Clinical Cancer Research

Dual Block with Lapatinib and Trastuzumab Versus Single-Agent Trastuzumab Combined with Chemotherapy as Neoadjuvant Treatment of HER2-Positive Breast Cancer: A Meta-analysis of Randomized Trials

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Abstract

Purpose: (Neo)adjuvant treatment with chemotherapy plus trastuzumab reduces recurrence and death risk in HER2-positive ($HER2^+$) breast cancer. Randomized trials assessed HER2 dual block by adding lapatinib to trastuzumab and chemotherapy in the neoadjuvant setting using pathologic complete response (pCR) as the outcome measure. We conducted a meta-analysis of randomized trials testing neoadjuvant dual block with lapatinib and trastuzumab versus trastuzumab alone in $HER2^+$ breast cancer.

Experimental Design: Trials were identified by Medline (PubMed), ISI Web of Science (Science Citation Index Expanded), Embase, Cochrane library, and reference lists of published studies, review articles, editorials, and by hand-searched reports from major cancer meeting reports.

Results: Six randomized trials including 1,155 patients were identified, of whom 483 (41.8%) were hormone receptor–negative, 672 (58.2%) hormone receptor–positive, 534 (46.2%) received taxanes alone, and 621 (53.8%) anthracyclines plus taxanes or the docetaxel–carboplatin regimen. Overall, the dual block was associated with a significant 13% absolute improvement in pCR rate compared with single-agent trastuzumab (summary risk difference, SRD 0.13; 95% CI, 0.08–0.19). The activity was greater in hormone receptor–negative patients who received chemotherapy with taxanes alone (SRD 0.25; 95% CI, 0.13–0.37), compared to hormone receptor–positive or hormone receptor–negative disease treated with anthracyclines plus taxanes or the docetaxel–carboplatin regimen (SRD 0.09; 95% CI, 0.02–0.15; $P_{interaction} = 0.05$).

Conclusions: On the basis of ΔpCR data, the dual block with trastuzumab and lapatinib plus chemotherapy is a very active treatment only in $HER2^+$ and hormone receptor–negative breast cancer treated with taxane monochemotherapy. *Clin Cancer Res; 22(18); 4594–603. ©2016 AACR.*

Introduction

Adjuvant systemic treatment with anti-HER2 mAb trastuzumab reduces the risk of recurrence and death from HER2-positive ($HER2^+$) early breast cancer, as demonstrated by a series of large phase III clinical trials comparing the addition of trastuzumab to chemotherapy versus chemotherapy alone (1–5). Most of these trials required thousands of patients and many years of follow-up to demonstrate a significant benefit in terms of disease free survival (DFS) and overall survival (OS) favoring the trastuzumab arm.

In breast cancer, neoadjuvant treatment is used to select active agents or strategies to be tested in the adjuvant phase using pathologic complete response (pCR) rate as surrogate biomarker, that is, the disappearance of invasive cancer cells in the breast (ypT0/is) or in the breast and axilla (ypT0/is and ypN0). Recently, the neoadjuvant model was approved for accelerated drug approval in breast cancer by regulatory agencies (6–10).

pCR is a strong prognostic factor in breast cancer (11, 12), as demonstrated by a pooled analysis on individual patient data in 12,000 patients enrolled in 12 randomized trials (13). The most favorable risk reduction in event-free survival (EFS) and OS after pCR was obtained in (i) hormone receptor–negative and HER2-negative ($HER2^-$) breast cancer treated with neoadjuvant chemotherapy [EFS: HR 0.25; 95% confidence interval (CI), 0.18–0.34; OS: HR 0.19; 95% CI, 0.12–0.31] and (ii) hormone receptor–negative, $HER2^+$ breast cancer treated with neoadjuvant chemotherapy plus trastuzumab (EFS: HR 0.15; 95% CI, 0.09–027; OS: HR 0.08; 95% CI, 0.03–0.22; refs. 11–13). The prognostic effect of pCR was much less evident in hormone receptor–positive and $HER2^-$ breast

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Translational Relevance

We aimed to quantify the absolute increase in pCR (ΔpCR) by double HER2 targeting with lapatinib plus trastuzumab versus trastuzumab alone in the neoadjuvant setting across biologic subsets (hormone receptor status) and chemotherapy strategies (monochemotherapy with taxane alone versus the whole anthracycline and taxane sequence or the docetaxel–carboplatin regimen). Overall, dual block was associated with a significant 13% ΔpCR compared with trastuzumab alone. ΔpCR by dual block was greater in hormone receptor–negative than positive disease (18% vs. 8%, respectively). ΔpCR by dual block was heavily influenced by the type of chemotherapy: polychemotherapy was associated with limited ΔpCR (10%) compared with monochemotherapy with taxane alone (16%). On the basis of ΔpCR data, the dual block with trastuzumab and lapatinib plus chemotherapy is a very active treatment only in HER2$^+$ and hormone receptor–negative breast cancer treated with taxane monochemotherapy.

cancer, in which the rate of pCR was low (from 7.5% in grade 1/2 to 16.2% in grade 3 disease; ref. 13).

In HER2$^+$ breast cancer, the probability to obtain pCR and, more importantly, the absolute increase in pCR (ΔpCR) by adding trastuzumab to chemotherapy is influenced by the hormone receptor status, with a ΔpCR of 20% in hormone receptor–negative versus 12% in hormone receptor–positive disease (13–16).

The role of pCR as a surrogate marker of DFS and OS in breast cancer is still controversial. Cortazar and colleagues demonstrated little association between pCR and long-term outcomes in terms of EFS and OS in the overall breast cancer population (R^2 = 0.03 and 0.24, respectively; ref. 13). In addition, a trial-based meta-regression analysis of 29 randomized prospective studies in more than 14,000 patients failed to support the use of pCR as a surrogate endpoint of DFS and OS (17). However, in the HER2$^+$ subgroup treated with neoadjuvant chemotherapy and trastuzumab, the association between pCR and long-term outcomes EFS and OS was greater (ref. 13 and Supplementary Appendix S4).

