Lapatinib plus chemotherapy or endocrine therapy (CET) versus CET alone in the treatment of HER-2-overexpressing locally advanced or metastatic breast cancer: systematic review and meta-analysis

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Background: This paper reports a systematic review and meta-analysis of all randomized controlled trials comparing the efficacy of lapatinib plus chemotherapy or endocrine therapy (CET) versus CET alone in human epidermal growth factor receptor 2-overexpressing (HER-2+) locally advanced or metastatic breast cancer.

Methods: Several databases were searched, including MEDLINE, EMBASE, LILACS, and CENTRAL. The primary endpoints were progression-free survival and overall survival. The side effects of each treatment were analyzed. The data extracted from the studies were combined by using the hazard ratio or risk ratio with their corresponding 95% confidence interval (CI).

Results: A total of 113 references were identified and screened. The final analysis included four trials comprising 1,073 patients with HER-2+. The overall response rate was higher in patients who received the combination of CET plus lapatinib (risk ratio 0.78; 95% CI 0.71–0.85; \( P < 0.00001 \)) but with significant heterogeneity (\( \chi^2 = 15.61, df = 3, P = 0.001; I^2 = 81\% \)). This result remained favorable to the use of lapatinib when a random-effects model analysis was performed (risk ratio 0.76; 95% CI 0.62–0.94; \( P = 0.01 \)). Progression-free survival was also higher in patients who received CET plus lapatinib (hazard ratio 0.57; 95% CI 0.49–0.66; \( P < 0.00001 \)) with no heterogeneity detected on this analysis (\( \chi^2 = 3.05, df = 3, P = 0.38; I^2 = 0\% \)). Overall survival was significantly longer in patients who received CET plus lapatinib (hazard ratio 0.80; 95% CI 0.69–0.92; \( P = 0.002 \)) without heterogeneity on this analysis (\( \chi^2 = 1.26, df = 3, P = 0.74; I^2 = 0\% \)). Regarding adverse events and severe toxicities (grade \( \geq 3 \)), the group receiving CET plus lapatinib had higher rates of neutropenia (risk ratio 2.08; 95% CI 1.64–2.62; \( P < 0.00001 \)), diarrhea (risk ratio 4.82; 95% CI 3.14–7.41; \( P < 0.00001 \)), and rash (risk ratio 8.03; 95% CI 2.46–26.23; \( P = 0.0006 \)).

Conclusion: The combination of CET plus lapatinib increased the overall response rate, progression-free survival, and overall survival in patients with HER-2+ locally advanced or metastatic breast cancer.

Keywords: chemotherapy, lapatinib, breast cancer, meta-analysis
Background

Breast cancer is the most common cancer among women worldwide. Each year, about 1.4 million new cases of breast cancer are diagnosed worldwide, and over 450,000 women will die of the disease annually. Women have a one in nine lifetime risk of developing breast cancer. The incidence of breast cancer increases with age, doubling every 10 years until menopause, after which the rate of increase slows down. Advanced or metastatic breast cancer is defined as a clinical stage that corresponds to cancer stage III and IV, based on the tumor itself, on lymph node involvement, and on metastases. Approximately 16%–20% of women with breast cancer have advanced or metastatic breast cancer and 50% of early-stage breast cancers ultimately develop into metastatic breast cancer. The human epidermal growth factor receptor 2 gene (ErbB2, usually cited as HER-2) appears to be amplified in around 15%–22% of breast cancer patients, and this carries a bad prognosis.

On March 13, 2007, the US Food and Drug Administration (FDA) approved lapatinib, an oral, small molecule, dual tyrosine kinase inhibitor of ErbB-2 and ErbB-1, for use in combination with chemotherapy (capecitabine) in the treatment of patients with human epidermal growth factor receptor 2-overexpressing (HER-2+) metastatic breast cancer who had received prior therapy including anthracycline, a taxane, and trastuzumab. This approval was based on a randomized Phase III trial published by Geyer et al showing a longer time to progression in favor of the group receiving lapatinib.

