



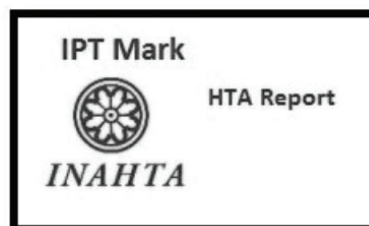
TARGETED THERAPIES IN COMBINATION WITH NEOADJUVANT CHEMOTHERAPY FOR HER2-POSITIVE BREAST CANCER AND ECONOMIC EVALUATION

MaHTAS Malaysian Health
Technology Assessment
Section

Medical Development Division
Ministry of Health Malaysia

HEALTH TECHNOLOGY ASSESSMENT REPORT

**TARGETED THERAPIES
IN COMBINATION
WITH NEOADJUVANT
CHEMOTHERAPY FOR
HER2-POSITIVE BREAST
CANCER AND ECONOMIC
EVALUATION**



Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

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- Technical Advisory Committee for Health Technology Assessment
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EXECUTIVE SUMMARY

Background

Breast cancer is the most prevalent type of malignancy in females. It is a heterogeneous disease which can be divided into several subtypes. Based on severity, breast cancer is broadly categorised into three groups which are early breast cancer (EBC), locally advanced breast cancer (LABC) and metastatic breast cancer (MBC). Human epidermal growth factor receptor 2 (HER2) is a growth-promoting protein on the outside of all breast cells. About 15 to 20% women with breast cancer have overexpression of HER2 and called as HER2-positive. HER2-positive is an aggressive subtype that exhibits unique epidemiological, clinical and prognostic differences with poor response to standard chemotherapy regimens compared with HER2-negative. The treatment of breast cancer generally depends on the stage of disease and characteristics of the tumour which involves surgery, chemotherapy, radiotherapy and hormonal therapy. Neoadjuvant therapy in breast cancer refers to the administration of treatment with the intent of down staging the tumour and improves operability and surgical outcomes. The current practices in Malaysia for management of EBC include neoadjuvant chemotherapy only while management of LABC include neoadjuvant chemotherapy and anti-HER2 therapy for operable and inoperable conditions. In Ministry of Health Medicines Formulary (MHMF) Malaysia, trastuzumab injection was approved in adjuvant setting only for patients with HER2-positive, over-expressed by FISH (Fluorescence in situ hybridization) and high risk group (>30% lifetime risk but no known genetic variant). Both drugs (pertuzumab and lapatinib) are registered under National Pharmaceutical Regulatory Agency (NPRA) but not included in the MHMF. Pertuzumab injection is indicated for neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either >2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer and indicated in combination with trastuzumab and docetaxel for patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for metastatic breast cancer. While, lapatinib is indicated in combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumours overexpressed HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab or in combination with letrozole for the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer. As these agents may play an important role in neoadjuvant therapy setting, their effectiveness and economic implications need to be assessed. This HTA was requested by a Clinical Oncologist from Hospital Kuala Lumpur (HKL).



Technical features

Targeted drugs are designed to precisely identify and block the growth and spread of specific cancer cells which are different from chemotherapy drugs that attack all growing cells including cancer cells. Four types of targeted therapies used for treatment of HER2-positive breast cancer are monoclonal antibodies, small molecule tyrosine kinase inhibitors, antibody-drugs conjugates and other emerging anti-HER2.

a) Monoclonal antibodies

Monoclonal antibodies are immune system proteins (antibodies) that are designed to attach to the HER2 protein on cancer cells, which can help stop the cells from growing. Monoclonal antibodies approved by United States Food and Drug Administration (US FDA) for breast cancer include trastuzumab, pertuzumab and bevacizumab. Trastuzumab (Herceptin®) was the first monoclonal antibody drugs against the extracellular domain of HER2 approved by FDA which is well-tolerated in patients with little toxicity followed by pertuzumab (Perjeta®). Trastuzumab biosimilars that have been approved by FDA were Hertraz, Zuhera, Herzuma, Kanjinti, Ogivri, Ontruzant and Trazimera. Even though previous studies have proved the tolerable therapeutic efficacy of trastuzumab, some HER2-positive breast cancer patients showed intrinsic or acquired resistance to it. Hence, research on developing anti-HER2 agents is still on-going. Later, the combination of pertuzumab with trastuzumab and docetaxel was approved by US FDA on September 2013 as neoadjuvant treatment of patients with HER2-positive for early-stage breast cancer, locally advanced or inflammatory.