In the NOAH trial (14), ΔpCR from trastuzumab added to neoadjuvant chemotherapy was 20% translating in an absolute 11% 5-year OS improvement. In general, ΔpCR without biologic treatments is nearly 10% (minimum 3.0%, maximum 12.5%) among trials comparing different chemotherapy regimens in terms of duration, dose intensity, use of taxanes added to anthracyclines, or capecitabine added to anthracyclines and taxanes (18–24).

Pertuzumab (25–27), lapatinib (28, 29), and trastuzumab emtansine (30, 31) represent different effective options for the treatment of HER2$^+$ metastatic breast cancer. Pertuzumab and lapatinib have also been studied in randomized trials conducted in the neoadjuvant setting combined with trastuzumab-based therapy to increase pCR rate and, possibly, obtain a benefit in DFS and OS.

Importantly, the introduction of these biologic targeted therapies in HER2$^+$ breast cancer may potentially reduce or even substitute the administration of chemotherapy. For instance, the NEOSPHERE trial demonstrated a pCR of 17% with the use of trastuzumab plus pertuzumab without chemotherapy (32), whereas the BCIRG-006 study substituted the association anthracycline–taxane with carboplatin–taxane obtaining the same efficacy while reducing cardiac toxicity and the risk of AML/MDS (3). Finally, two single-arm trials conducted in the adjuvant setting by Tolaney and colleagues (33) and Jones and colleagues (34) demonstrated that in selected low-risk HER2$^+$ breast cancer the association of trastuzumab plus a monochemotherapy with a taxane obtained optimal DFS and OS results without the use of anthracyclines. The association of trastuzumab plus pertuzumab or lapatinib (dual block) might, therefore, be used to avoid chemotherapy treatment, retaining similar results in terms of DFS/OS while reducing toxicity.

We performed a meta-analysis of data from published trials conducted in HER2$^+$ breast cancer in the neoadjuvant setting comparing pCR obtained with chemotherapy and the dual block with lapatinib and trastuzumab versus chemotherapy and single-agent trastuzumab. More specifically, we aimed to add some precision to the quantification of ΔpCR with double targeting across subsets (hormone receptor status) and strategies (monochemotherapy composed by taxane alone vs. the whole anthracycline and taxane sequence or the docetaxel–carboplatin regimen).

Materials and Methods

For this meta-analysis, we sought data from randomized trials published as full articles or abstracts that compared the anti-HER2 dual block treatment trastuzumab plus lapatinib combined with chemotherapy to single-agent trastuzumab combined with chemotherapy in the neoadjuvant treatment of HER2$^+$ breast cancer. The NEOSPHERE trial (32) using the dual block with pertuzumab and trastuzumab and the NSABP FB-7 trial using the dual block with neratinib and trastuzumab (35) were excluded.

We conducted this meta-analysis in accordance with standards of quality of the PRISMA statement (36). Studies were identified by searching Medline (PubMed), ISI Web of Science (Science Citation Index Expanded), Embase, and the Cochrane library, by examining the reference lists of published studies, review articles, and editorials and by hand-searched reports from the following major cancer associations/symposia reports: American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), San Antonio Breast Cancer Symposium (SABCS). For database searches, the following search terms were adopted: "Breast Neoplasms (MESH)," "Neoadjuvant Chemotherapy (MESH) OR Neoadjuvant Treatment (MESH)," "Lapatinib (MESH)," "Trastuzumab (MESH," "Receptor, erbB-2 [MESH]" OR "Genes, erbB-2 [MESH]" and also the following search string: ["Breast Neoplasms" AND "Neoadjuvant Treatment" AND "Lapatinib" AND "Trastuzumab" AND "(HER2 OR c-erbB-2 OR HER2-positive)"]. Additional filters in the database search: "clinical trial," "full text," "publication date: 5 years," "species: human." The database was searched for articles published through March 30, 2016.

Eligibility criteria

All trials had to fulfill the following criteria to be included in this meta-analysis: (i) study design: randomized clinical trials; (ii) treatment: neoadjuvant treatment of HER2$^+$ breast cancer;

(iii) type of intervention: HER2 dual block with trastuzumab plus lapatinib versus single-agent trastuzumab, all arms combined with chemotherapy; (iv) primary endpoint: pCR; (v) sample size: at least 30 patients/arm evaluable for pCR.

Data extraction

The following data were extracted from each study: the number of randomly assigned patients, neoadjuvant chemotherapy schedules associated with neoadjuvant dual block or single-agent trastuzumab; pCR definition; the number of patients, percentage of total pCR and according to hormone receptor status (hormone receptor–negative vs. positive). All data were checked for internal consistency.

Statistical analysis

Number of events (pCR) was directly extracted from the published reports. We estimated the risk difference (RD) as the difference between the risk of event in the experimental group and the risk of event in the control group. Weighted averages of treatment effects, referred to as summary risk differences (SRD) in the Results section, were calculated by pooling RD estimates across the studies using random effects modeling from the method of DerSimonian and Laird (37), with the estimate of heterogeneity being taken from the Mantel–Haenszel model. SRD can be interpreted as the difference, in percentage ($\times 100$), of pCR between the experimental and the control arm (ΔpCR). For example, a SRD of 0.13 is a difference of 13% in rate of pCR between experimental and control arms: on average, subjects enrolled in the experimental arm experienced 13% more pCR than subjects enrolled in the control arm. Heterogeneity in the results of the studies was evaluated both visually, by means of Forest plots, and using the *I*-squared (I^2) parameter, which represents the percentage of total variation across studies that is attributable to heterogeneity rather than to chance. *P* values ≤ 0.10 were considered significant for heterogeneity and an $I^2 <$ 25% was considered as a low level of heterogeneity. Sensitivity analyses were carried out to verify the effect of single studies (leave-one-out procedure) on the stability of the SRDs. To assess for the risk of publication bias, we visually inspected funnel plots, but we did not conduct statistical tests for funnel plot asymmetry because of the limited test power when less than 10 studies are included (38). In all analyses, we adopted random effects modeling, which, in case of low heterogeneity, gives superimposable results to the fixed model. All analyses were conducted with the use of STATA (version 13; Stata Corporation). All *P* values were two sided and the cut-off value for statistical significance was set at 0.05.

