Impact of hormone receptor status on the efficacy of HER2-targeted treatment

Bin Zhao1, Hong Zhao2 and Jiaxin Zhao1,3

1The Second Affiliated Hospital & Yuying Children's Hospital, Wenzhou Medical University, Wenzhou, China
2The Third Affiliated Hospital of Harbin Medical University, Harbin, China
3The Fourth Affiliated Hospital of Harbin Medical University, Harbin, China

Correspondence should be addressed to B Zhao or H Zhao or J Zhao: doctorbinzhao@126.com or doctorhongzhao@126.com or doctorzhaojiaxin@163.com

Abstract

The introduction of human epidermal growth factor receptor 2 (HER2)–targeted drugs into routine clinical practice has a dramatic effect on the outlook for patients with HER2-positive breast cancer (BC). However, the association between efficacy of HER2-targeted therapy and hormone receptor (HR) status is still unclear. Here we conducted a meta-analysis of randomized controlled trials (RCTs) to address this issue in both neoadjuvant and adjuvant settings. PubMed and EMBASE were searched from inception to October 2017 for studies involving trastuzumab, lapatinib, pertuzumab, trastuzumab emtansine and neratinib. Efficacy endpoints were pathological complete response (pCR) for neoadjuvant therapy and disease-free survival (DFS) for adjuvant therapy. In neoadjuvant setting, pCR was reported in 7 trials with 2868 subjects. Hormone receptor (HR)–negative women derived substantially greater benefit from HER2-targeted agents than did HR-positive patients (odds ratio (OR), 2.34; 95% confidence interval (CI), 1.99–2.75). Additionally, the impact of HR status on pCR was independent of anti-HER2 agents. In adjuvant setting, DFS was investigated in 7 studies with 12,768 patients. HR-positive patients benefit more from anti-HER2 treatment than did HR-negative subjects (OR, 0.81; 95% CI, 0.74–0.89). Moreover, patients who did not receive any endocrine or anti-HER2 neoadjuvant treatment showed similar outcome but with a smaller effect (OR, 0.88; 95% CI, 0.78–0.99). In summary, compared with HER2-positive/HR-negative subjects, HER2-positive/HR-positive patients achieved greater benefit from HER2-targeted treatment although the efficacy from neoadjuvant therapy was relatively poor.

Introduction

Approximately 20% patients with breast cancer (BC) have HER2-positive disease. These patients are often associated with a highly aggressive tumor behavior and poor outcomes (Slamon et al. 1987). Therefore, HER2 has become an important biomarker and target of therapy in BC. Numerous studies (Untch et al. 2010, 2012, Baselga et al. 2012, Gianni et al. 2012, Goldhirsch et al. 2013, Goss et al. 2013, Robidoux et al. 2013, Schneeweiss et al. 2013, de Azambuja et al. 2014, Perez et al. 2014, Carey et al. 2016, Chan et al. 2016, Piccart-Gebhart et al. 2016) have consistently demonstrated the benefit of HER2-targeted therapy. However, clinicians still need to understand the most appropriate use of anti-HER2 therapy across different treatment settings and clinicopathological characteristics. Identifying such factors can be valuable for future clinical study design and interpretation, as well as developing
new generation of HER2-targeted drugs. A recent meta-analysis demonstrated that women with HER2-positive tumor <2 cm derived substantial prognostic benefit from adjuvant trastuzumab treatment (O’Sullivan et al. 2015). Nevertheless, the impacts of other biological factors on the benefit of women treated with HER2-targeted drugs are still unclear. For example, because of the crosstalk between HR and HER2 receptors pathways (Schettini et al. 2016), HR-positive and HR-negative BC are increasingly recognized as different diseases, and the impacts of HR status on clinical outcomes treated by HER2-targeted agents are controversial (Bruksky et al. 2005, Perez et al. 2014).

With recently accumulating evidence, our aim here, therefore, was to evaluate the impact of HR status on the efficacy of anti-HER2 agent in both neoadjuvant and adjuvant therapy by conducting a meta-analysis among patients with HER2-positive BC.

Methods

The present study was conducted in compliance with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines (Liberati et al. 2009).

