Dual neoadjuvant blockade plus chemotherapy versus monotherapy for the
treatment of women with non-metastatic HER2-positive breast cancer: a
systematic review and meta-analysis.

Juan Carlos Vazquez (1)
Silvia Antolin (2)
Manuel Ruiz-Borrego (3)
Sonia Servitja (4)
Emilio Alba (5)
Agusti Barnadas (6)
Ana Lluch (7)
Miguel Martin (8)
Alvaro Rodriguez-Lescure (9)
Ivan Sola (10)
Xavier Bonfill (11)
Gerard Urrutia (12)
Pedro Sanchez-Rovira (13)

(1) Iberoamerican Cochrane Centre, Biomedical Research Institute Sant Pau
(IIB Sant Pau), Barcelona, Spain. Hospital de la Santa Creu i Sant Pau; C/ Sant
Antoni Maria Claret, 167, Pavelló 18, planta 0, 08025 Barcelona, España.
(jvazquezn@santpau.cat) ORCID Identifier: 0000-0002-7780-4387
(2) Medical Oncology Unit, Complejo Hospitalario Universitario A Coruña.
(3) Medical Oncology Unit, Hospital Universitario Virgen del Rocío de Sevilla.
(4) Medical Oncology Unit, Hospital del Mar de Barcelona. GEICAM Spanish
(5) UGCI Oncología Médica, Hospitales Regional y Virgen de la Victoria. IBIMA.
Málaga. Centro de Investigación Biomédica en Red de Oncología, CIBERONC-


(9) Medical Oncology Unit, Hospital General Universitario de Elche. GEICAM Spanish Breast Cancer Group, Spain.

(10) Iberoamerican Cochrane Centre, Biomedical Research Institute Sant Pau (IIB Sant Pau), CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona. Spain.

(11) Iberoamerican Cochrane Centre, Biomedical Research Institute Sant Pau (IIB Sant Pau), CIBER Epidemiología y Salud Pública (CIBERESP), Universitat Autònoma de Barcelona, Barcelona. Spain.

(12) Iberoamerican Cochrane Centre, Biomedical Research Institute Sant Pau (IIB Sant Pau), CIBER Epidemiología y Salud Pública (CIBERESP), Universitat Autònoma de Barcelona, Barcelona. Spain.

(13) Medical Oncology Unit. GEICAM Spanish Breast Cancer Group. Medical Oncology Unit, Jaen Universitary Hospital, Avda Ejercito Español s/n, 23006 Jaén. Spain.

Corresponding author: Pedro Sanchez-Rovira. Medical Oncology Unit. GEICAM Spanish Breast Cancer Group. Medical Oncology Unit, Jaen Universitary Hospital, Avda Ejercito Español s/n, 23006 Jaén. Spain. (oncopsr@yahoo.es).
ABSTRACT

Background: Various anti-HER2 biological therapies have been used in HER2 subtype breast cancer aimed to improve survival in the neoadjuvant setting. We aimed to determine the effect of dual anti-HER2 blockade compared to monotherapy on clinically important results in women having this type of cancer.

Methods: We searched Medline, Embase, The Cochrane Library, and the list of references of relevant published articles. Results: We identified eight randomized clinical trials (2384 patients). When comparing paclitaxel plus dual treatment versus paclitaxel plus trastuzumab or lapatinib, dual treatment was associated with a higher probability of achieving a pathological complete response (OR 2.82, 95% CI 1.92 to 4.25). Addition of a taxane to an anthracycline plus cyclophosphamide and fluorouracil, plus lapatinib or trastuzumab, showed that the dual treatment was better than lapatinib alone (OR 2.47, 95% CI 1.41 to 4.34), or trastuzumab alone (OR 1.89, 95% CI 1.13 to 3.16). Dual treatment may result in an increase in survival outcomes and tumour clinical response, although such benefits were not consistent for all the combinations studied. Conclusions: The use of double blockade with combinations of trastuzumab and pertuzumab may be recommended for the neoadjuvant treatment of women with HER2-positive breast cancer. (PROSPERO Registration number: CRD42018110273)

Key words: breast cancer; neoadjuvant; human epidermal growth factor receptor; lapatinib; trastuzumab; pathologically complete response
INTRODUCTION

Breast cancer is the most common type of cancer in women worldwide, accounting for 16% of all female cancers. According to the World Health Organization, in 2015, 571,000 women died from breast cancer, being therefore among the five types of cancer leading to the highest number of deaths.\(^1\) Most deaths from this cause (69%) are registered in developing countries.\(^2\) It is predicted that its incidence will increase to 85 per 100,000 women by the year 2021.\(^3\) Between 2005 and 2015, breast cancer was also the main contributor to the disability-adjusted life years (DALYs)), with around 15 million DALYs.\(^4\)

During the last decades, four principal intrinsic molecular subtypes of breast cancer have been identified (Luminal A, Luminal B, HER2-positive or enriched, and basal-like). Specifically, the positive HER2 subtype is found in around 15 to 20% of all breast cancers.\(^5,6\) In tumours with overexpression of the HER2 gene, various antiHER2 biological agents have been used to improve survival in this group of patients.