Subgroup analyses

Subgroup analyses were performed to assess the influence of hormone receptor status (hormone receptor–negative vs. positive) and type of chemotherapy on the activity of dual block. Different preoperative chemotherapy schedules were used in the included trials. Chemotherapy regimens were divided into two groups: a taxane-alone group, including trials in which patients received preoperative taxane-based alone chemotherapy with anthracyclines being administered as adjuvant treatment after surgery, and a polychemotherapy group, in which patients received sequential anthracycline and taxane-based chemotherapy or the carboplatin–docetaxel regimen without anthracycline prior to surgery. Consequently, meta-regression modeling was utilized. This analysis, which can be considered equivalent to a test for interaction when individual patient data is not available, was conducted by testing the difference among the SRD estimates in different subgroups of studies; the regression coefficient indicates how the intervention effect in each subgroup differs from the effect in a specified reference subgroup and the *P* value of the regression coefficient indicates whether this difference is statistically significant. Because no correction for multiple testing was used, *P* values should be considered with caution.

Results

We identified six randomized trials that compared neoadjuvant dual block with lapatinib and trastuzumab plus chemotherapy versus trastuzumab alone plus chemotherapy: NEOALTTO (39), CALGB 40601 (40), NSABP B-41 (41), EORTC 10054 (42), TRIO-US B07 (43), and CHERLOB (44) trials. Five trials were published as full article in peer-reviewed journals and one was published as conference abstract. One trial (45) was excluded because the number of patients/arm analyzed for pCR data was less than 30. The flowchart of study selection is shown in Fig. 1.

Characteristics of included studies

Six studies, fulfilling all the inclusion criteria, were included in this meta-analysis and the main characteristics are presented in Table 1. The studies were published or presented between December 2010 and February 2016. Overall, 1,155 $HER2^+$ breast cancer patients were enrolled. Of these, 483 (41.8%) had hormone receptor–negative and 672 (58.2%) had hormone receptor–positive disease. The highest percentage of hormone receptor–negative breast cancer was in the NEOALTTO (49.5%) and EORTC 10054 (50.0%), the lowest in the NSABP B-41 trial (33.9%). Five of six trials reported pCR rate according to hormone receptor status. In four trials (NEOALTTO, CALGB 40601, NSABP B-41, and EORTC 10054) pCR was defined as the absence of invasive cancer in the breast only (ypT0/is), whereas in two trials (TRIO-US B07 and CHERLOB), pCR was defined as the absence of invasive cancer in the breast and the axilla (ypT0/is and ypN0). Patients enrolled in the lapatinib alone plus chemotherapy arm in the NEOALTTO, CALGB 40601, NSABP B-41, EORTC 10054, TRIO-US B07, and CHERLOB trials were excluded from our meta-analysis.

Dual block activity overall and by hormone receptor status and chemotherapy regimen

Overall, dual block, compared with single-agent trastuzumab, was associated with a significant 13% absolute increase in ΔpCR rate (SRD 0.13; 95% CI, 0.08–0.19; Fig. 2). No heterogeneity was detected among the studies ($I^2 = 0.0$, $P = 0.452$).

The analysis of pCR rates stratified by hormone receptor status revealed a 18% significantly increased ΔpCR rate in hormone receptor–negative tumors (SRD 0.18; 95% CI, 0.09–0.27) and a modest, albeit significant, 8% increase in hormone receptor–positive tumors (SRD 0.08; 95% CI, 0.01–0.16; Fig. 3). A trend to a quantitative interaction between dual block and hormone receptor status was evident even if the statistical test was not formally significant ($P = 0.157$).