Literature search and study selection

A comprehensive systematic search of PubMed and Embase from inception to October 2017 was carried out without any language restrictions. The main keywords used were trastuzumab, lapatinib, pertuzumab, trastuzumab emtansine, neratinib, breast cancer and randomized controlled trial. Both inclusion and exclusion criteria were pre-specified. To be eligible, trials had to meet the following criteria: (1) population: over 200 patients (>18 years old) with HER2-positive BC, and HR status of these patients were examined; (2) intervention: treated with HER2-targeted regimens irrespective of dose and duration; (3) main outcome: pathological complete response for neoadjuvant treatment or disease-free survival for adjuvant treatment; and (4) median follow-up: at least 2 years for DFS analysis. Studies were excluded if they were retrospective or prospective observational cohort studies. In addition, phase I and non-randomized phase II were excluded. Other publications on the topic, including review articles, basic science papers, conference abstracts, editorials, early versions of data later published and articles not dealing with HER2 agents, were excluded (Fig. 1). Considering recent trials with HER2-targeted agents might be unpublished, electronic searches were also conducted using the major international congresses’ proceedings (American Society of Clinical Oncology Annual Meeting, European Society of Medical Oncology and San Antonio Breast Cancer Symposium). Moreover, the reference lists of all studies fulfilling the eligibility criteria were further examined for any relevant studies missed by the electronic searches. When multiple publications of the same clinical trial appeared or if there was a case mix between different publications, only the most recent and/or most complete reporting study was included. Any discrepancies were settled by discussion and consensus.

Risk of bias assessment

All the reviewers independently carried out the risk of bias assessment using the Cochrane risk of bias tool (Higgins et al. 2011). We examined every trial and scored as positive, negative or unclear risk of bias to the following criteria: random sequence generation; allocation concealment; blinding of participants and personnel to the study protocol; blinding of outcome assessment; incomplete
outcome data and selective reporting. Any disagreements were resolved by discussion and consensus.

**Statistical analysis**

The primary analysis investigated the association between HR status and pathological complete response (pCR) in neoadjuvant treatment or DFS in adjuvant therapy among patients with HER2-positive BC. All analyses were carried out using Stata version 12.0 (StataCorp LP, Texas Station, TX, USA). For each study, the odds ratio (OR) and its 95% confidence interval (CI) were extracted from the research manuscript directly or calculated using other available statistical information. Both random-effects models and fixed-effects models were utilized to calculate pooled ORs, 95% CIs and P values.

Statistical heterogeneity between different trials and subgroups was assessed by Cochrane’s Q statistic. The F statistic was calculated to assess the extent of inconsistency contributable to the heterogeneity across different studies (Higgins et al. 2003). The assumption of homogeneity was considered invalid for $F > 25\%$ and $P < 0.10$ (Cochrane’s Q statistic). Potential publication bias was assessed by visual inspection of a funnel plot, and evaluated using the tests of Egger et al. (1997) and Begg & Mazumdar (1994). Two-sided $P$ values <0.05 were considered statistically significant.

**Results**

**Literature search**

A total of 3147 related studies were identified by the initial search strategy. 1078 articles were removed because of duplications. After eligibility screening of the titles and abstracts, 2039 studies were excluded since they did not meet the inclusion criteria. When carefully reviewed the full texts of the remaining 30 potentially eligible papers, 13 articles which included 14 RCTs were chosen for the final analysis (Untch et al. 2010, 2012, Baselga et al. 2012, Gianni et al. 2012, Goldhirsch et al. 2013, Goss et al. 2013, Robidoux et al. 2013, Schneeweiss et al. 2013, de Azambuja et al. 2014, Perez et al. 2014, Carey et al. 2016, Chan et al. 2016, Piccart-Gebhart et al. 2016). A flow chart showing the study selection is shown in Fig. 1. The methodological quality of the included trials was generally moderate to good. The main issue affecting quality was lack of blinding because all but two trials (Goss et al. 2013, Chan et al. 2016) were open-label. Details of risk bias are provided in Supplementary Fig. 1 (see section on supplementary data given at the end of this article).

**HR and pCR**

For neoadjuvant therapy, 7 trials with a total of 2868 HER2-positive patients were included for pCR analysis (Untch et al. 2010, 2012, Baselga et al. 2012, Gianni et al. 2012, Robidoux et al. 2013, Schneeweiss et al. 2013, Carey et al. 2016). 1600 of them (56%) were also HR-positive, while the rest 1268 subjects (44%) were HR-negative. The clinicopathological characteristics of eligible studies are summarized in Table 1. All studies were open-label RCTs conducted in the United States and Europe. Five trials were phase III RCTs, while NeoSphere (Gianni et al. 2012) and TRYPHAENA (Schneeweiss et al. 2013) were phase II trials.