Trastuzumab is a chimeric monoclonal antibody that recognizes the extracellular region of the HER2 protein, and has been shown to be effective in this type of cancer. It is used in metastatic disease, both as a first-line treatment and beyond and combined with other chemotherapeutic drugs; therefore, several clinical practice guidelines recommend its use in this cancer subtype.\(^7,8\)

However, drug resistance and post-treatment recurrences have been observed,\(^9\) probably due to obstacles that prevent the binding of trastuzumab to HER2, the decrease of HER2 in the signalling pathways, signalling through alternative routes, or failure to initiate an immunologically mediated mechanism of destruction of tumour cells.\(^10\) For this reason, other drugs have been added in recent years to the treatment of HER2-positive breast tumours, such as lapatinib, pertuzumab, TDM-1, and neratinib, dual inhibitors of epidermal growth factor receptors and HER2, available orally, which have been shown to be effective in reducing the proliferation of tumour cells. Due to its different
mechanisms of action, its use combined with trastuzumab could be useful to improve the effectiveness of both drugs separately, as well as the effectiveness of chemotherapy alone.\textsuperscript{11,12} Except lapatinib, which has been associated to asthenia and diarrhoea, antiHER2 therapies are in general well tolerated; however, all these pharmacological treatments have adverse effects that can be enhanced with the use of multiple medications, so it is important to evaluate whether the combined use leads to significant improvements in terms of both efficacy (survival) and acceptability (safety).\textsuperscript{13-16}

This systematic review aimed to determine the effect of dual anti-HER2 blockade compared to monotherapy on clinical results and acceptability in patients with HER2-positive breast tumours.
METHODS

Literature review

The review was elaborated according to the methodological guidance from Cochrane for the systematic reviews of the literature, and adhered the PRISMA statement for the report of its results.

Search strategy

We designed a search strategy in MEDLINE (accessed via PubMed) and The Cochrane Library (Appendix III). We also carried out a manual search of relevant reviews and studies, and contacted experts in the field to find out if they were aware of other unpublished or on-going studies. The last search was made on October 2020.

Inclusion criteria

We considered for inclusion randomized controlled trials comparing the impact of a dual anti-HER2 treatment to anti-HER2 monotherapy in women with HER2-positive breast cancer.

Outcomes

The primary outcomes were pathological complete response (pCR), clinical response, event-free survival, and overall survival. Secondary outcomes were breast-conserving surgery and adverse effects. We considered also economic analyses related with this topic.

Data extraction

Two review authors (JCV, IS) extracted in duplicate the data from the eligible studies, as well as the main characteristics of interest of the selected studies.
Assessment of the risk of bias and the quality of the evidence

The risk of bias of the clinical trials considered was evaluated using the Cochrane Risk of bias tool. Specifically, domains were evaluated for selection bias, detection bias and attrition bias. In presence of bias in any of these aspects, it was considered that the trial was exposed to a high risk of bias. In addition, we also assessed the performance bias and the report bias of the outcomes of interest. The information obtained from the evaluation of the risk of bias was incorporated to classify the quality of the evidence.

Data analysis and synthesis

We calculated the Odds Ratios (ORs) with the 95% confidence intervals from the data obtained from the included studies for each outcome of interest. We carried out meta-analyses when appropriate, and used the fixed or random effect models according to the presence or not of significant heterogeneity, measured with the $I^2$ statistic (heterogeneity was considered as significant when $I^2 > 50\%$). We calculated the estimates of effect and obtained the forest plots using the RevMan 5.3 software statistical package.

For each outcome of interest, we classified the quality of the evidence as high, moderate, low or very low according to the methodological guidelines of the GRADE system, which classifies grades of evidence as high certainty, moderate certainty; low certainty, and very low certainty.

We formulated the findings of the main outcome measure (pathological complete response) according clear statements, combining the certainty of evidence for each outcome and its effect size, as recommended by Santesso et al.
RESULTS

Search results

From the literature searches, we identified 19 systematic reviews looking at the treatment with anti-HER2 drugs. Of these, we excluded eight in a first analysis because they referred to adjuvant treatment, were narrative, were consensus reports, or did not provide relevant randomized clinical trials (RCTs).

From the 11 remaining reviews, we identified 14 potentially relevant RCTs common to many of them. After examining the full text articles, we decided to exclude six of them (see Fig.1 Flow diagram of studies search and selection). Seven additional studies not included in the reviews, reporting additional information from NeoSphere, NeoALTTO, CherLOB and NSABP B41 trials were eligible for inclusion, as well as Holmes 2013. In the 2020 update, we identified an additional study. (Figure 1) We also included three cost-effectiveness studies on the neoadjuvant treatment with pertuzumab.

In summary, we included eight randomized clinical trials and seven follow-up reports related to these, comparing dual anti-HER2 treatment with monotherapy and recruited a total of 2384 patients.