b) Tyrosine Kinase Inhibitors

Tyrosine kinase inhibitor (TKI) is a group of drugs which interrupts the HER2 and epidermal growth factor receptor (EGFR) pathways by disrupting the signal transduction pathways of protein kinases through several modes of inhibition. Kinase inhibitors are either irreversible or reversible. The irreversible kinase inhibitors tend to covalently bind and block the ATP site resulting in irreversible inhibition. The reversible kinase inhibitors can further subdivide into four major subtypes based on the confirmation of the binding pocket. Tyrosine kinase enzymes (TKs) can be categorised into receptor tyrosine kinases (RTKs), non-receptor tyrosine kinases (NRTKs), and a small group of dual-specificity kinases (DSK) which are phosphorylate serine, threonine, and tyrosine residues. Lapatinib (Tykerb®) is the second US FDA approved HER2 targeted drug after trastuzumab. In addition, FDA approved TKIs for breast cancer also include afatinib, neratinib and tucatinib (which targets HER1 and HER2), have substantial efficacy in the treatment of HER2-positive breast cancer.

c) Antibody drugs conjugates (ADCs)

Trastuzumab–emtansine (T-DM1) is a HER2-targeted antibody-drug conjugate which contains the humanised anti-HER2 IgG1, trastuzumab, covalently linked to the microtubule inhibitory drug DM1 (a maytansine derivative) via the stable thioether linker 4-[N-maleimidomethyl] cyclohexane-1-carboxylate (MCC). Emtansine refers to the MCC-DM1 complex. An average of 3.5 DM1 molecules is



conjugated to each molecule of trastuzumab. Conjugation of DM1 to trastuzumab confers selectivity of the cytotoxic agent for HER2-overexpressing tumour cells, thereby increasing intracellular delivery of DM1 directly to malignant cells. Upon binding to HER2, trastuzumab-emtansine undergoes receptor-mediated internalisation and subsequent lysosomal degradation, resulting in release of DM1-containing cytotoxic catabolites (primarily lysine-MCC-DM1).

Policy question

Should targeted therapies i.e. trastuzumab (tzmb), pertuzumab (pzmb) and lapatinib (lpnb) in combination with chemotherapy be used as a neoadjuvant treatment for HER2-positive early and locally advanced breast cancer in Ministry of Health facilities?

Objective

To conduct a systematic review:

- I. To assess the effectiveness and safety of trastuzumab, pertuzumab, lapatinib in combination with chemotherapy in neoadjuvant setting for patient with HER-positive breast cancer.
- II. To determine whether to use one or dual targeted therapies in combination with chemotherapy in neoadjuvant setting for HER2-positive breast cancer.
- III. To evaluate the cost-effectiveness of trastuzumab, pertuzumab, lapatinib in combination with chemotherapy for HER2-positive breast cancer in neoadjuvant setting.
- IV. To assess the organisational or societal implication related to the use of trastuzumab, pertuzumab, lapatinib in neoadjuvant setting for HER2 positive breast cancer.