The summary incidences of pCR events in HR-negative patients (54%; 95% CI, 45–63%) were higher than those in HR-positive patients (37%; 95% CI, 27–41%; $P < 0.01$) (Fig. 2). However, the incidence of pCR events depended on the treatment strategy; patients treated with two HER2-targeted agents combination have higher incidence than those treated with one HER-target in both HR-positive subgroup (45% vs 32%, $P < 0.01$) and HR-negative subgroup (71% vs 44%, $P < 0.001$).

Overall, the pooled model showed that patients with HR-negative BC had a significantly greater incidence rate of pCR events than those with HR-positive BC (OR, 2.34; 95% CI, 1.99–2.75; $P < 0.001$) (Fig. 2). No substantial heterogeneity was observed ($P = 0.55$, $F = 0.0%$). The advantage of pCR in HR-negative patients stratified by different anti-HER2 agents was further examined; no statistically significant difference was observed among different subgroups ($P = 0.58$). It might suggest that the greater benefit HR-negative women achieved over HR-positive patients was independent of anti-HER2 agents.

**HR and DFS**

For adjuvant therapy, 7 trials with a total of 12,768 HER2-positive patients were included for DFS analysis (Goldhirsch et al. 2013, Goss et al. 2013, de Azambuja et al. 2014, Perez et al. 2014, Chan et al. 2016, Piccart-Gebhart et al. 2016). Two trials, NSABP B-31 and NCTCT N9831, were jointly analyzed in one article (Perez et al. 2014). The clinicopathological characteristics of eligible studies are summarized in Table 2. Five of the included trials were open-label, phase III RCTs (Goldhirsch et al. 2013, de Azambuja et al. 2014, Perez et al. 2014, Piccart-Gebhart et al. 2016), and TEACH and ExteNET were double-blind, phase III RCTs (Goss et al. 2013, Chan et al. 2016).
Table 1  Characteristics of eligible neoadjuvant studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>Region</th>
<th>Disease</th>
<th>Neoadjuvant chemotherapy</th>
<th>Neoadjuvant anti-HER2 agents</th>
<th>Duration (weeks)</th>
<th>Age, median (range)</th>
<th>Primary outcomes</th>
<th>Definition of pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 40601 (Carey et al. 2016)</td>
<td>III</td>
<td>US</td>
<td>Stage II–III</td>
<td>T</td>
<td>Tzmb and/or Lpnb</td>
<td>16</td>
<td>49 (24–75)</td>
<td>pCR</td>
<td>Absence of residual invasive carcinoma</td>
</tr>
<tr>
<td>GeparQuattro (Untch et al. 2010)</td>
<td>III</td>
<td>Europe</td>
<td>Locally advanced BC</td>
<td>EC→Tzmb</td>
<td>Tzmb</td>
<td>24</td>
<td>50 (22–78)</td>
<td>pCR</td>
<td>No tumor cells and residual tumor in breast and lymph nodes</td>
</tr>
<tr>
<td>NeoALTTO (Baselga et al. 2012)</td>
<td>III</td>
<td>International</td>
<td>Early BC</td>
<td>T</td>
<td>Tzmb and/or Lpnb</td>
<td>18</td>
<td>50 (42–59)</td>
<td>DFS/pCR</td>
<td>Absence of invasive tumor cells in breast</td>
</tr>
<tr>
<td>NeoSphere (Gianni et al. 2012)</td>
<td>II</td>
<td>International</td>
<td>Locally advanced, inflammatory or early BC</td>
<td>T</td>
<td>Tzmb and/or Pzmb</td>
<td>12</td>
<td>50 (22–80)</td>
<td>pCR</td>
<td>Absence of invasive tumor cells in breast</td>
</tr>
<tr>
<td>GeparQuinto (Untch et al. 2012)</td>
<td>III</td>
<td>Europe</td>
<td>Operable or locally advanced BC</td>
<td>EC→Tzmb</td>
<td>Tzmb or Lpnb</td>
<td>24</td>
<td>50 (21–74)</td>
<td>pCR</td>
<td>No evidence of disease in the breast and lymph nodes</td>
</tr>
<tr>
<td>NSABP B-41 (Robidoux et al. 2013)</td>
<td>III</td>
<td>US, Canada</td>
<td>Operable BC</td>
<td>AC→Tzmb</td>
<td>Tzmb and/or Lpnb</td>
<td>24</td>
<td>NR</td>
<td>pCR</td>
<td>Absence of residual invasive carcinoma in breast</td>
</tr>
<tr>
<td>TRYPHAENA (Schneeweiss et al. 2013)</td>
<td>II</td>
<td>International</td>
<td>Early BC</td>
<td>FEC→Tzmb</td>
<td>Tzmb and Pzmb</td>
<td>18</td>
<td>50 (24–81)</td>
<td>pCR</td>
<td>Absence of invasive tumor cells</td>
</tr>
</tbody>
</table>