On January 29, 2010, the FDA granted accelerated approval to lapatinib for use in combination with endocrine therapy (letrozole) for the treatment of postmenopausal women with HER-2+ metastatic breast cancer and for whom hormonal therapy is indicated. The approval was based on a clinically meaningful increase in progression-free survival observed in a single trial. Until then, there was no randomized controlled trial (RCT) demonstrating gains in overall survival. Recently, Guan et al published the first RCT demonstrating benefits in overall survival of patients who used lapatinib with chemotherapy versus chemotherapy alone.

The objective of this research was to analyze all published RCTs comparing the efficacy of lapatinib plus chemotherapy or endocrine therapy (CET) versus CET alone in the treatment of patients with HER-2+ locally advanced (a T4 primary tumor and stage IIIB or IIC disease) or metastatic breast cancer.

Materials and methods

Study selection criteria

RCTs with a parallel design comparing use of CET regimens associated with lapatinib against others without lapatinib were included. Patients with locally advanced or metastatic breast cancer and with HER-2+ (immunohistochemistry 3+/fluorescence in situ hybridization-positive or chromogenic in situ hybridization-positive for HER-2). RCTs comparing the efficacy of lapatinib plus chemotherapy or endocrine therapy (CET) versus CET alone in the treatment of patients with HER-2+ locally advanced (a T4 primary tumor and stage IIIB or IIC disease) or metastatic breast cancer.

Search strategy for identification of studies

A wide search of the main computerized databases of interest was conducted, including EMBASE, LILACS, MEDLINE, SCI, CENTRAL, The National Cancer Institute Clinical Trials service, and The Clinical Trials Register of Trials Central. In addition, abstracts published in the proceedings of the American Society of Clinical Oncology, the European Society for Medical Oncology, and San Antonio Breast Cancer Symposium were also searched.

For MEDLINE, we used the search strategy methodology recommended by the Cochrane Collaboration. For EMBASE, adaptations of this same strategy were used, and for LILACS, we used the search strategy methodology reported by Castro et al. An additional search of the Science Citation Index (SCI) database was performed, looking for studies cited on the included RCTs. The specific terms pertinent to this review were added to the overall search strategy methodology for each database.

The overall search strategy was as follows: #1, “lapatinib” (Supplementary Concept) OR “lapatinib” (All Fields); #2, “breast neoplasms” (MeSH Terms) OR “breast cancer” (All Fields); #3, “Randomized Controlled Trial” (Publication Type). Searches of electronic databases combined the terms #1 AND #2 AND #3.
Critical evaluation of selected studies
All the references retrieved by the search strategies had their title and abstract evaluated by two of the researchers. Every reference with the least indication of fulfilling the inclusion criteria was listed as preselected. The complete articles of all preselected references were retrieved and analyzed by two different researchers, and later included or excluded according to the criteria reported previously. The excluded trials and the reason for their exclusion are listed in this paper. Data were extracted from all the trials included.

Details regarding the main methodology characteristics empirically linked to bias\(^6\) were extracted, with the methodologic validity of each selected trial assessed by two reviewers (TEAB and OACC). Particular attention was given to some items, including the generation and concealment of the sequence of randomization, blinding, application of intention-to-treat analysis, sample size predefinition, loss of follow-up description, adverse events reports, and whether the trial was multicenter and/or sponsored.

Data extraction
The data were extracted by two independent reviewers. The name of the first author and year of publication were used to identify the study. All data were extracted directly from the text or calculated from the available information when necessary. The data from all trials were based on the intention-to-treat principle, so they compared all patients allocated to one treatment with all those allocated to another.

The primary endpoints were progression-free survival and overall survival. The definition of progression-free survival adopted was time from randomization to either death or disease progression (whichever occurs first). If data on progression-free survival were not available, data on time to progression or event-free survival were assessed.

Other clinical outcomes were evaluated: overall response rate (complete response and partial response) and more frequent adverse hematologic events (anemia and neutropenia) and nonhematologic events (headache, diarrhea, vomiting, rash, nausea, hand-foot syndrome, fatigue, dyspnea, myalgia, and cardiac toxicity). Cardiac events were defined as a symptomatic decline in left ventricular ejection fraction or, if asymptomatic, as a 20% decrease in left ventricular ejection fraction relative to baseline that was less than the institution’s lower normal limit.