Methods

Part A: Systematic Review of Literature

Electronic databases were searched through the Ovid interface: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R)-1946 to March 26, 2021. Google Scholar was used to search for additional web-based materials and information. Additional articles were identified from reviewing the references of retrieved articles. Last search was conducted on 5th of August 2021. Three reviewers (AS, MAR and AA) independently screened the titles and



abstracts against the inclusion and exclusion criteria. The risk of bias or quality assessment (methodology quality) of all retrieved literatures were assessed by three reviewers depending on the type of the study design; using the relevant checklist of National Collaborating Centre for Methods and Tools (ROBIS) for Systematic Review, Cochrane assessing of bias tools (RoB 2) for Randomised Controlled Trials and Critical Appraisal Skill Programme (CASP) checklist for cohort and economic studies. Data on the effectiveness, safety and outcomes of using targeted therapies were presented in tabulated format with narrative summaries. Meta-analysis using RevMan 5.0 was conducted for this Health Technology Assessment for selected outcomes namely pathological complete response (pCR) rate and safety data. The data was pooled when heterogeneity, I^2 was less than 75%. Risk ratio (RR), Odds ratio (OR) were calculated using fixed-effect model with 95% Confidence Interval (CI). Statistical significance was set at $p < 0.05$ for all outcomes.

Results

A total of 1031 records were identified through Ovid interface and other sources (references of retrieved articles). After applying inclusion and exclusion criteria, 19 studies were included in this review: two systematic review (SR) and network meta-analysis (NMA), nine randomised controlled trials (RCTs), three cohort studies, one cross-sectional study and four economic analyses.

Combination of pertuzumab and trastuzumab plus chemotherapy (with or without anthracyclines) improved pCR compared with single-targeted therapy followed by combination of lapatinib plus trastuzumab plus chemotherapy (with or without anthracyclines). In addition, for both types of interventions (addition of pertuzumab or lapatinib), combination chemotherapy (with or without anthracyclines) was superior than mono chemotherapy. From indirect meta-analysis, there was no difference in pCR between the two groups with and without anthracyclines. However, according to the SUCRA rank, the group without anthracyclines had the highest rank for pCR for both addition of pertuzumab or lapatinib. The use of trastuzumab biosimilar plus chemotherapy (with or without anthracyclines) was as effective as the combination of pertuzumab plus trastuzumab plus docetaxel. There was a good level of retrievable evidence that showed the rates of PFS, DFS, EFS and OS were higher in dual-targeted therapy (for addition of pertuzumab or lapatinib) than single-targeted therapy.

In terms of safety, grade 3 to 5 treatment-related side effects were significantly higher in patients who received pertuzumab (neutropaenia), lapatinib (diarrhoea and skin disorders) and chemotherapy with commonly reported side effects of diarrhoea and skin disorders. For incidence of cardiac events, there was no significant difference observed in all treatment arms. Trastuzumab biosimilar had comparable side-effects to trastuzumab.

Based on two cost-effectiveness analyses studies, mono chemotherapy (pertuzumab plus trastuzumab plus taxol) was more effective with the highest health benefits (10.73 QALYs) and less costly (US \$ 415 833) compared to combination chemotherapy (taxol plus carboplatin plus pertuzumab plus



trastuzumab or taxol plus pertuzumab plus trastuzumab plus anthracyclines). However, de-escalated strategies found that combination of trastuzumab plus taxol became the most cost-effective option in both HR-positive and HR-negative patients. One cost minimisation analysis showed SC trastuzumab resulted in savings of MYR 7561 every patient to the MOH and MYR 7820 every patient to the society in comparison with IV trastuzumab.

Part B: Economic Evaluation

Objective

The general objective of this economic evaluation was to assess the cost-effectiveness of additional targeted therapy in the neoadjuvant treatment of high risk early HER2-positive breast cancer patients.

The specific objective was to calculate the incremental cost-effectiveness ratio (ICER) between single and dual targeted therapy (Trastuzumab and Pertuzumab/ Trastuzumab respectively) with standard neoadjuvant chemotherapy for early HER2-positive breast cancer patients with high risk of recurrence.

Methods

A hybrid model (Decision tree and Markov cohort simulation) was developed using Microsoft 365 Excel Workbook® to estimate the lifetime costs and quality adjusted life years (QALYs) of using targeted agents in combination with neoadjuvant chemotherapy in early HER2+ breast cancer. This type of model was chosen for its ability to extrapolate efficacy data from short-term clinical trials in early HER2+ breast cancer to longer term cost-effectiveness results.