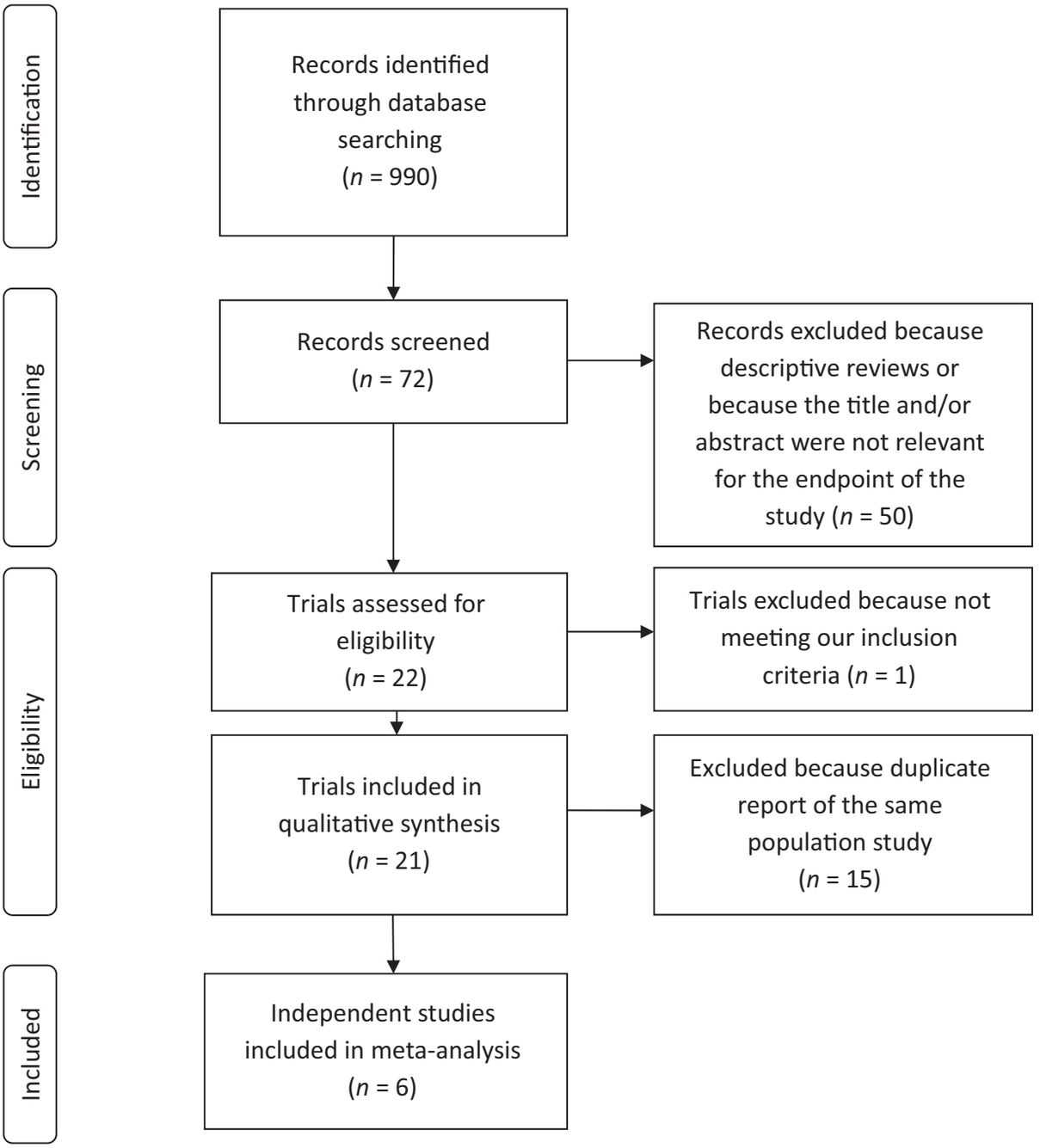

Figure 1.
Flow-chart diagram of selected studies included in the meta-analysis.

Stratifying the analysis by type of chemotherapy in 534 patients in the taxane-alone group and 621 patients in the polychemotherapy group, ΔpCR was 16% (SRD 0.16; 95% CI, 0.05–0.28) in favor of the dual block in the taxane-alone group, whereas it was 10% (SRD 0.10; 95% CI, 0.03–0.18) in the polychemotherapy group ($P_{\text{interaction}} = 0.336$; Fig. 4).

The analysis of the different subgroups according to type of chemotherapy and hormone receptor status in Fig. 5 showed a 25% in ΔpCR rate (SRD 0.25; 95% CI, 0.13–0.37) by the dual block in the subgroup taxane-alone and hormone receptor negative, in contrast to a modest, if any, increase of pCR in all the remaining three subgroups: taxane-alone and hormone receptor positive (SRD 0.10; 95% CI, −0.09 to 0.28), polychemotherapy and hormone receptor negative (SRD 0.10; 95% CI, −0.03 to 0.23), polychemotherapy, and hormone receptor positive (SRD 0.06; 95% CI, −0.04 to 0.17).

Table 1. Characteristics of the identified studies in the meta-analysis

Trial	Chemo	HER2 therapy	*N*	*N* HoRe−	*N* HoRe+	% pCR All	% pCR HoRe−	% pCR HoRe+	% Difference All	% Difference HoRe−	% Difference HoRe+
Taxane-alone											
NEOALTTO[a]	wP ×12	L + T	152	75	77	51%	61%	42%	22%	25%	19%
		T	149	74	75	29%	36%	23%			
CALGB 40601[a]	wP ×16	L + T	116	47	69	56%	79%	41%	10%	25%	0%
		T	117	48	69	46%	54%	41%			
Polychemotherapy											
NSABP B-41[a]	AC ×4 – wP ×12	L + T	171	63	108	62%	73%	56%	10%	8%	9%
		T	177	55	122	52%	65%	47%			
EORTC 10054[a]	D ×3 – FEC ×3	L + T	48	25	23	60%	68%	52%	8%	16%	0%
		T	52	25	27	52%	52%	52%			
TRIO-US B07[b]	DCa ×6	L + T	58	24	34	52%	67%	40%	5%	10%	0%
		T	34	14	20	47%	57%	40%			
CHERLOB[b]	wP ×12 – FEC ×4	L + T	45	UNK		46%	UNK		21%	UNK	
		T	36	UNK		25%					

Abbreviations: D, docetaxel every 3 weeks; wP, weekly paclitaxel; AC, doxorubicin-cyclophosphamide; DCa, docetaxel–carboplatin; FEC, fluorouracil–epirubicin–cyclophosphamide; T, trastuzumab; L, lapatinib; HoRe−, hormone receptor negative; HoRe+, hormone receptor positive; UNK, unknown.
[a]pCR: ypT0/is.
[b]pCR: ypT0/is and ypN0.

The test for interaction comparing the taxane-alone and hormone receptor–negative group versus the remaining groups was statistically significant ($P = 0.05$), indicating a greater efficacy of the dual block in hormone receptor–negative tumors treated with taxane-alone regimens.

Discussion

This meta-analysis confirms that, in HER2$^+$ breast cancer, a preoperative treatment with HER2 dual block by lapatinib and trastuzumab significantly increases the pCR rate by an absolute level of 13% as compared with single block with trastuzumab.