Analysis and presentation of results
Data were analyzed using the Review Manager 5.0.24 statistical package Cochrane Collaboration Software, Copenhagen, Denmark. Dichotomous clinical outcomes are reported as the risk ratio (RR) and survival data as the hazard ratio (HR).\(^7\) The corresponding 95% confidence interval (CI) was calculated, considering \(P\)-values less than 5\% \((P < 0.05)\). A statistic for measuring heterogeneity was calculated using the \(I^2\) method (25\% was considered low-level heterogeneity, 25\%–50\% moderate-level heterogeneity, and >50\% high-level heterogeneity).\(^18,19\)

To estimate the absolute gains in progression-free survival and overall survival, we calculated the meta-analytic survival curves as suggested by Parmar et al.\(^17\) A pooled estimate of the HR was computed using a fixed-effect model according to the inverse-variance method.\(^20\) Thus, for effectiveness or side effects, an HR or RR >1 favors the standard arm (control), whereas an HR or RR <1 favors treatment with lapatinib.

If statistical heterogeneity was found in the meta-analysis, an additional analysis was performed, using the random-effects model described by DerSimonian and Laird,\(^21\) that provides a more conservative analysis.

In the analysis of efficacy, a subgroup analysis was planned to evaluate the influence of the use of CET plus lapatinib only in first-line treatment, according to the type of systemic therapy (ie, lapatinib plus chemotherapy or endocrine therapy, or chemotherapy alone).

Results
Figure 1 represents the flow of identification and inclusion of trials, as recommended by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.\(^26\) Overall, 113 references were identified and screened. Nine studies were selected and retrieved for full-text analysis. Of these, five studies were excluded for various reasons (not randomized, adjuvant treatment, HER-2(−), and lapatinib in both arms).

Characteristics of included studies
The final analysis included four trials comprising 1,073 patients with HER-2(+).\(^7,9,11,27–30\) All results from these studies were analyzed on an intention-to-treat principle. Lapatinib was associated with chemotherapy in three tri-
Trials potentially relevant identified and screened (n = 113)

Trials excluded: not randomized, not breast cancer, not lapatinib, neoadjuvant treatment, lapatinib with trastuzumab (n = 104)

Trials excluded: not randomized, adjuvant treatment, HER-2 (negative), lapatinib in both arms (n = 5)

Trials selected and retrieved for full-text analysis (n = 9)

Trials included (n = 4)

Figure 1 Trial selection flow.

Abbreviation: HER-2, human epidermal growth factor-2.

One study9,30 associated lapatinib with endocrine therapy (letrozole; Table 1). The different schemes used for CET and lapatinib are detailed in Table 2.

Overall survival was the primary endpoint of the Guan et al11 study, whereas progression-free survival was the primary endpoint of the study reported by Johnston et al.9,30 In another two studies,7,27,28 the primary endpoint was time to progression, defined as time from randomization to disease progression or death resulting from breast cancer (Table 1).

Two of the eligible studies allowed patients in the “no lapatinib” arm to cross over to lapatinib at disease progression, while the other trials did not permit or did not mention cross over. Data were extracted from updates for some studies, including those reported by Geyer et al and Cameron et al,7,27,28 and by Johnston et al and Schwartzberg et al.9,30 With the exception of only one study,7,27,28 the overall response rate was significantly higher in the groups receiving lapatinib.

Progression-free survival was favorable to the association of CET with lapatinib in all studies singly, while overall survival was significantly superior in favor of lapatinib in only one recently published study11 (Table 2). The toxicity profile for the HER-2+ subpopulation was described in three trials or in their updates.7,9,11,27,28,30

Meta-analyses

The overall response rate was higher in patients who received the combination of CET plus lapatinib (RR 0.78; 95% CI 0.71–0.85; P < 0.00001; NNT = 7), but with significant heterogeneity ($\chi^2 = 15.61; df = 3; P = 0.001; F = 81%$; Figure 2).

As planned, a random-effects model analysis was performed to explore this heterogeneity further. In this analysis, the result remained favorable to the use of CET plus lapatinib (RR 0.76; 95% CI 0.62–0.94; P = 0.01, Figure 3).