AC→T, doxorubicin hydrochloride, cyclophosphamide followed by paclitaxel; BC, breast cancer; Ca, capecitabine; DFS, disease-free survival; FEC, fluorouracil, epirubicin hydrochloride and cyclophosphamide; Lpnb, lapatinib; NR, not reported; pCR, pathological complete response; Pzmb, pertuzumab; T, docetaxel or paclitaxel; Tzmb, trastuzumab.
Of all the eligible 12,768 patients, 7081 (55%) were HR-positive, and the rest 5687 subjects (45%) were HR-negative. All patients had local (axillary) node positive BC or high-risk node negative disease.

Different treatment strategies were applied in these seven trials. Patients in three RCTs, namely NSABP B-31, NCCTG N9831 and TEACH, were treated with HER2-targeted agents; some of the subjects in HERA trials had neoadjuvant therapy but not with anti-HER2 agents (usually anthracycline). HR-positive patients in ALTTO were treated by endocrine agents combined with HER2-targeted drugs. HR-positive patients in NeoALTTO and ExteNET had anti-HER2 neoadjuvant therapy, endocrine therapy and HER2-targeted adjuvant treatment. Given the fact that endocrine therapy and anti-HER2 neoadjuvant therapy might contribute to the long-term benefit in women with HR-positive disease, the advantage of DFS stratified by different treatment strategies was examined (Fig. 3). Overall, compared with HR-negative patients, the pooled model showed that patients with HR-positive BC achieved greater benefit from HER2-targeted treatment (OR, 0.81; 95% CI, 0.74–0.89; \( P < 0.01 \)). It was noted that even for those 6703 subjects from 4 RCTs (Goldhirsch et al. 2013, Goss et al. 2013, Perez et al. 2014) who did not receive any endocrine therapy or anti-HER2 neoadjuvant therapy, the pooled model showed that HR-positive women achieved greater benefit compared with HR-negative patients (OR, 0.88; 95% CI, 0.78–0.99; \( P < 0.05 \)), though the difference in benefit appeared rather smaller than that for the other treatment strategies.

Figure 2
Forest plots showing associations between pathological complete response (pCR) and hormone receptor (HR) status in patients treated with neoadjuvant HER2-targeted therapy. CI, confidence interval; Lpnb, lapatinib; NR, not reported; OR, odds ratio; Tzmb, trastuzumab.
Table 2 Characteristics of eligible adjuvant studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>Disease</th>
<th>Adjuvant anti-HER2 agents</th>
<th>Other treatments</th>
<th>No. of patients</th>
<th>Follow-up, median (range, months)</th>
<th>Duration, median (range, months)</th>
<th>Age, median (range, year)</th>
<th>Primary outcomes</th>
<th>DFS/pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERA (Goldhirsch et al. 2013)</td>
<td>III</td>
<td>Invasive early BC</td>
<td>Neo and/or Adj</td>
<td>Tzmb</td>
<td>1517</td>
<td>101</td>
<td>12</td>
<td>HR+</td>
<td>DFS/OS</td>
<td>47 (0-60)</td>
</tr>
<tr>
<td>N9831/B31 (Perez et al. 2014)</td>
<td>III</td>
<td>Invasive early BC</td>
<td>Adj</td>
<td>Tzmb</td>
<td>917</td>
<td>58</td>
<td>12</td>
<td>NR</td>
<td>DFS</td>
<td>639 (0-77)</td>
</tr>
<tr>
<td>DECIS (Goss et al. 2013)</td>
<td>III</td>
<td>Invasive early BC</td>
<td>Adj</td>
<td>Lpnb and/or Tzmb</td>
<td>932</td>
<td>47 (22-87)</td>
<td>12</td>
<td>51 (18-82)</td>
<td>DFS</td>
<td>203 (403-2403)</td>
</tr>
<tr>
<td>ALTTO (Piccart-Gebhart et al. 2016)</td>
<td>III</td>
<td>Invasive early BC</td>
<td>Tzmb and/or Lpnb</td>
<td>Lpnb and/or Tzmb</td>
<td>93</td>
<td>51 (24-39)</td>
<td>12</td>
<td>52 (45-59)</td>
<td>DFS/pCR</td>
<td>232 (243-232)</td>
</tr>
<tr>
<td>NeoALTTO (de Azambuja et al. 2014)</td>
<td>III</td>
<td>Early BC</td>
<td>Neo</td>
<td>Neo</td>
<td>96</td>
<td>52 (45-59)</td>
<td>12</td>
<td>52 (45-59)</td>
<td>DFS</td>
<td>816 (816-816)</td>
</tr>
<tr>
<td>NEO/ALTTO (Chan et al. 2016)</td>
<td>III</td>
<td>metastatic BC</td>
<td>Adj</td>
<td>End</td>
<td>932</td>
<td>52 (44-60)</td>
<td>12</td>
<td>52 (45-59)</td>
<td>DFS</td>
<td>816 (816-816)</td>
</tr>
</tbody>
</table>