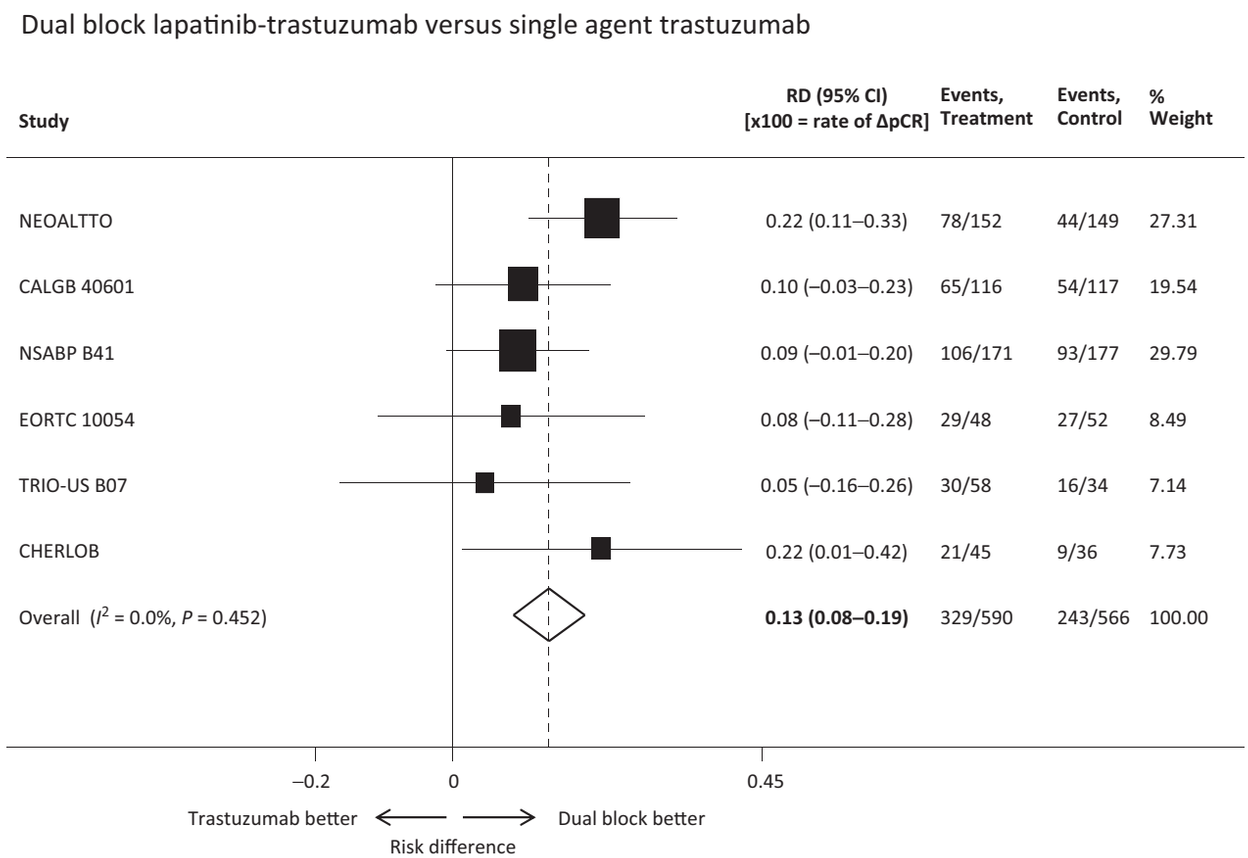

Figure 2.
pCR rate by dual block versus single-agent trastuzumab in HER2$^+$ breast cancer women in the neoadjuvant setting: overall effect.