Four studies were conducted in USA, two in Italy, one in France, and one in Asia. All the studies used as neoadjuvant chemotherapy a taxane, either paclitaxel or docetaxel; four studies used an anthracycline (epirubicin in three, doxorubicin in one); four used cyclophosphamide, and three fluorouracil. (See Table 1. Characteristics of included studies)

The cost-effectiveness study was an analysis based on the NeoSphere and TRYPHAENA trials, which used a Markov model.

Study risk of bias
Overall, four studies were classified as low risk of bias,\textsuperscript{32,36,39,41} and in three the risk of bias was uncertain,\textsuperscript{31,37,40} mainly because they did not provide information on the method of allocation generation, the concealment of the randomization sequence or the blinding of participants, investigators and evaluators. Carey 2016\textsuperscript{38} was an open label trial where participants, investigators and outcome assessors were not blinded to the treatment assignment, so it was considered as high risk of bias.

Regarding other biases, seven of the eight studies included declared to have been supported by the industry. However, for four of them\textsuperscript{32,36,39,41} the risk of bias was deemed as low, since the pharmaceutical companies did not participate in either the trial design or the data analysis. Carey 2016\textsuperscript{38} was supported by a National Cancer Institute (NCI) grant, so it was considered as low risk of bias for this domain.

**Outcomes of interest**

**Pathological complete response**

The eight included trials considered the pCR as the main outcome. We performed meta-analyses by pooling Baselga 2012 and Carey 2016 studies, since they used the same comparator, paclitaxel, as chemotherapy; as well as for Bonnefoi 2015, Guarneri 2012 and Holmes 2013 studies, which used as neoadjuvant chemotherapy the combination of taxane, epirubicin, fluorouracil and cyclophosphamide. Another meta-analysis was done with the inclusion of data from Gianni 2012 and Shao 2019, since both used the same drugs (trastuzumab, pertuzumab, and docetaxel).

*Paclitaxel plus dual treatment (lapatinib plus trastuzumab) versus paclitaxel plus lapatinib or trastuzumab* (Figure 2)
The meta-analysis of the effect of paclitaxel plus dual treatment (lapatinib plus
trastuzumab) versus paclitaxel plus lapatinib included two studies,\textsuperscript{36,38} and
showed that dual treatment was associated with a higher probability of
achieving a pCR (OR 2.82, 95% CI 1.92 to 4.25, \( p < 0.001, I^2 = 0\% \), \( n = 491 \), two
trials) (Figure 2a). The quality of the evidence was deemed as low, as one of
the studies\textsuperscript{38} was an open label trial, with high risk of bias due to the lack of
blinding of participants, physicians and evaluators (Supplement SoF Table 1).

A similar result was found when comparing the effect of paclitaxel plus dual
treatment versus paclitaxel plus trastuzumab (OR 2.01, 95% CI 1.42 to 2.85, \( p
< 0.001, n = 539 \), two trials) (Figure 2b). The quality of the evidence was low,
because information on key aspects was scarce, and there was also moderate
heterogeneity (\( I^2 = 45\% \)) (Supplement SoF Table 2).

A follow-up report from the NeoALTTO trial\textsuperscript{28} found that cancers with high levels
of TMG2 (TRBV co-use metagen 2) had significantly better pCR than dual
treatment (68\% versus 21\%, \( p = 0.001 \)), as did in the subgroup of
immunologically deficient tumours (50\% versus 6\%, \( p = 0.009 \)).

\textit{Taxane added to an anthracycline plus cyclophosphamide and fluorouracil, plus
lapatinib or trastuzumab (Figure 3)}

Three studies\textsuperscript{31,37,40} assessed the use of a taxane added to an anthracycline
plus cyclophosphamide and fluorouracil, plus lapatinib or trastuzumab,
compared to lapatinib plus trastuzumab. The pooled analysis showed that the
dual treatment was better than lapatinib alone (OR 2.47, 95% CI 1.41 to 4.34, \( p
= 0.002, I^2 = 0\% \), \( n = 224 \), three trials) (Figure 3a). Compared with trastuzumab
alone, dual treatment was associated with a higher likelihood of achieving a
pCR (OR 1.89, 95% CI 1.13 to 3.16, \( p = 0.02, I^2 = 0\% \), \( n = 251 \), three trials)
(Figure 3b). In both cases, the quality of the evidence was deemed to be
moderate, because there was scarce information on key aspects such as
generation of the sequence, allocation concealment, blinding of participants,
physicians and evaluators (Supplement SoF Table 4 and 5).
A follow-up report of the CherLOB trial\textsuperscript{29} found that the presence of tumour infiltrating leukocytes significantly predicted pCR for patients in the chemotherapy + lapatinib group (OR 1.05, 95% CI 1.02 to 1.09, \( p = 0.005 \)), and for patients in the chemotherapy + trastuzumab + lapatinib group (OR 1.03, 95% CI 1.00 to 1.06, \( p = 0.04 \)), but not for those in the chemotherapy + trastuzumab group (OR 1.03, 95% CI 0.99 to 1.06, \( p = 0.13 \)). The same study found that, according to the intrinsic subtypes, without differentiating according to treatment arm, the HER2-positive subtype had a significantly higher pCR (HER2-positive: 11 (50%, \( p = 0.026 \)), basal-like: 3 (25%); Luminal B: 3 (21.4%); Luminal A: 2 (9.5%)).

