptor positive | 2b [4, 6] | 92 | 185 | 48.87 | 35.16–62.57 | 74 | 197 | 34.76 | 11.18–58.33 | 1.76 | 1.06–2.93 |
| Hormone receptor negative | 2b [4, 6] | 92 | 138 | 67.19 | 55.74–78.64 | 63 | 129 | 50.80 | 22.42–79.19 | 2.06 | 1.08–3.91 |

The p value for the OR and heterogeneity tests are as follows: breast and lymph nodes, p = .001 (p = .55, I² = 0%); breast only, p = .0007 (p = .22, I² = 35%); hormone receptor-positive subgroup, p = .03 (p = .23; I² = 29%); hormone receptor-negative subgroup, p = .03 (p = .21; I² = 37%). There was no difference of effect of the dual therapy between hormone receptor-positive and -negative subgroups (p = .71).


Hormone receptor status was subcategorized in the breast-only definition of pCR. Breast only indicates no invasive disease remaining in the breast. Breast and lymph nodes indicates no remaining invasive disease in breast or lymph nodes.

Abbreviations: CI, confidence interval; OR, odds ratio; pCR, pathologic complete response.

increase in the odds of becoming free of invasive breast cancer compared with controls. Similar results were found regardless of pCR definitions, and the effect did not differ between HR+ and HR− breast cancer subtypes. Inhibiting the function of HER2 by multiple mechanisms is a well-known way of achieving durable responses in cancers driven by HER2 amplification [2]. In the meta-analysis by Valachis et al. [26], the authors reported an improvement in pCR when lapatinib was combined with trastuzumab in patients receiving neoadjuvant chemotherapy. All trials that used combination therapy with lapatinib and trastuzumab analyzed by Valachis et al. were included in our meta-analysis [4, 6, 24, 25]; however, our study included additional data from the phase III CALGB 40601 trial [5], which was not included in the publication by Valachis et al. Compared with our results, the investigators reported a pCR rate of 53% for the combination of lapatinib and trastuzumab [26]. By increasing the number of patients who received dual HER2 therapy with the addition of CALGB 40601 in our analysis, the pCR rate of combination therapy remained >50% and was significantly better than in the arm of patients treated with trastuzumab alone.

This analysis remains hypothesis generating, and caution should be used when interpreting these results because this study has several limitations. Data were abstracted from published clinical trial results; therefore, individual patient information was not available. Clinical verification of the amount of residual disease at the time of definitive surgery was not possible in this analysis. The studies included were conducted by multiple investigators at different institutions; therefore, pCR rates may not have been reported consistently across studies because of subjectivity and disparities in investigator interpretation. Lack of a standard definition of pCR rate could make cross-trial comparisons more difficult to interpret.

Dual HER2 inhibition with pertuzumab and trastuzumab plus chemotherapy in the neoadjuvant setting is approved by the U.S. Food and Drug Administration (FDA) based on the NEOSPHERE and TRYPHAENA trials [27, 28]. Despite our analysis and data from multiple randomized clinical trials [4–6, 24, 25], the combination of lapatinib plus trastuzumab has not received the same accolades from the FDA as its pertuzumab counterpart [27, 28]. Reasons for this observation may be secondary to the discrepancy in the magnitude of the pCR difference between treatment arms across neoadjuvant trials in conjunction with the increase in toxicity seen with the addition of lapatinib [4–6, 24, 25]. Importantly, the results of the ALTTO trial [29] did not show an improvement in disease-free or overall survival when lapatinib was administered in combination with trastuzumab postoperatively for 1 year to patients with early stage HER2+ breast cancer. These data lead one to hypothesize that pCR rate may be an imperfect surrogate marker of breast cancer recurrence. The final disease-free and overall survival results of the neoadjuvant trials using dual HER2 inhibition may help elucidate the final role of this approach in early stage disease.

CONCLUSION

Patients with early stage HER2+ breast cancer have a statistically significant increase in the odds of achieving pCR with the addition of lapatinib to trastuzumab and NAC. This result is clinically relevant as the oncology community continues to learn more about the impact of pCR on recurrence and breast cancer-related death. Although lapatinib combined with trastuzumab may be an important treatment strategy, the increase in toxicity [26] should be weighed against the potential overall benefit. Long-term breast cancer recurrence data from these large randomized studies will be crucial to
understanding the impact of this combination on breast cancer-related mortality.

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Author Contributions

Conception/Design: Melissa Hicks, Erin R. Macrae, Mahmoud Abdel-Rasoul, Jenny Querry, Robert Wesolowski

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