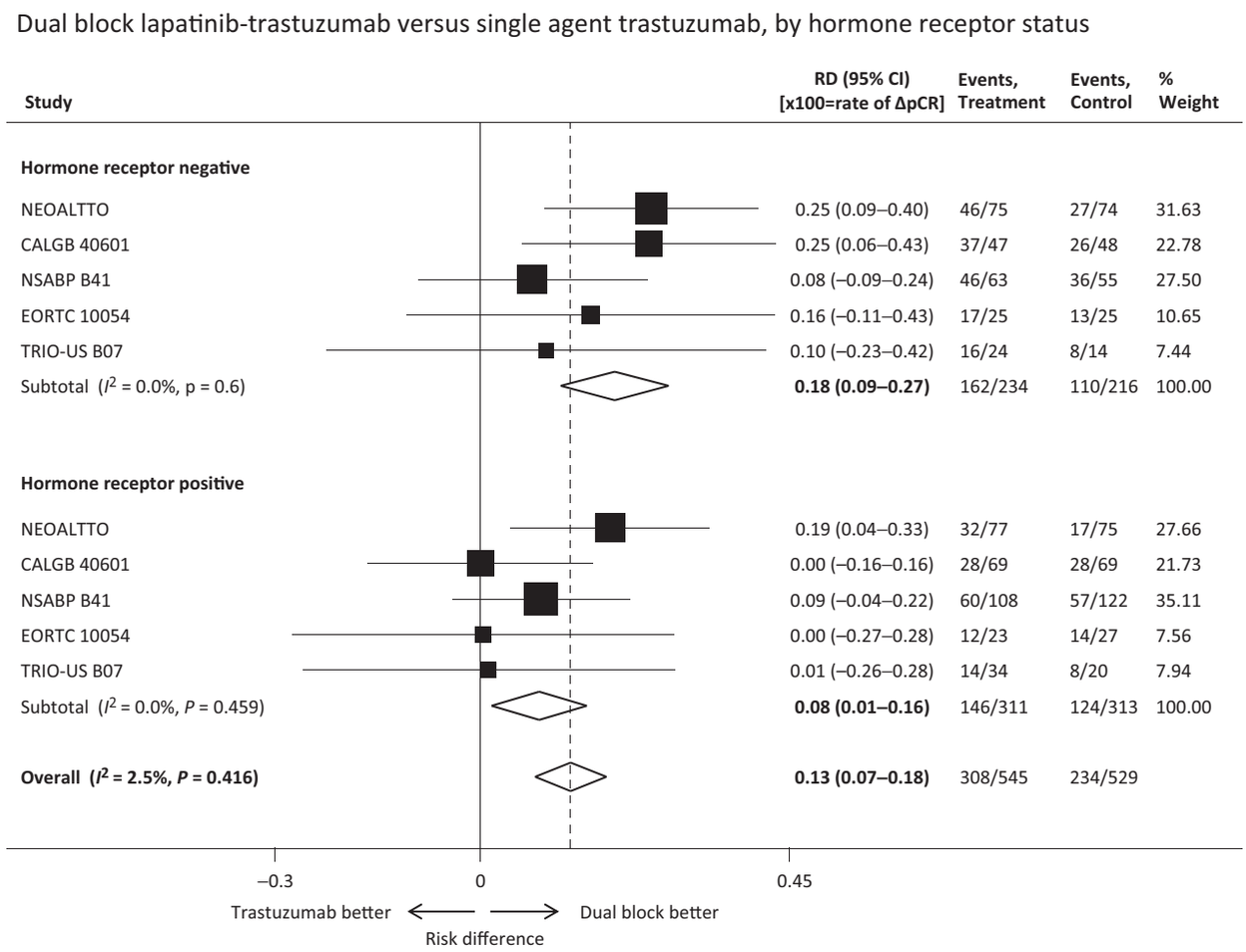

Figure 3.
Subgroup analysis by hormone receptor status (negative vs. positive), $P_{interaction} = 0.157$.

Dual block had a different impact on ΔpCR rate according to the type of chemotherapy in the neoadjuvant phase. Patients receiving taxane monochemotherapy achieved a greater benefit from the dual block compared with patients receiving polychemotherapy (anthracycline plus taxane or carboplatin-docetaxel combination), with an absolute difference of 16% in pCR, even if the interaction by type of chemotherapy was not significant ($P = 0.336$). In particular, hormone receptor–negative patients in the taxane-alone group achieved the best absolute improvement on pCR rate in comparison with the remaining three groups combined (taxane-alone/hormone receptor–positive, and all polychemotherapy groups, $P_{interaction} = 0.05$). Conversely, the dual block added to polychemotherapy increased pCR by only 10% compared with single-agent trastuzumab. This benefit is probably not sufficient to increase long-term outcomes EFS and OS, as demonstrated by previous meta-analysis (13). Indeed, only an absolute increase of 20% in pCR provided by the addition of single-agent trastuzumab to neoadjuvant polychemotherapy in the NOAH study (46) translated into a significant improvement in 5-year event-free survival (58% vs. 43%, respectively; HR 0.64; 95% CI, 0.44–0.93; $P = 0.016$) and 5-year overall survival (74% vs. 63%, respectively; HR 0.66; 95% CI, 0.43–1.01; $P = 0.055$). Our findings seem to suggest that the impact of dual block lapatinib–trastuzumab over and above optimal polychemotherapy may be more limited. In addition, the greater the number of drugs administered, the more difficult is to dissect the benefit from the addition of one specific component.

This meta-analysis also demonstrates that the benefit from the dual block lapatinib–trastuzumab is more evident in hormone receptor–negative than positive, with an absolute increase of 18% and 8% on pCR, respectively ($P = 0.157$). In general, in HER2$^+$ and hormone receptor–positive, pCR is a favorable prognostic factor (EFS: 0.58; 95% CI, 0.42–0.82; ref. 13). However, the small increase on pCR in hormone receptor–positive by dual block is probably not sufficient to improve prognosis. Results from two trials conducted in the neoadjuvant setting with the dual block confirmed this hypothesis, although the small number of patients and events prevents definitive conclusions. In the NEALTTO trial, a significant absolute difference in pCR of 22% in favor of the dual block did not translate into an EFS benefit. However, the HR was 0.65 (95% CI, 0.32–1.28) among hormone receptor–negative patients and 0.96 (95% CI, 0.46–2.01) in positive (47). Likewise, the NEOSPHERE trial showed a significant absolute 17% improvement in pCR in the docetaxel plus dual block arm