Progression-free survival was also longer in patients who received CET plus lapatinib (HR 0.57; 95% CI 0.49–0.66; Table 1 Characteristics of studies that evaluated different schemes of CET in patients with HER-2+ locally advanced or metastatic breast cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>n HER-2+</th>
<th>Patients</th>
<th>Analysis</th>
<th>Primary end point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy with or without lapatinib</td>
<td></td>
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<tr>
<td>Guan et al11</td>
<td>Randomized, double-blind, placebo-controlled, multicenter</td>
<td>444</td>
<td>Metastatic breast cancer</td>
<td>ITT</td>
<td>OS</td>
</tr>
<tr>
<td>Di Leo et al39</td>
<td>Randomized, double-blind, placebo-controlled, multicenter</td>
<td>86</td>
<td>Locally advanced or metastatic breast cancer</td>
<td>ITT</td>
<td>PFS</td>
</tr>
<tr>
<td>Geyer et al7</td>
<td>Randomized, nonblinded, open-label, multicenter</td>
<td>324</td>
<td>Locally advanced or metastatic breast cancer</td>
<td>ITT</td>
<td>PFS</td>
</tr>
<tr>
<td>Cameron et al27,28</td>
<td>Endocrine therapy with or without lapatinib</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Johnston et al9</td>
<td>Randomized, double-blind, placebo-controlled, multicenter</td>
<td>219</td>
<td>Locally advanced or metastatic breast cancer</td>
<td>ITT</td>
<td>TTP</td>
</tr>
<tr>
<td>Schwartzberg et al30</td>
<td></td>
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</table>

Abbreviations: ITT, intention-to-treat; OS, overall survival; PFS, progression free survival; TTP, time to progression; HER-2, human epidermal growth factor receptor-2; CET, chemotherapy or endocrine therapy.
Table 2 Characteristics and results of randomized studies that evaluated different schemes of CET in patients with HER-2+ locally advanced or metastatic breast cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Line of treatment</th>
<th>n</th>
<th>HER-2+</th>
<th>Interventions</th>
<th>ORR n (%)</th>
<th>PFS HR, 95% CI</th>
<th>OS HR, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemotherapy with or without lapatinib</strong></td>
<td></td>
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<tr>
<td>Guan et al&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>First-line</td>
<td>222</td>
<td>222</td>
<td>Lapatinib + paclitaxel</td>
<td>154 (69%)</td>
<td>9.7 months</td>
<td>27.8 months</td>
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<td></td>
<td></td>
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<td></td>
<td>Placebo + paclitaxel</td>
<td>110 (50%)</td>
<td>6.5 months</td>
<td>20.5 months</td>
</tr>
<tr>
<td>Di Leo et al&lt;sup&gt;c&lt;/sup&gt;</td>
<td>First-line</td>
<td>49</td>
<td>37</td>
<td>Lapatinib + paclitaxel</td>
<td>31 (63.3%)</td>
<td>8.8 months</td>
<td>26.2 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Paclitaxel + placebo</td>
<td>14 (37.8%)</td>
<td>5.5 months</td>
<td>20.6 months</td>
</tr>
<tr>
<td>Geyer et al&lt;sup&gt;d&lt;/sup&gt;,&lt;sup&gt;e&lt;/sup&gt;</td>
<td>At least</td>
<td>163</td>
<td></td>
<td>Lapatinib + capecitabine</td>
<td>36 (22%)</td>
<td>8.4 months</td>
<td>18.8 months</td>
</tr>
<tr>
<td>Cameron et al&lt;sup&gt;f&lt;/sup&gt;,&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Second-line</td>
<td>161</td>
<td></td>
<td>Capecitabine</td>
<td>23 (14%)</td>
<td>4.4 months</td>
<td>16.2 months</td>
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<tr>
<td><strong>Endocrine therapy with or without lapatinib</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Johnston et al&lt;sup&gt;h&lt;/sup&gt;</td>
<td>First-line</td>
<td>111</td>
<td></td>
<td>Lapatinib + letrozole</td>
<td>31 (28%)</td>
<td>8.2 months</td>
<td>33.3 months</td>
</tr>
<tr>
<td>Schwartz et al&lt;sup&gt;i&lt;/sup&gt;</td>
<td></td>
<td>108</td>
<td></td>
<td>Placebo + letrozole</td>
<td>16 (15%)</td>
<td>3.0 months</td>
<td>32.3 months</td>
</tr>
</tbody>
</table>