In the study Robidoux 2013,\textsuperscript{41} a taxane, an anthracycline and cyclophosphamide were also used as chemotherapy, but not fluorouracil. When pooling this study with the previous three, the favourable effect of the dual treatment on the achievement of pCR was sustained, compared to the addition of lapatinib alone (OR 1.75, 95% CI 1.25 to 2.47, \( p = 0.001, \ l^2 = 7\%; \ n = 566, \) four trials). When the addition of trastuzumab alone was compared with the dual treatment, statistical significance was reached in favour of dual treatment (OR 1.63, 95% CI 1.17 to 2.26, \( p = 0.004, \ l^2 = 0\%; \ n = 599, \) four trials). Again, in both cases the quality of the evidence was deemed as moderate, because there was scarce information on key aspects such as the generation of the sequence, the concealment of the assignment, the blinding of the participants, the doctors and the evaluators.

A follow-up report of this trial\textsuperscript{30} found that pCR rate among patients with HER2 subtype was statistically significantly greater, compared to other subtypes combined (60.9% versus 25.7%, 95% CI 16.4 to 36.0%; \( p < 0.001 \)).

\textit{Docetaxel plus pertuzumab or trastuzumab}

The meta-analysis including two studies\textsuperscript{32,39} found that, when comparing trastuzumab to the combined therapy, the OR favoured dual treatment with
respect to the achievement of the pCR (OR 2.20, 95% CI 1.50 to 3.24, p < 0.0001, n = 543, two trials; I² = 0%). The quality of the evidence was deemed as high.

A similar finding was seen when comparing pertuzumab alone to the combined therapy, although in this case, only one trial provided data for the comparison (OR 2.68, 95% CI 1.478 to 4.90, p = 0.001, n = 203).

A follow-up report from the NeoSphere trial found that high expression of HER2 was associated with a significantly higher pCR in the pertuzumab + trastuzumab + docetaxel group (p = 0.0002). The same report found that low serum TGFα was associated with a significantly higher pCR in the pertuzumab + trastuzumab group (p = 0.045).

**Event-free survival**

*Paclitaxel plus dual therapy (lapatinib plus trastuzumab) versus paclitaxel plus lapatinib*

A follow-up report from the NeoALTTO trial found that 6 years event-free survival was 67% in the lapatinib and trastuzumab groups, and 74% in the lapatinib + trastuzumab group. The EFS in dual therapy group was not statistically different compared with that in monotherapy (HR 0.81, 95% CI 0.52 to 1.26, p = 0.35).

*Docetaxel plus pertuzumab or trastuzumab*

A follow-up report from the NeoSphere trial found that 5 years event-free survival was 81% for the trastuzumab + docetaxel group; 84% for the pertuzumab + trastuzumab + docetaxel group; 80% for the pertuzumab + trastuzumab group; and 75% for the pertuzumab + docetaxel group.
Progression free survival 5 years after treatment was higher in pertuzumab + trastuzumab + docetaxel group than in trastuzumab + docetaxel group (HR 0.69, 95% CI 0.34 to 1.40), lower in pertuzumab + trastuzumab group than in trastuzumab + docetaxel group (HR 1.25, 95% IC 0.68 to 2.30), and lower in pertuzumab + docetaxel group than in pertuzumab + trastuzumab + docetaxel group (HR 2.05, 95% CI 1.07 to 3.93) (p values not provided).

Overall survival

Paclitaxel plus dual treatment (lapatinib plus trastuzumab) versus paclitaxel plus lapatinib

A follow-up report from the NeoALTTO trial\textsuperscript{27} found that 6 years overall survival was 82% in the lapatinib group, 79% in the trastuzumab group, and 85% in the lapatinib + trastuzumab group. The report found no significant differences between patients treated with combination therapy and those treated with trastuzumab alone (HR 0.72, 95% CI 0.41 to 1.27, p = 0.26).

Docetaxel plus pertuzumab or trastuzumab

A follow-up report from the NeoSphere trial\textsuperscript{24} found that 5 years overall survival was 81% in the trastuzumab + docetaxel group; 86% in the pertuzumab + trastuzumab + docetaxel group; 73% in the pertuzumab + trastuzumab group; and 73% in the pertuzumab + docetaxel group. The differences were significant in favour of the pertuzumab + trastuzumab + docetaxel group versus pertuzumab + docetaxel (HR 2.05, 95% CI 1.07 to 3.93) (p values not provided).

Tumour clinical response

Four trials analysed this outcome. We present the findings in a narrative manner because each study examined a different treatment regimen.
Paclitaxel plus dual treatment (lapatinib plus trastuzumab) versus paclitaxel plus lapatinib

Baselga 2012 compared paclitaxel plus dual treatment versus lapatinib or trastuzumab alone, and found that dual treatment was associated with a higher frequency of clinical tumour response when compared to lapatinib alone (OR 1.84, 95% CI 1.16 to 2.92, p = 0.01, n = 306, one trial). The quality of the evidence for this outcome was high. When compared to trastuzumab alone, a similar result was obtained (OR 4.71, 95% CI 2.90 to 7.67, n = 301). The quality of the evidence was moderate due to imprecision, based on the wide 95% confidence interval.