Note: *Neo, neoadjuvant treatment; Adj, adjuvant treatment; End, endocrine treatment; Lpnb, lapatinib; Tzmb, trastuzumab.

Discussion

This study, including 14 randomized controlled trials (RCTs) with 15,636 women, is the first meta-analysis focusing on the impact of HR status on the treatment efficacies in HER2-positive BC. Our results showed that HR-negative women achieved greater benefit from HER2-targeted agents in neoadjuvant therapy. On the contrary, in adjuvant therapy, HR positivity remained a favorable long-term factor in HER2-positive patients with BC.

Accumulating evidence suggested HER2-positive BC had distinct molecular and clinical characteristics according to HR status (Ellis 2014). Based on gene expression, patients with HR-positive/HER2-positive BC were classified as ‘luminal-B’ subtype because they over-expressed luminal type genes such as BCL2, GATA3 and ESR1, whereas ‘HER2-enriched’ subtype was predominantly HR-negative (Perou et al. 2000, Koboldt 2012). These two subtypes of BC showed significant molecular heterogeneity in DNA copy number, messenger RNA and microRNA expression, DNA methylation and the expression of cancer-related proteins and phosphoproteins (Koboldt 2012). In clinic, the impact of HR on the efficacy of anti-HER2 agents in the long-term clinical outcomes was discrepant and controversial. Montemurro et al. (2012) and Vici et al. (2016) reported that estrogen receptor (ER)-positive BC was associated with a significantly decreased survival benefit from trastuzumab treatment. Moreover, a multicenter study even revealed that trastuzumab administration could not improve the survival prognosis in HR-positive/HER2-positive patients (Wang et al. 2015). In contrast, Brufsky et al. (2005) and Dawood et al. (2010) demonstrated that HR-positive disease was associated with improved clinical outcomes in patients with metastatic BC. Recently, a large cohort study in German also showed that anti-HER2 agents improved patients’ survival regardless of HR status (Ignatov et al. 2016). It is noted that all these trials were retrospective studies and the primary aims of each trials were different, so these result should be interpreted with caution. A prospective cohort study in the National Comprehensive Cancer Network demonstrated that the efficacy of trastuzumab was significantly dependent on the HR status.

Publication bias

Egger’s test and Begg’s funnel plot were conducted to evaluate the publication bias. The shapes of the funnel plot did not show any evidence of obvious asymmetry (Fig. 4).
Women with HR-negative/HER2-positive tumors were more likely to present unfavorable survival prognosis, whereas HR-positive/HER2-positive disease was associated with a better DFS and overall survival (OS). Our study extends the literature by showing that compared with HER2-positive/HR-negative women, HER2-positive/HR-positive subjects achieved greater benefit from HER2-targeted agent although the pCR of these patients was relatively poor. Our large sample size ensures the observed associations between HR status and clinical outcomes in HER2-positive BC. These findings warrant further stratification of the survival analysis based on both HR and HER2 status. In fact, one predictive model has been developed based on the NSABP B31 adjuvant trial (Pogue-Geile et al. 2013). In this model, the degree of benefit was precisely predicted by eight genes; five were associated with ER (NAT1, CA12, ESR1, GATA3 and IGF1R) and three with HER2 (f37 or c17, ERBB2 and GRB7).