Based on the systematic review and meta-analysis conducted in this HTA report earlier, the most efficacious with no substantial differences in tolerability was the trastuzumab (biosimilar) plus pertuzumab based dual targeted therapy with combination chemotherapy. Taking the current practice and availability of drugs available in MOHMF, the single targeted therapy assessed was the trastuzumab biosimilar and chemotherapy; whereas the dual targeted therapy assessed was the pertuzumab-trastuzumab combination. A hypothetical cohort of high-risk stage II/ III HER2-positive breast cancer patients were simulated in three strategies:-

- i) Standard six cycles of neoadjuvant chemotherapy
- ii) Addition of single targeted therapy with chemotherapy given concurrently 3-weekly intravenously - Trastuzumab biosimilar
- iii) Addition of dual targeted therapy with chemotherapy given concurrently 3-weekly intravenously- Pertuzumab/ Trastuzumab



Model Structure

The model structure was constructed with reference to other published studies and in consultation with an expert committee consisting of multidisciplinary experts namely clinical oncologists, breast and endocrine surgeons, pathologist, radiologist, health economists, public health physicians and pharmacists. This economic evaluation was designed from the Ministry of Health (MOH) perspective. The model decision analyses were projected to lifetime horizon (20 years) and the transition cycle was one year. Half cycle correction was performed to increase the applicability.

Model Estimation

The epidemiological and disease-related data were obtained from local sources of data whenever available, or literature review when local data was not available.

Results and Conclusion

From the decision analytic modelling that has been conducted, addition of six cycles of neoadjuvant trastuzumab biosimilar on top of standard neoadjuvant chemotherapy was considered as a cost-effective strategy for high-risk early breast cancer with HER2 positive, yielding an ICER of MYR 16,471.59 per QALY gained. Whereas addition of neoadjuvant Pertuzumab/ Trastuzumab on top of standard neoadjuvant chemotherapy yielded an ICER of MYR 98,013.20 per QALY gained. However, if suggested cost-effectiveness threshold for Malaysia is taken into consideration which is ≤ 1 GDP per capita, addition of single targeted therapy may be the most cost-effective strategy. Definition of one Malaysian GDP per capita per QALY gained is USD10, 500 (~MYR 43, 884.75).

Based on one-way sensitivity analysis performed, these components have shown to be sensitive parameters for ICER determination: discount rate, recurrence state transitional probability values, and cost of targeted therapies.

In general, we found that targeted therapies whether as dual-targeted or single-targeted therapy produced favourable and improvement outcomes in HER2-positive early and locally advanced breast cancer patients. From our review, the dual targeted therapy which is the combination of pertuzumab and trastuzumab with combination of chemotherapy (with or without anthracyclines) was the most effective treatment as compared to single-targeted therapy or mono chemotherapy. Based on economic modelling, only single-targeted therapy is considered the cost-effective option. However, if the price of dual targeted therapy be reduced to 50%, dual-targeted therapy may also be cost-effective. The current treatment to be most cost-effective for Malaysian population was the combination of neoadjuvant chemotherapy with trastuzumab biosimilar.



Recommendation

Targeted therapy in combination with chemotherapy is recommended to be used in early and locally advanced breast cancer. Combination of chemotherapy plus trastuzumab biosimilar is the most cost-effective option for Malaysian population.

However, dual-targeted therapy may be used to achieve the highest effectiveness treatment, if cost reduction of the dual targeted therapy of at least 50% could be negotiated.