Paclitaxel, doxorubicin and cyclophosphamide plus dual treatment against lapatinib or trastuzumab alone

Robidoux 2013 compared chemotherapy with paclitaxel, doxorubicin and cyclophosphamide plus dual treatment versus lapatinib or trastuzumab alone. No differences were found regarding clinical tumour response between dual treatment and lapatinib alone (OR 1.43, 95% CI 0.87 to 2.33, p = 0.01, n = 327, one trial). When compared with trastuzumab alone, a similar result was obtained (OR 0.73, 95% CI 0.42 to 1.24, n = 331, one trial). The quality of the evidence in both cases was high.

Docetaxel plus pertuzumab or trastuzumab

Gianni 2012 compared docetaxel with pertuzumab or trastuzumab alone. Authors found that dual treatment was associated with a higher clinical tumour response when compared to pertuzumab alone (OR 2.97, 95% CI 1.39 to 6.31, p = 0.01, n = 192, one trial). The quality of the evidence for this result was moderate due to imprecision, based on a wide 95% confidence interval. However, no difference was found between dual treatment and trastuzumab alone (OR 1.88, 95% CI 0.86 to 4.08, n = 200, one trial). The quality of the evidence for this outcome was high.
Taxane added to an anthracycline plus cyclophosphamide and fluorouracil, plus lapatinib or trastuzumab

Bonnefoi 2015\textsuperscript{37} analysed the neoadjuvant chemotherapy comparison plus dual treatment versus the administration of trastuzumab alone, and found no differences between the groups (OR 0.47, 95% CI 0.11 to 2.10, p = 0.32, n = 90, one trial). The quality of the evidence was moderate due to the scarce information provided on key aspects such as generation of the sequence, allocation masking, blinding of participants, physicians and evaluators.

**Breast-conserving surgery**

Taxane added to an anthracycline plus cyclophosphamide and fluorouracil, plus lapatinib or trastuzumab

Two studies\textsuperscript{37,40} evaluated the use of a taxane added to an anthracycline, cyclophosphamide and fluorouracil, plus lapatinib or trastuzumab, regarding breast-conserving surgery. The pooled analysis showed no differences between the dual treatment and the administration of lapatinib alone (OR 1.13, 95% CI 0.58 to 2.21, p = 0.72, \( I^2 = 21\% \), n = 157, two trials) (Figure 4a). No differences were also found between dual treatment and trastuzumab (OR 1.25, 95% CI 0.69 to 2.26, p = 0.47, \( I^2 = 0\% \), n = 185, two trials) (Figure 4b). Quality of the evidence was moderate in both cases, due to the scarce information provided on key aspects such as the generation of the sequence and the masking of the allocation, as well as the blinding of the participants, the doctors and the evaluators.

**Adverse effects**

Consistently, all the included studies found an increase in the frequency of adverse events grade 1-2 and 3-4 in the groups of patients receiving lapatinib, compared with those who received trastuzumab. The most frequent adverse
events were diarrhoea, neutropenia, skin disorders (rash) and elevation of liver enzymes.

Gianni 2012,39 which compared docetaxel plus dual treatment with pertuzumab or trastuzumab as monotherapy, found that adverse events were more frequent in the groups in which paclitaxel was administered, mainly neutropenia, febrile neutropenia and leukopenia. Overall, cardiac events were not frequent and no differences were found between groups. A follow-up report of this trial24 described the frequency of neutropenia Grade 3 or higher in the four treatment arms (trastuzumab + docetaxel: 71/107 (66%), pertuzumab + trastuzumab + docetaxel: 59/107 (55%), pertuzumab + trastuzumab 40/108 (37%), pertuzumab + docetaxel: 60/94 (64%)). In this report, the frequency of febrile neutropenia and leukopenia was low.

Shao 201732 also found a similar occurrence of serious adverse events in both groups (pertuzumab + trastuzumab + docetaxel: 22/218 (10.1%) versus trastuzumab + docetaxel 9 of 110 (8.2%)). However, diarrhoea, mostly grade 1-2, was more frequent in the group receiving dual therapy (84/218 (38.5%) versus 18/110 (16.4%)).

A follow-up report from the NeoALTTO trial26 found that toxicity was similar between the lapatinib and lapatinib + trastuzumab groups. Authors found differences in age, having younger patients more episodes of rash in both groups (p < 0.05). No differences were reported regarding diarrhoea and liver-related adverse events.

**Economic analyses**

We found three published studies analysing the economic issues related to the administration of pertuzumab as neoadjuvant therapy for women with HER2-positive early breast cancer.33-35
In a cost-effectiveness analysis based on the NeoSphere and TRYPHAENA trials, Attard 2015\textsuperscript{33} concluded that the addition of pertuzumab resulted in an increase in 0.33 life-years and 0.31 quality-adjusted life years (QALYs). The incremental cost per QALY ranged from $25,388 (CAD; NeoSphere) to $46,196 (CAD; TRYPHAENA). Sensitivity analyses provided additional support for the use of pertuzumab, with cost-effectiveness ratios ranging from $9230 to $64,421.