Neoadjuvant therapy, first recognized as a treatment option to downstage advanced cancer or make inoperable tumors operable, now became a reliable and rapid approach to evaluate the anti-cancer activity of both new agents and standard treatments (Zardavas & Piccart 2015).

Pathological complete response could predict long-term clinical outcome in many neoadjuvant trials and therefore was treated as a potential surrogate marker for clinical outcome (Kaufmann et al. 2006). In 2012, the FDA released a specific guidance to use pCR as a surrogate endpoint to accelerate drug approval in a far shorter time frame for patients with high-risk early-stage BC. This guidance soon resulted in the accelerated approval of pertuzumab, a monoclonal antibody for the treatment of HER2-positive BC (Amiri-Kordestani et al. 2014). However, the biological differences between the subjects who achieved pCR in response to neoadjuvant therapy and those patients who did not were still unclear. It is reported that pCR rates varied significantly across different subtypes of BC, ranging from 31.1% in triple negative cases to 8.3% in HR-positive cases (Houssami et al. 2012). Accordingly, some scientists and clinicians expressed their concerns on the use of pCR as a surrogate endpoint to evaluate an investigational agent (Wolff et al. 2008, Zardavas & Piccart 2015). Additionally, CTNeoBC demonstrated that increase in pCR rate did not always translate in a corresponding improvement of clinical outcomes; pCR predicted OS only in enriched HER2-positive but not in
Beggs funnel plot with pseudo 95% confidence limits

Figure 4
Beggs funnel plot comparing ORs for (A) pCR in trials of neoadjuvant, and (B) DFS in trials of adjuvant therapy. Each trial's effect estimate plotted against its standard error. The outer lines represent the confidence interval boundary within which 95% of trials are expected to lie in the absence of bias or heterogeneity. The middle horizontal line represents the summary treatment effect.

suggested that up-regulation of HR expression could result in an escape mechanism causing the resistance to HER2-targeted therapy in patients with HR-positive, HER2-positive BC (Montemurro et al. 2013). Pre-clinical studies showed that in the initially lapatinib-sensitive, HER2-positive, HR-positive BC cell lines, enhanced ER pathway acquired resistance to lapatinib and this resistance could be prevented by the inhibition of HER2 and ER (Xia et al. 2006). To further explain the exact role of HR in the onset of resistance to HER2-targeted agents, Wang et al. discovered that HR functioned as an important survival pathway in HR-positive, HER2-positive cells when these cells were under the circumstance of sustained HER2 inhibition (Wang et al. 2011). Eventually, HR became the primary controller of cell proliferation and survival. All these results highlighted the importance of dual inhibition of both HR and HER2 to achieve the best long-term clinical outcome in patients with HR-positive, HER2-positive BC. In fact, several guidelines (NCCN breast cancer guidelines 2015, AIOM breast cancer guidelines 2014 and ESO-ESMO 2nd international consensus guidelines) recommended the use of a combination of trastuzumab or lapatinib in combination with letrozole or anastrozole as first-line treatment for postmenopausal patient with HER2-positive, HR-positive BC. Here, we investigate the impact of HR status on DFS in patients treated with different therapy strategies. Although the extent of benefit HR-positive women achieved over HR-negative patients was dependent on the treatment strategy, this effect was only marginally significant (P=0.04). It might partly due to the limited RCTs included in our study. Accordingly, further trials with more power are needed to validate our results.

This meta-analysis has several strengths. We performed a comprehensive review and utilized the most up-to-date published data. All the included original studies were phase II or phase III RCTs. Moreover, with the accumulating evidence and enlarged sample sizes (i.e., the study population was similar to the general population), this study enhanced the statistical power with more reliable and precise clinical outcome estimates.

luminal/HER2-positive patients (Cortazar et al. 2014). In line with a previous study (Nagayama et al. 2014), our data showed that HR-negative disease was associated with a higher rate of pCR from neoadjuvant therapy in BC. Although it had been proposed that patients with HR-negative disease benefit more from HER2-targeted therapy, our data revealed that HR-positive patients have a better outcome in spite of their pCR rate being low, suggesting pCR may be a prognostic factor instead of a surrogate marker for treatment benefit in BC.