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ABBREVIATION

ADC	Antibody drugs conjugate
AEs	Adverse events or adverse effects
CASP	Critical Appraisal Skill Programme
CI	Confidence interval
CDSR	Cochrane Database of Systematic Reviews
CI	Confidence interval
CEA	Cost-effectiveness analysis
DFS	Disease-free survival
EBC	Early breast cancer
EFS	Event-free survival
EGFR	Epidermal growth factor receptor
ER	Estrogen receptor
HER2	Human epidermal growth factor receptor 2
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
IV	Intravenous
LABC	Locally advanced breast cancer
MaHTAS	Malaysian Health Technology Assessment Section
MBC	Metastatic breast cancer
MNCR	Malaysia National Cancer Registry
MOH	Ministry of Health
NMA	Network meta-analysis
NPRA	National Pharmaceutical Regulatory Agency
OR	Odds ratio
OS	Overall survival
pCR	Pathologic complete response
PFS	Progression-free survival
RCT	Randomised controlled trial
RFS	Relapse-free survival
RoB	Risk of bias
RR	Relative risk
SC	Subcutaneous
SR	Systematic review
TKI	Tyrosine Kinase Inhibitor
QALY	Quality adjusted life year
US FDA	United States Food Drug Administration
WHO	World Health Organization



TARGETED THERAPIES IN COMBINATION WITH NEOADJUVANT CHEMOTHERAPY FOR HER2-POSITIVE BREAST CANCER AND ECONOMIC EVALUATION

1.0 BACKGROUND

Breast cancer is the most prevalent type of malignancy in females. It is a heterogeneous disease which can be divided into several subtypes.¹ Based on severity, breast cancer is broadly categorised into three groups which are early breast cancer (EBC), locally advanced breast cancer (LABC) and metastatic breast cancer (MBC).¹ Human epidermal growth factor receptor 2 (HER2) is a growth-promoting protein on the outside of all breast cells. About 15 to 20% women with breast cancer have overexpression of HER2 and called as HER2-positive.^{1,2} HER2-positive is an aggressive subtype that exhibits unique epidemiological, clinical and prognostic differences with poor response to standard chemotherapy regimens compared with HER2-negative.²⁻³ In addition, HER2 may become positive from initially negative tumours over time especially after treatment of endocrine targeting therapy estrogen receptor (ER).¹

Breast cancer is the commonest cancer in Malaysia with the prevalence of 19% among Malaysian as revealed in the Malaysian National Cancer Registry Report (2012-2016). The new cases of breast cancer had increased from 32.1% (2007-2011) to 34.1% (2012-2016) of overall cancer among women.⁴ The incidence started to increase at the age of 25 and peak at the age of 60 to 64 years. The incidence was highest among Chinese (40.7 per 100,000) followed by Indian (38.1 per 100,000) and Malay (31.5 per 100,000).⁴

In general, the overall survival rates of breast cancer have improved even though it varies worldwide due to improvement in medical care and availability of more effective treatment. Majority were diagnosed at an earlier and localised stage.⁵ In many countries, the five-year survival rate for women diagnosed with stage one or two breast cancer range between 80% to 90%.⁵ According to Malaysian Clinical Practice Guideline in Management of Breast Cancer (Third Edition), the early breast cancer include stage I, stage IIA and stage IIB while locally advanced breast cancer includes stage III.⁶ In 2012-2016, the percentage of women in Malaysia diagnosed with breast cancer at stage I was 17.5%, stage II was 34.5% and stage III was 25.2%. Hence, approximately more than third-quarter of breast cancer patients were included in the early and locally advanced breast cancer population (77.2%).⁴

The treatment of breast cancer generally depends on the stage of disease and characteristics of the tumour which involves surgery, chemotherapy, radiotherapy and hormonal therapy.^{1,2} Neoadjuvant therapy in breast cancer refers to the administration of treatment with the intent of down staging the tumour and improve operability and surgical outcomes.⁶ Half of HER2-positive breast cancers are ER-positive but they generally have lower ER levels and many have p53 alterations.¹ The current practice in Malaysia for management of EBC include neoadjuvant chemotherapy only while management of LABC

include neoadjuvant chemotherapy and anti-HER2 therapy for operable and inoperable conditions. These tumours have higher proliferation rates, extra aneuploidy and are associated with poorer patient prognosis. The poor outcome is improved with appropriate chemotherapy combined with the HER2-targeting drug.¹ Pathological complete response (pCR) have been achieved in 75% patients with metastatic HER2-positive breast cancer, hence improved their prognosis.² Despite the achievements, however, the persisting high toll of deaths resulting from HER2-positive breast cancer calls for continued intensive clinical research of newer therapies and combinations.⁷