A study conducted in Spain\textsuperscript{34} estimated the advantages of adding pertuzumab to neoadjuvant therapy when used in women with HER2-positive breast cancer, in terms of avoiding costs linked to metastatic and loco-regional events. The estimation was based on progression free survival at year 5. Authors concluded that the average cost calculated for a loco-regional event was €24,000 and €153,000 for a metastatic breast cancer event. For a cohort of 100 patients, the accumulated cost-offsets for avoided events were estimated to be €636,000.

Squires et al.\textsuperscript{35} published a technology appraisal about the clinical and cost-effectiveness of pertuzumab for the treatment of women with high-risk, early-stage, HER2-positive breast cancer, when used alongside trastuzumab and docetaxel, and compared to such drugs used alone. The analysis showed a probabilistic incremental cost-effectiveness ratio of £21,869 per quality-adjusted life-year gained for pertuzumab alongside trastuzumab and docetaxel. Based on these data, National Institute for Health and Care Excellence Appraisal Committee recommended pertuzumab in this group of patients.
This systematic review and meta-analysis examines the efficacy and safety of the use of dual therapy with two anti-HER-2 drugs (pertuzumab+trastuzumab, or trastuzumab+lapatinib), compared to monotherapy with one of these agents, in patients with non-metastatic breast HER2-positive cancer receiving neoadjuvant chemotherapy. Overall, we found that dual treatment added to neoadjuvant chemotherapy is likely to be associated to better results with respect to the pathological complete response and the clinical tumour response than monotherapy.

The primary outcome of the review was the pathological complete response and, in general, the definitions of the included studies were quite homogeneous (absence or disappearance of invasive tumour cells in the primary tumour). Regarding this outcome, results were consistent and found a superiority of dual treatment respect to monotherapy. These findings agree with other previous reviews,\(^2\),\(^4\) which also found significant improvements in the pCR with the use of dual treatment. It was also similar for other outcomes studied, such as clinical tumour response and breast-conserving surgery. However, it is important to note that the combination with chemotherapy in the NeoSphere trial (docetaxel),\(^2\) administered after surgery, is different from that routinely used (sequential combination of anthracyclines and taxanes, or the TCH combination, as in the KRISTINE trial).\(^4\) The pCR rates in the TRYPHAENA study,\(^4\) in which a sequential regimen of anthracyclines and taxanes was administered instead of docetaxel, were higher than in the NeoSphere study. Another systematic review\(^6\) showed that, despite the higher number of pCR, double blockade using lapatinib did not offer a better result than trastuzumab alone regarding overall survival and had more toxicity.

Respect to important outcomes such as event-free survival and global survival, there was also a trend towards better results with dual treatment, but it was possible to include only few studies and events in each comparison, so the confidence in these results is low.
Other systematic reviews have addressed this topic and have found similar results. Hicks 2015 included five studies, all of them included here, and concluded that patients with early stage HER2-positive breast cancer are more likely to achieve a pCR when lapatinib is added to chemotherapy with trastuzumab. Also in agreement with the findings of the current review, authors pointed out that the increase in toxicity should be balanced with this possible general benefits.

A more recent review by Chen et al. examined studies not included in this review because they did not have a dual treatment arm, or administered trastuzumab in all treatment arms. Our review focused on studies in which the difference between the treatment arms was based specifically on the administration of dual treatment with both anti-HER2 drugs, compared to monotherapy with one of them, so that the different chemotherapy modalities used in clinical trials were analysed separately, as they could influence the effectiveness of treatment with anti-HER2 drugs. Despite these differences in the included studies, Chen and colleagues also concluded that the combination of trastuzumab and lapatinib was superior to the treatment with a single agent with respect to pCR, not detecting differences regarding the improvement in the rate of breast-conserving surgery, and highlighted the concerns about the increasing toxicity with the combination.

Our review also found that disease-free survival and progression-free survival were better in patients receiving combination therapy with lapatinib and pertuzumab, as well as in the groups receiving pertuzumab plus trastuzumab plus docetaxel. These findings are in line with a network meta-analysis, which recommends the combination of chemotherapy plus trastuzumab and pertuzumab as the best option for the treatment of women with early-stage HER2 positive breast cancer. In addition, a more recent network meta-analysis also found that the combination of chemotherapy, trastuzumab and pertuzumab ranked first for the chance of achieving pCR, while chemotherapy, trastuzumab and lapatinib ranked second for the same outcome measure.
Strengths

This systematic review was carried out following the Cochrane guidelines for Systematic Review of Interventions, and we included only randomized clinical trials, which are the studies considered as the gold standard to draw valid conclusions about the comparative effectiveness of two interventions. The bibliographic search was structured and extensive, and complemented with manual search in relevant articles and reviews. Several recognized experts in the field were consulted for potential relevant studies. Therefore, we do not consider that any relevant study has been missed.