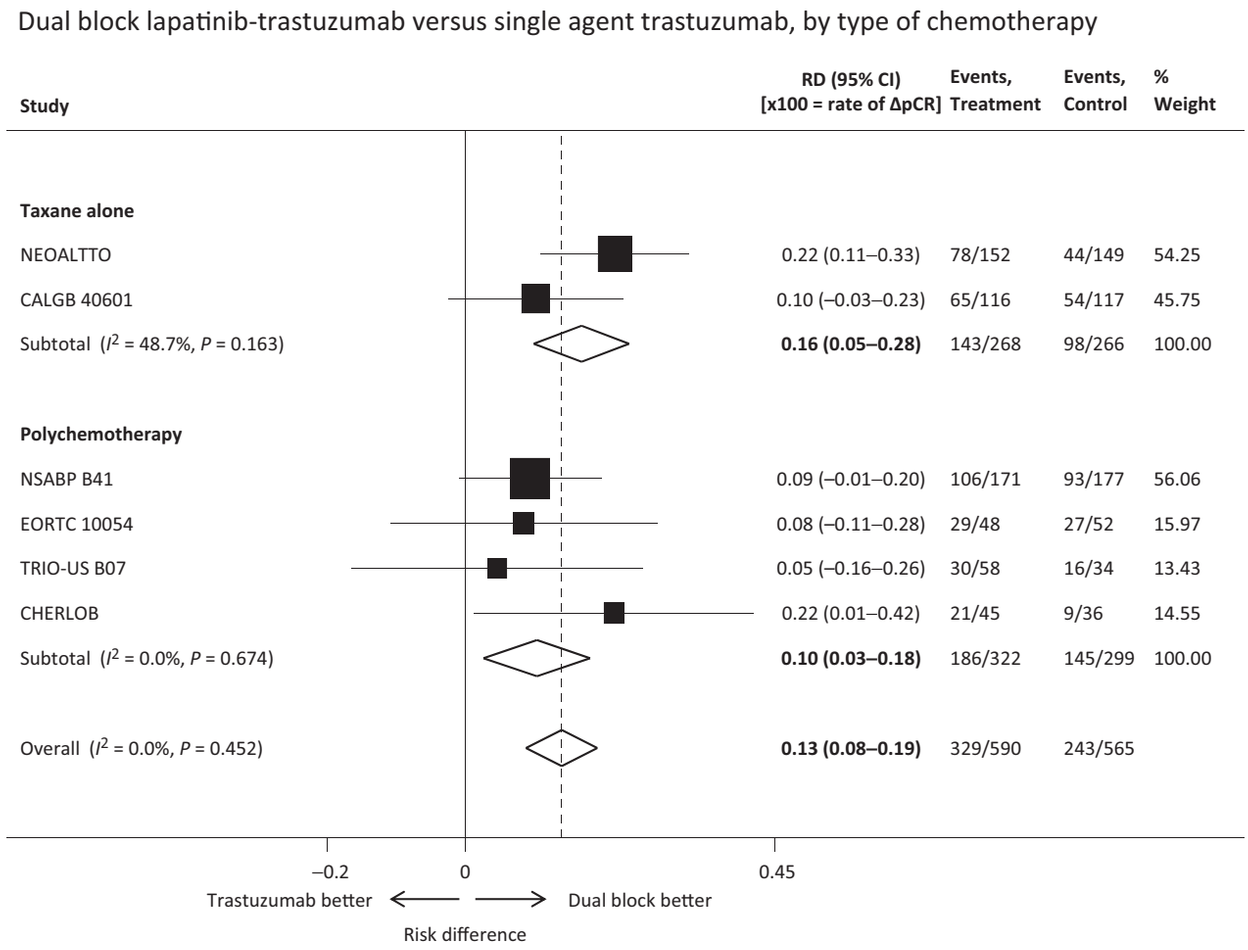

Figure 4.
Subgroup analysis by type of chemotherapy (taxane alone vs. polychemotherapy), $P_{interaction} = 0.336$.

pertuzumab–trastuzumab versus docetaxel and trastuzumab alone arm (45.8% vs. 29.0%, respectively, $P = 0.014$). Also, in this trial, ΔpCR was more evident among hormone receptor–negative (63% vs. 37%) than hormone receptor–positive (26% vs. 20%, respectively) in favor of the dual block pertuzumab–trastuzumab (32). EFS and DFS data at 5 years were similar, with only 17 events in the dual block arm versus 19 in the control arm. However, although the overall HR was not significant (HR 0.69; 95% CI, 0.34–1.40), there were some differences between hormone receptor–negative (HR 0.60; 95% CI, 0.24–1.48) and positive tumors (HR 0.86; 95% CI, 0.27–2.75; ref. 48). These data, combined with the results of our meta-analysis, seem to suggest that ΔpCR by dual block could have a clinical impact, potentially increasing EFS and OS, only in $HER2^+$ and hormone receptor–negative disease. The biologic mechanisms underlying the different effect according to hormone receptor status is unclear, but hormone receptor expression has been associated with anti-HER2 drugs resistance in preclinical and clinical models, possibly due to cross-talk inhibition between growth-promoting pathways (49–52).

Our meta-analysis differs from Nagayama and colleagues (53), who addressed different treatment comparisons in $HER2^+$ disease but did not specifically focus on the efficacy of the double targeting with lapatinib–trastuzumab in the neoadjuvant setting. In fact, Nagayama and colleagues selected trials including different treatment arms and different comparisons, specifically: (i) single-agent trastuzumab plus chemotherapy versus chemotherapy alone; (ii) lapatinib plus chemotherapy versus trastuzumab plus chemotherapy; (iii) dual block pertuzumab-trastuzumab plus chemotherapy versus trastuzumab plus chemotherapy; (iv) single-agent pertuzumab plus chemotherapy; (v) dual block pertuzumab and trastuzumab without chemotherapy. All these treatment arms and comparisons were excluded from our meta-analysis which focused on the comparison between dual block lapatinib–trastuzumab plus chemotherapy versus single-agent trastuzumab plus chemotherapy. Second, only the NEOALTTO and CHERLOB trials concerning the dual block lapatinib–trastuzumab were included in the meta-analysis by Nagayama and colleagues, whereas our meta-analysis included also CALGB 40601, NSABP B-41, EORTC 10054, and TRIO-US-B07 trials. Third, our meta-analysis demonstrated that the efficacy of dual block is influenced by the type of chemotherapy administered in the neoadjuvant phase and the hormone receptor status, a finding which is