In Ministry of Health Medicines Formulary (MOHMF), Malaysia, trastuzumab injection was approved in **adjuvant setting** only for patients with HER2-positive, over-expressed by FISH (Fluorescence in situ hybridization) and high risk group (>30% lifetime risk but no known genetic variant).⁸ Both drugs (pertuzumab and lapatinib) are registered under National Pharmaceutical Regulatory Agency (NPRA) but not included in the MOHMF.⁸⁻⁹ Pertuzumab injection is indicated for **neoadjuvant treatment** of patients with **HER2-positive, locally advanced, inflammatory, or early stage breast cancer** (either >2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer and indicated in combination with trastuzumab and docetaxel for patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for metastatic breast cancer.⁹ While, lapatinib is indicated in combination with capecitabine for the treatment of patients with **advanced or metastatic breast cancer** whose tumours overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab or in combination with letrozole for the treatment of postmenopausal women with **hormone receptor-positive metastatic breast cancer**.⁹ As these agents may play an important role in neoadjuvant therapy setting, their effectiveness and economic implications need to be assessed. This HTA was requested by a Clinical Oncologist from Hospital Kuala Lumpur (HKL).



2.0 TECHNICAL FEATURES

2.1 TARGETED THERAPIES

Targeted drugs are designed to precisely identify and block the growth and spread of specific cancer cells which are different from chemotherapy drugs that attack all growing cells including cancer cells.¹⁰ Four types of targeted therapies used for treatment of HER2-positive breast cancer are monoclonal antibodies, small molecule tyrosine kinase inhibitors, antibody-drugs conjugates and other emerging anti-HER2.¹⁰