Key steps like trial selection, data extraction and risk of bias assessment were performed independently by two authors with experience in systematic review methodology, and the interpretation of the data and the conclusions were discussed and agreed with a panel of experts with extensive clinical and research experience.

Limitations

Only for the main outcome (pathological complete response) it was possible to include a maximum of four trials and a relatively large number of patients. For the remaining meta-analyses, only as much as two trials were included and in some comparisons only one study provided data. This fact, along with the insufficient information on key issues such as the generation of the randomization sequence and allocation concealment and blinding, led to decrease the quality of the evidence from high to moderate in some comparisons. In addition, there were doubts regarding the risk of other biases, such as the funding by the industry of some of the clinical trials. Although a clear association between the results of the trials and the source of funding has not been found, it is more likely for such studies to report statistical conclusions favouring new with respect to conventional treatments.\(^{52}\)
Despite the updated and exhaustive search strategy, the small number of papers identified did not allow additional analyses of the risk of bias (for example, using the Egger test)\(^5^3\).

Another issue to point out is the lack of information on important outcomes for patients, such as satisfaction with treatment and preferences. Therefore, the therapeutic decisions in this case should be taken along with patients, after providing them the available information on possible adverse events such as diarrhoea, neutropenia, rash and alteration of liver enzymes, which in this review showed to be more frequently associated to the use of lapatinib. There was also not enough information on the economic aspects that may also be important when making therapeutic decisions.

There are some considerations about the use of surrogate endpoints in cancer studies, which has been an increasing practice in the last decades\(^5^4,\!^5^5\). Cancer drugs approved on the basis of surrogate measures may have a shorter development duration compared with drugs approved on the basis of overall survival, being a key criterion the assumption that the effect of the intervention on the surrogate endpoint also results in meaningful changes for the clinical endpoint\(^5^5,\!^5^6\). In fact, important regulatory agencies recognise that alternative endpoints can be useful in specific disease settings\(^5^7\).

However, these advantages may be surpassed by several disadvantages\(^5^5,\!^5^6\). The magnitude of benefit associated with the drugs might be overestimated due to the extrapolation of the results, despite the fact that the strength of the correlation between surrogate and clinical outcomes in cancer trials is unclear\(^5^8\).

For example, complete response has the advantages that can be assessed in single-arm studies, and assessed earlier and in smaller studies, compared to overall survival. However, it is neither a direct measure of clinical benefit, nor a comprehensive measure of drug activity\(^5^6\).
Therefore, evidence of overall survival benefit should never emerge for cancer drugs approved on the basis of surrogate measures alone.\textsuperscript{55}

Priorities for future research

There is a need to know the impact of double blockade in women at higher risk (with negative hormonal receptors, or lymph node involvement). It is also suggested that future studies collect and provide information on other important clinical aspects such as survival and acceptability, and that they be conducted following rigorous methodological standards, including an adequate statistical power.

Based on the results of the present systematic review and meta-analyses, we conclude that the use of double blockade with combinations of trastuzumab and pertuzumab likely benefits patients meeting the conditions of the included clinical trials, with HER2-positive breast cancer, and is suitable for neoadjuvant treatment. This conclusion is based on the increase in the rates of complete pathological response with respect to monotherapy with trastuzumab. However, its effect on conservative breast surgery rates is not so clear.

There was also a trend towards an improvement in event-free survival and global survival, although it was possible to include only data from few studies in each of these comparisons. The occurrence of adverse events, more frequent in the groups receiving lapatinib, is a cause for concern, since safety issues may influence the selection and compliance with treatment and should be part of the therapeutic decisions to be made by the doctor and the patient.

Supplementary information is available at the British Journal of Cancer’s website.
REFERENCES


22. www.guidelinedevelopment.org/handbook (Last access March 4, 2020)


in Asia: The PEONY Phase 3 Randomized Clinical Trial. JAMA Oncol Oct 24; 6(3), e193692 (2019).


38. Carey LA, Berry DA, Cirrincione CT, Barry WT, Pitcher BN, Harris LN, et al. Molecular Heterogeneity and Response to Neoadjuvant Human


55. Naci H, Davis C, Savović J, Higgins JPT, Sterne JAC, Gyawali B, Romo-Sandoval X, Handley N, Booth CM. Design characteristics, risk of bias, and reporting of randomised controlled trials supporting approvals of