Notes: *Experimental group received paclitaxel (80 mg/m² intravenously once per week for 3 weeks every 4 weeks) and lapatinib (1,500 mg once per day), and control group received paclitaxel (80 mg/m² intravenously once per week for 3 weeks every 4 weeks) and placebo (once per day); **experimental group received paclitaxel (175 mg/m² intravenously over 3 hours on day 1, every 3 weeks) with lapatinib (1,500 mg per day once daily) and control group received paclitaxel (175 mg/m² intravenously over 3 hours on day 1, every 3 weeks) plus placebo once daily; ***experimental group received capecitabine at a dose of 2,000 mg/m² in two divided doses on days 1 through 14 of a 21-day cycle plus lapatinib at a dose of 1,250 mg daily and the control group received capecitabine at a dose of 2,000 mg/m² in two divided doses on days 1 through 14 of a 21-day cycle; experimental group received letrozole 2.5 mg orally daily plus lapatinib 1,500 mg orally, and the control group received letrozole 2.5 mg daily with matching lapatinib placebo pill.

Abbreviations: ORR, overall response rate; OS, overall survival; PFS, progression free survival; HR, hazard ratio; CET, chemotherapy or endocrine therapy; HER-2, human epiderman growth factor-2.

$P < 0.00001$; NNT = 2, with no heterogeneity detected in this analysis ($\chi^2 = 3.05; df = 3, P = 0.38; I = 1\%$, Figure 4).
Overall survival was significantly longer in patients who received CET plus lapatinib (HR 0.80; 95% CI 0.69–0.92; $P = 0.002$; NNT = 5), without heterogeneity in this analysis ($\chi^2 = 1.26; df = 3, P = 0.74; I = 0\%$, Figure 5).

Regarding overall adverse events (toxicities of any grade), patients receiving CET plus lapatinib had higher rates of neutropenia (RR 1.63; 95% CI 1.39–1.91; $P < 0.00001$; NNT = 12), and anemia (RR 1.55; 95% CI 1.2–1.99; $P = 0.0007$; NNT = 17, Figure 6), and diarrhea (RR 2.44; 95% CI 1.91–3.11; $P < 0.00001$; NNT = 2), nausea (RR 1.23; 95% CI 1.06–1.43; $P = 0.006$; NNT = 14), vomiting (RR 1.50; 95% CI 1.22–1.85; $P = 0.0001$; NNT = 12), and rash (RR 2.4; 95% CI 2.03–2.83; $P < 0.00001$; NNT = 4, Figure 7). The proportion of patients with cardiac events

![Figure 2 Comparison of objective response rates on CET with lapatinib versus CET alone.](https://www.dovepress.com/)

**Abbreviations:** CET, chemotherapy or endocrine therapy; CI, confidence interval; M-H, Mantel-Haenszel.
was similar in both groups (RR 1.6; 95% CI 0.92–2.80; 

\( P = 0.10 \), Figure 7).

Concerning severe toxicities (of grade \( \geq 3 \)), patients 

receiving CET plus lapatinib had higher rates of neutropenia 

(RR 2.08; 95% CI 1.64–2.62; \( P < 0.00001; \) NNT = 9), 

diarrhea (RR 4.82; 95% CI 3.14–7.41; \( P < 0.00001; \) NNT = 8), 

and rash (RR 8.03; 95% CI 2.46–26.23; \( P = 0.0006; \) 

NNT = 33).

Because there was significant heterogeneity in adverse 

events, we undertook an analysis with and without inclusion 

of the study reported by Di Leo et al,29 given that 

this study reported toxicity in patients with HER-2+ and 

HER-2– disease. There was no difference in the results.

As planned, we also performed a random-effects model 

analysis to explore this heterogeneity further and the result 

remained favorable to the control group. According to funnel 

plot22 analysis, the possibility of publication bias was low 

for all endpoints.