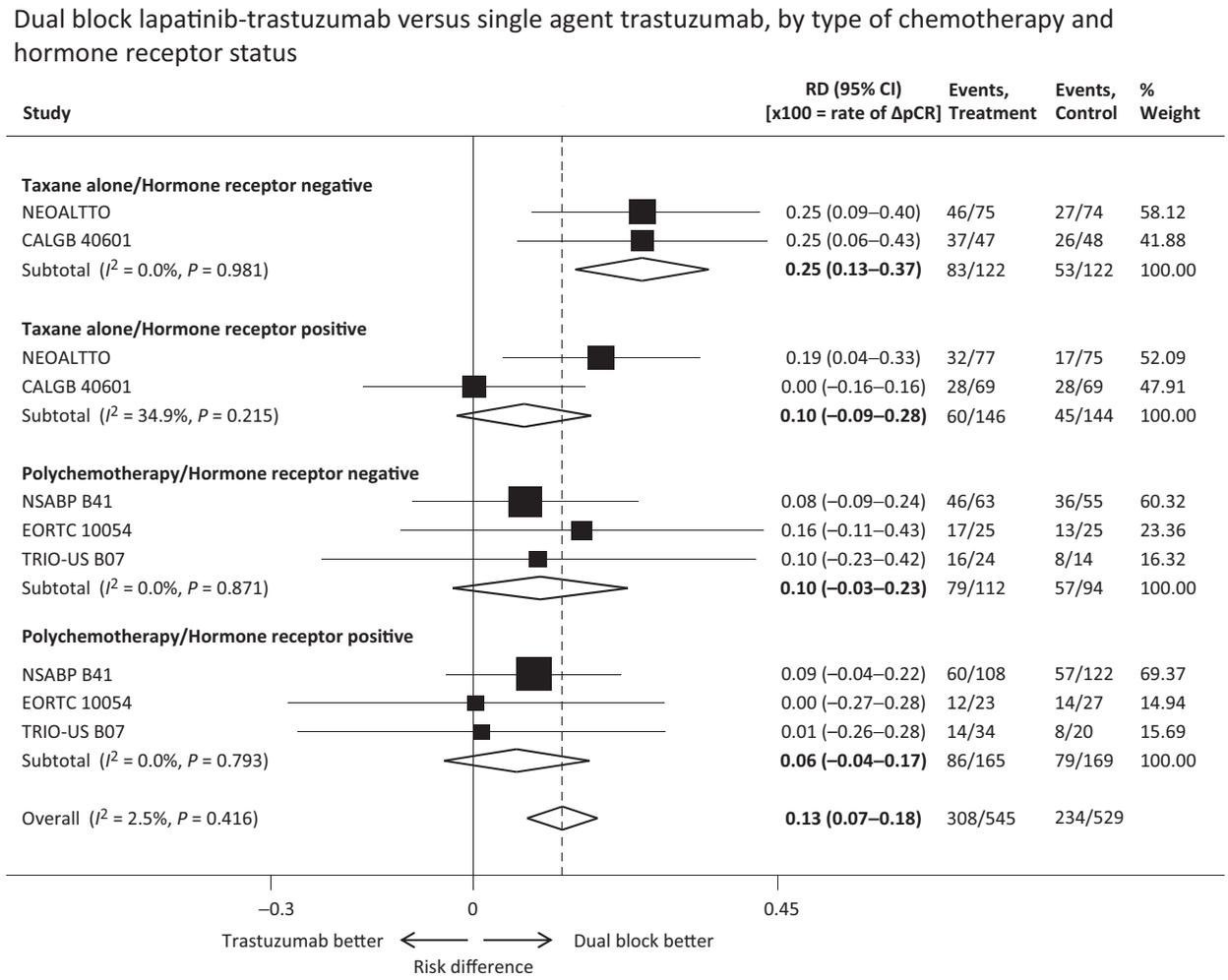

Figure 5.

Subgroup analysis by type of chemotherapy (taxane alone versus polychemotherapy) and by hormone receptor status (negative versus positive) combined; p for interactions: taxane alone/hormone receptor negative vs. taxane alone/hormone receptor positive, $P = 0.148$; taxane alone/hormone receptor negative vs. polychemotherapy/hormone receptor negative, $P = 0.135$; taxane alone/hormone receptor negative vs. polychemotherapy/hormone receptor positive, $P = 0.065$; taxane alone/hormone receptor negative vs. others, $P = 0.05$.

lacking in the meta-analysis by Nagayama and colleagues. However, our meta-analysis has some important limitations.

First, DFS and OS are influenced by subsequent adjuvant treatment, including adjuvant trastuzumab administered after surgery, adjuvant endocrine therapy in hormone receptor–positive disease, and adjuvant anthracyclines in patients treated with taxane monochemotherapy in the neoadjuvant phase. Thus, the effect of pCR improvement from dual block could be diluted by subsequent adjuvant treatments.

Second, data from the ALTTO trial in the adjuvant setting showed the absence of significant difference in DFS and OS with dual block lapatinib–trastuzumab versus trastuzumab alone. One possible explanation of these results is that lapatinib is not the best companion of chemotherapy given the 16% absolute increase grade 3 and 4 toxicities in the dual block and chemotherapy arm (41% vs. 25%, $P < 0.0001$), particularly diarrhea (11.3% vs. 1.3%, $P < 0.0001$). Toxicity frequently led to dose reduction and only 66% of patients received at least 85% the planned dose of lapatinib in the dual block arm, possibly hampering overall efficacy (54). At variance, pertuzumab is an optimal companion of chemotherapy with only 6% increase of febrile neutropenia and grades 3 and 4 diarrhea compared to chemotherapy and single-agent trastuzumab (25). Results from the large adjuvant randomized APHINITY trial are awaited (55).

Additional limitations include: (i) the low number of studies and events in our meta-analysis which clearly requires caution in the interpretations of our findings; (ii) the different definition of pCR as primary endpoint among studies (breast pCR or breast and axilla pCR); (iii) the heterogeneity in the pCR determination by trial and center; (iv) the inclusion of patients with different disease stages, frequently with locally advanced disease, in neoadjuvant studies; (v) the lack of complete information in one unpublished trial (TRIO-US B07). All these factors can influence the results in terms of %pCR obtained. In fact, %pCR with trastuzumab alone ranged between 25% and 52% whereas with the dual block lapatinib-trastuzumab

arm it ranged between 46% and 62%. A risk of bias assessment in each single study included in the meta-analysis is reported in Supplementary Tables S1 to S7.

In conclusion, this meta-analysis demonstrated a significant improvement in pCR in favor of the HER2 dual block lapatinib–trastuzumab versus single-agent trastuzumab. However, the results are strongly influenced by the hormone receptor status and type of chemotherapy administered in the neoadjuvant phase. On the basis of ΔpCR data, dual block trastuzumab–lapatinib plus chemotherapy is a very active treatment only in $HER2^+$ and hormone receptor–negative breast cancer treated with taxane monochemotherapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: M. Clavarezza, M. Puntoni, A. DeCensi
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