<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Country</th>
<th>Participants</th>
<th>Chemotherapy</th>
<th>Outcomes</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baselga 2012</td>
<td>Randomized, multicentre, open, Phase III clinical trial (NeoALTTO)</td>
<td>United States</td>
<td>455 patients. Lapatinib: n = 154 Trastuzumab: n = 149 Lapatinib + trastuzumab: n = 152</td>
<td>Paclitaxel</td>
<td>Primary: pCR Secondary: loco-regional pCR, tumour response, negative node disease at the time of surgery, breast-conserving surgery, conversion to breast-conserving surgery, safety and tolerability; global and disease-free survival, molecular characteristics of tumours, expression of biomarkers</td>
<td>Low</td>
</tr>
<tr>
<td>Carey 2016</td>
<td>Randomized clinical trial (CALGB 40601)</td>
<td>United States</td>
<td>305 patients. Lapatinib: n = 67 Trastuzumab: n = 120 Lapatinib + trastuzumab: n = 118</td>
<td>Paclitaxel</td>
<td>Primary: pCR Secondary: toxicity</td>
<td>High</td>
</tr>
<tr>
<td>Gianni 2012</td>
<td>Randomized, multicentre, international, open, Phase II clinical trial (NeoSphere)</td>
<td>Italy, United States, United Kingdom, Thailand</td>
<td>417 patients. Trastuzumab + docetaxel: n = 107 Pertuzumab + trastuzumab + docetaxel: n = 107 Pertuzumab + trastuzumab: n = 107 Pertuzumab + docetaxel: n = 96</td>
<td>Docetaxel</td>
<td>Primary: pCR Secondary: clinical response, time to clinical response, breast-conserving surgery, safety</td>
<td>Low</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Country</td>
<td>Participants</td>
<td>Chemotherapy</td>
<td>Outcomes</td>
<td>Risk of bias</td>
</tr>
<tr>
<td>------------</td>
<td>------------------------------------------------------------------------</td>
<td>---------------</td>
<td>---------------------------------------</td>
<td>---------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Guarneri 2012</td>
<td>Randomized, multicentre, non-comparative, Phase IIb, clinical trial (CherLOB)</td>
<td>Italy</td>
<td>121 patients. Lapatinib: n = 39 Trastuzumab: n = 36 Lapatinib + trastuzumab: n = 46</td>
<td>Paclitaxel, 5-fluorouracil, epirubicine, cyclophosphamide</td>
<td>Primary: pCR Secondary: objective clinical response, breast-conserving surgery, safety, time to treatment failure from the start of primary treatment, inhibition of biomarkers, correlation between gene expression at diagnosis and pathological response</td>
<td>Unclear</td>
</tr>
<tr>
<td>Holmes 2013</td>
<td>Randomized open, Phase II clinical trial</td>
<td>United States</td>
<td>100 patients. Lapatinib: n = 34 Trastuzumab: n = 33 Lapatinib + trastuzumab: n = 33</td>
<td>Paclitaxel, 5-fluorouracil, epirubicine, cyclophosphamide</td>
<td>Of interest to the review: pCR</td>
<td>Unclear</td>
</tr>
<tr>
<td>Robidoux 2013</td>
<td>Randomized, open, Phase III clinical trial (NSABP B41)</td>
<td>United States</td>
<td>529 patients. Lapatinib: n = 174 Trastuzumab: n = 181 Lapatinib + trastuzumab: n = 174</td>
<td>Paclitaxel, doxorubicine, cyclophosphamide</td>
<td>Primary: pCR Secondary: pCR in the breast and the lymph nodes, complete clinical response, serious cardiac events, non-cardiac toxicity</td>
<td>Low</td>
</tr>
<tr>
<td>Shao 2019</td>
<td>Randomized, multicenter, double-blind, placebo-controlled Phase 3 trial</td>
<td>China, Korea, Taiwan, Thailand</td>
<td>329 patients. Pertuzumab + trastuzumab + docetaxel: n = 219 Placebo + trastuzumab + docetaxel: n = 110</td>
<td>Docetaxel</td>
<td>Primary: pCR Secondary: Objective response rates, clinical complete response rates, adverse events</td>
<td>Low</td>
</tr>
</tbody>
</table>

pCR: Pathological complete response
Figures

Fig. 1 Flow diagram of studies search and selection

2280 records identified

2261 excluded (no RCTs, comments or letters, study protocols, no relevant for the review, no report outcomes of interest, other reasons)

19 systematic reviews

8 excluded (adjuvant treatment, narrative, did not provide relevant RCTs)

11 systematic reviews

13 RCTs assessed for eligibility

6 excluded (no useful data, did not include a dual therapy group, administered dual therapy in both treatment arms)

7 RCTs included (7 updates)

1 RCT (last update)

8 RCTs (15 publications)
Forest plots

Figure. 2 Forest plot. Comparison paclitaxel + dual treatment versus paclitaxel + lapatinib or trastuzumab. Pathological complete response

Figure 2a. Paclitaxel + dual treatment versus paclitaxel + lapatinib

Figure 2b. Paclitaxel + dual treatment versus paclitaxel + trastuzumab

Figure. 3 Forest plot. Comparison taxane + CEF + dual treatment versus taxane + CEF + lapatinib or trastuzumab. Pathological complete response

Figure 3a. Taxane + CEF + dual treatment versus taxane + CEF + lapatinib

Figure 3b. Taxane + CEF + dual treatment versus taxane + CEF + trastuzumab
Figure. 4 Forest plot. Comparison taxane + CEF + dual treatment versus taxane + CEF + lapatinib or trastuzumab. Breast conserving surgery

Figure. 4a. Taxane + CEF + dual treatment versus taxane + CEF + lapatinib

Figure. 4b. Taxane + CEF + dual treatment versus taxane + CEF + trastuzumab