### Subgroup analysis

According to the type of systemic therapy (CET), lapatinib 

associated only with chemotherapy was more effective 

than the use of CET alone, showing a better overall 

response rate (RR 0.76; 95% CI 0.68–0.84; \( P < 0.00001; \) 

NNT = 6), longer progression-free survival (HR 0.53; 95% 

CI 0.45–0.62; \( P < 0.00001; \) NNT = 2), and longer overall

---

**Table 1.1.1**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Log[hazard ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard ratio IV, fixed, 95% CI</th>
<th>Hazard ratio IV, fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.1 Endocrine therapy with or without lapatinib</td>
<td></td>
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</tr>
<tr>
<td>Johnston et al15</td>
<td>-0.34249031</td>
<td>0.14918027</td>
<td>24.8%</td>
<td>0.71 [0.53, 0.95]</td>
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<tr>
<td>Subtotal (95% CI)</td>
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<tr>
<td>Heterogeneity: not applicable</td>
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<tr>
<td>Test for overall effect: ( Z = 2.30 ) (( P = 0.02 ))</td>
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<tr>
<td>1.1.2 Chemotherapy with or without lapatinib</td>
<td></td>
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<tr>
<td>Cameron et al27, 28</td>
<td>-0.597837</td>
<td>0.16247938</td>
<td>20.0%</td>
<td>0.55 [0.40, 0.76]</td>
<td></td>
</tr>
<tr>
<td>Di Leo et al29</td>
<td>-0.65392647</td>
<td>0.26391123</td>
<td>7.9%</td>
<td>0.52 [0.31, 0.87]</td>
<td></td>
</tr>
<tr>
<td>Guan et al31</td>
<td>-0.65392647</td>
<td>0.10896838</td>
<td>46.4%</td>
<td>0.52 [0.42, 0.64]</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td></td>
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<tr>
<td>Heterogeneity: chi² = 0.09, ( df = 2 ) (( P = 0.96 )); ( P = 0% )</td>
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<tr>
<td>Test for overall effect: ( Z = 7.46 ) (( P &lt; 0.00001 ))</td>
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<tr>
<td>Total (95% CI)</td>
<td>100.00%</td>
<td>0.57 [0.49, 0.66]</td>
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<tr>
<td>Heterogeneity: chi² = 3.05, ( df = 3 ) (( P = 0.38 )); ( P = 1% )</td>
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<tr>
<td>Test for overall effect: ( Z = 7.61 ) (( P &lt; 0.00001 ))</td>
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<tr>
<td>Test for subgroup differences: chi² = 2.96, ( df = 1 ) (( P = 0.09 )); ( P = 66.2% )</td>
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</table>

**Figure 3** Comparison of objective response rates on CET with lapatinib versus CET alone (random-effects model analysis).

**Figure 4** Comparison of progression-free survival on CET with lapatinib versus CET alone.

**Abbreviations:** CET, chemotherapy or endocrine therapy; CI, confidence interval; SE, standard error; IV, inverse variance.
Anti-HER-2 agents have been widely investigated as a strategy for improving survival in advanced or metastatic breast cancer. Trastuzumab, a recombinant humanized monoclonal antibody, was the first molecular targeted agent, and was approved by the FDA for treatment of HER-2+ breast cancer in 1998. It is known that not all metastatic breast cancer and HER-2+ patients respond to treatment with trastuzumab, and even in those who do respond, the response is transient and rarely exceeds one year. The benefit of continued survival (HR 0.81; 95% CI 0.70–0.94; \( P = 0.006 \); NNT = 5). However, no statistically significant interaction was found between type of lapatinib combination (endocrine or chemotherapy) and the endpoints analyzed.

In accordance with the line of treatment, use of lapatinib plus CET only as first-line treatment also remained superior to the control group in relation to the overall response rate (RR 0.57; 95% CI 0.49–0.68; \( P = 0.0001 \); NNT = 6), progression-free survival (HR 0.81; 95% CI 0.70–0.94; \( P = 0.006 \); NNT = 5), and overall survival (HR 0.74; 95% CI 0.61–0.90; \( P = 0.003 \); NNT = 3).

**Discussion**

Anti-HER-2 agents have been widely investigated as a strategy for improving survival in advanced or metastatic breast cancer. Trastuzumab, a recombinant humanized monoclonal antibody, was the first molecular targeted agent, and was approved by the FDA for treatment of HER-2+ breast cancer in 1998. It is known that not all metastatic breast cancer and HER-2+ patients respond to treatment with trastuzumab, and even in those who do respond, the response is transient and rarely exceeds one year. The benefit of continued survival (HR 0.81; 95% CI 0.70–0.94; \( P = 0.006 \); NNT = 5).