HER2-positive BC is a heterogeneous disease in which several distinct genetic and histopathological types have been defined; about 50% of women with HER2-positive are also ER and/or progesterone receptor (PgR) over-expression positive (i.e. HR-positive) (Konecny et al. 2003, Lal et al. 2005). The underlying mechanisms involved in the associations between HR status and survivals in HER2-positive BC were uncertain. It was generally believed that the crosstalk between HR and HER2 pathways played a key role (Schettini et al. 2016). Recently, evidence
efficacy for HR-positive and HR-negative subgroups, there will be differences in the costs required to achieve clinical benefits.

This study is not without limitations. First, ideally, a meta-analysis of RCTs with OS as the primary endpoint should be addressed. However, the efficacy of HER2-targeted agents on OS has been diminished in most RCTs because of the following reasons: (1) Although HER2-positive cancer is highly aggressive, the five-year survival rate with no recurrence for patients with HER2-positive BC is still about 80% (Subbiah & Gonzalez-Angulo 2014). It takes a long time to obtain sufficient data for OS analysis. Accordingly, the eligible trials including this study mainly focus on DFS instead of OS. (2) Since HER2-targeted therapy is very effective, nearly all of the women who were assigned to the controlled arm crossed over to receive HER2-targeted treatment after disease progression. For these reasons, OS is not selected as the principal aim in this meta-analysis.

Additional limitations included: (1) regardless of the fact that most of the eligible trials conducted the randomization process adequately, an imbalance of patient characteristics between HR-positive subgroup and HR-negative subgroup could exist; thus it is possible that the results we revealed here might be caused by some confounder and not HR status. Additionally, some of our conclusions depended on subgroup analyses in the RCTs, so differences or similarities between subgroups may be caused by other variables. As a result, our results should be interpreted cautiously considering the fact that extracted data could not be randomized. (2) The heterogeneity across studies might not be fully explained. It has been indicated that the meta-analyses were influenced by individual study. Other factors, including the dose and duration of HER2-targeted agents, and distribution of tumor stages, can also be the source of heterogeneity. So further analysis should be carried out if individual woman’s data are available. (3) We were unable to pool hazards of death because time-to-death data were not reported. Instead, odd ratios were calculated in the current study. This measure was less robust compared with the hazard ratio. However, this was the only feasible method with the data available. (4) Of all the trials included in our meta-analysis, only two studies were double-blinded (Goss et al. 2013, Chan et al. 2016), and the rest trials were open-label. This could lead to potential bias. (5) Patients with BC experience altered both HR and HER2 status throughout tumor progression, while management of patients was frequently based on the primary tumor characteristics, which may impact the efficacy of treatments (Lindstrom et al. 2012, Aurilio et al. 2014).

Several critical questions arise on the basis of our findings. First, understanding which women are eligible for new treatments is critical in drug development, especially in the neoadjuvant setting; however, the lack of prognostic power of pCR makes the identification of an accurate marker or markers a priority for clinical tumor research. Second, the design of future clinical trials in the neoadjuvant setting should take several features into account to obtain better long-term outcomes: tumor heterogeneity, biomarker-based stratification of subjects who are most likely to benefit, expansion of the disease and the timing of the treatment.

In summary, compared with HER2-positive/HR-negative patients, HER2-positive/HR-positive subjects achieved greater benefit from HER2-targeted agent although the pCR of these patients was relatively poor. These findings have important implications for clinical data interpretation and trial design, economic analyses and potential drug development for HER2-targeted BC.

**Supplementary data**

This is linked to the online version of the paper at https://doi.org/10.1530/ERC-18-0029.

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

**Funding**

This work was funded by National Natural Science Foundation of China (No. 31571417 and No. 31600713), Natural Science Foundation of Heilongjiang Province (No. H2016023 and No. QC2015109), Health and Family Planning Commission Foundation of Heilongjiang Province (No. 2014-403), and Start-up Foundation of Harbin Medical University (No. 2016CZX37).

**References**


Ellis MJ 2014 HER2-positive breast cancer, intrinsic subtypes, and survival. *Journal of the National Cancer Institute* **106** dju212. (https://doi.org/10.1093/jnci/dju212)


http://erc.endocrinology-journals.org © 2018 Society for Endocrinology Published by Bioscientifica Ltd. Printed in Great Britain

Downloaded from Bioscientifica.com at 09/17/2019 09:36:21PM via free access


Received in final form 9 April 2018
Accepted 11 April 2018