However, no statistically significant interaction was found between type of lapatinib combination (endocrine or chemotherapy) and the endpoints analyzed.

In accordance with the line of treatment, use of lapatinib plus CET only as first-line treatment also remained superior to the control group in relation to the overall response rate (RR 0.57; 95% CI 0.49–0.68; \( P = 0.0001 \); NNT = 6), progression-free survival (HR 0.81; 95% CI 0.70–0.94; \( P = 0.006 \); NNT = 5), and overall survival (HR 0.74; 95% CI 0.61–0.90; \( P = 0.003 \); NNT = 3).

**Discussion**

Anti-HER-2 agents have been widely investigated as a strategy for improving survival in advanced or metastatic breast cancer. Trastuzumab, a recombinant humanized monoclonal antibody, was the first molecular targeted agent, and was approved by the FDA for treatment of HER-2+ breast cancer in 1998. It is known that not all metastatic breast cancer and HER-2+ patients respond to treatment with trastuzumab, and even in those who do respond, the response is transient and rarely exceeds one year. The benefit of continued survival (HR 0.81; 95% CI 0.70–0.94; \( P = 0.006 \); NNT = 5).

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Fig 7. Comparative effect non-hematologic toxicities (any grade) of chemo- or endocrine therapy (CET) with Lapatinib versus CET alone.

Abbreviations: CET, chemotherapy or endocrine therapy; CI, confidence interval; M–H, Mantel–Haenszel.
use of trastuzumab beyond disease progression remains controversial. Geyer et al7 published the first study demonstrating the benefits of another anti-HER-2 agent, ie, lapatinib, for patients with trastuzumab-refractory metastatic breast cancer.

As has been shown, studies with this drug in first-line treatment were published subsequently. Based on studies showing a gain in progression-free survival, international guidelines10,34 recommend use of the CET plus lapatinib combination in patients with stage IIIB, inoperable stage IIIC, stage IV, recurrent, or metastatic breast cancer. So far, there are no studies directly comparing the two drugs.

Two other previously published meta-analyses have indicated the benefits of using lapatinib plus CET for metastatic and HER-2+ breast cancer.31,35 The present meta-analysis incorporated the results of another published RCT11 and confirmed the benefits of lapatinib plus CET regardless of the treatment line and the efficacy endpoints evaluated, including overall survival. The fact that benefits in overall survival were observed even while some trials allowed cross over from “no lapatinib” to “lapatinib” arms reinforces the activity and effectiveness of this drug. Although no survival benefit was observed in lapatinib combined with endocrine therapy in the only trial that analyzed this combination, it is important to note that the absence of a statistically significant interaction between the lapatinib combination therapy subgroups (CET) and overall survival suggests that other factors, such as cross over, may have accounted for this result.

There was heterogeneity in the overall response rate. This heterogeneity can be attributed to different somatic tumor characteristics. Genomic variants in patients may influence the response to drug treatment. As reported in the following two references, alterations in the estrogen receptor, PI3K-PTEN-Akt signaling cascade, and downstream FOXO3a and FOXM1 are poor prognostic predictors of clinical response.36,37 In addition to HER-2 expression and amplification, other genomic variants should be considered in patients to be treated with lapatinib plus CET.

The group receiving CET plus lapatinib had higher rates of adverse hematologic events (neutropenia and anemia), adverse gastrointestinal events (diarrhea, nausea, and vomiting), and rash. The proportions of headache, hand-foot syndrome, fatigue, dyspnea, and myalgia were similar. The proportions of cardiac events were also similar. The majority of these cardiac events were grade 1 or 2, asymptomatic, transient, and reversible.7,9,11,29

Conclusion
The combination of CET plus lapatinib increased the overall response, progression-free survival, and overall survival rates in patients with HER-2+ locally advanced or metastatic breast cancer. Side effects resulting from the combination were mild and transient.

Author contributions
All the authors of this research paper participated directly in its planning, execution, or analysis. All authors read and approved the final version submitted.

Disclosure
The authors report no conflicts of interest in this work.

References