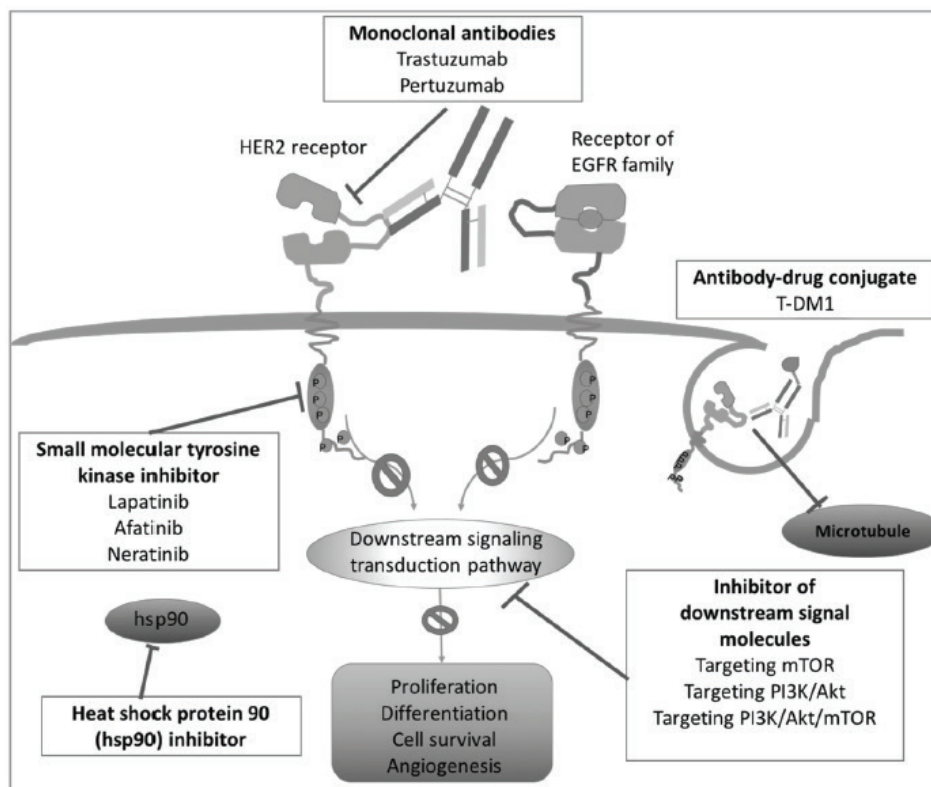


Figure 1. Mechanism of Action for Targeted Therapies on breast cancer cells (Source from: *International Molecular Sciences*. 2016; 17(12):2095)

a) Monoclonal antibodies

Monoclonal antibodies are immune system proteins (antibodies) that are designed to attach to the HER2 protein on cancer cells, which can help stop the cells from growing.⁷ Monoclonal antibodies approved by FDA for breast cancer include trastuzumab, pertuzumab and bevacizumab.¹¹ Trastuzumab (Herceptin®) was the first monoclonal antibody drugs against the extracellular domain of HER2 approved by United States Food and Drug Administration (US FDA) which is well-tolerated in patients with little toxicity followed by pertuzumab (Perjeta®).¹¹ Trastuzumab biosimilars that have been approved by FDA were Hertraz, Zuhera, Herzuma, Kanjinti, Ogivri, Ontruzant and Trazimera.¹² Even though previous studies have proved the tolerable therapeutic efficacy of trastuzumab, some HER2-positive breast cancer patients showed intrinsic or

acquired resistance to it.¹⁰ Hence, research on developing anti-HER2 agents is still on-going.¹⁰ Later, the combination of pertuzumab with trastuzumab and docetaxel was approved by US FDA on September 2013 as neoadjuvant treatment of patients with HER2-positive for early-stage breast cancer, locally advanced or inflammatory.¹¹

b) Tyrosine Kinase Inhibitors

Tyrosine kinase inhibitor (TKI) is a group of drugs which interrupts the HER2 and epidermal growth factor receptor (EGFR) pathways by disrupting the signal transduction pathways of protein kinases through several modes of inhibition.¹³ Kinase inhibitors are either irreversible or reversible. The irreversible kinase inhibitors tend to covalently bind and block the ATP site resulting in irreversible inhibition. The reversible kinase inhibitors can further subdivide into four major subtypes based on the confirmation of the binding pocket. Tyrosine kinase enzymes (TKs) can be categorised into receptor tyrosine kinases (RTKs), non-receptor tyrosine kinases (NRTKs), and a small group of dual-specificity kinases (DSK) which are phosphorylate serine, threonine, and tyrosine residues. Lapatinib (Tykerb®) is the second US FDA approved HER2 targeted drug after trastuzumab.⁷ In addition, FDA approved TKIs for breast cancer also include afatinib, neratinib and tucatinib (which targets HER1 and HER2), have substantial efficacy in the treatment of HER2-positive breast cancer.¹³⁻¹⁴

a) Antibody drugs conjugates (ADCs)

Trastuzumab–emtansine (T-DM1) is a HER2-targeted antibody-drug conjugate (ADC) which contains the humanised anti-HER2 IgG1, trastuzumab, covalently linked to the microtubule inhibitory drug DM1 (a maytansine derivative) via the stable thioether linker 4-[N-maleimidomethyl] cyclohexane-1-carboxylate (MCC). Emtansine refers to the MCC-DM1 complex. An average of 3.5 DM1 molecules is conjugated to each molecule of trastuzumab. Conjugation of DM1 to trastuzumab confers selectivity of the cytotoxic agent for HER2-overexpressing tumour cells, thereby increasing intracellular delivery of DM1 directly to malignant cells. Upon binding to HER2, trastuzumab-emtansine undergoes receptor-mediated internalisation and subsequent lysosomal degradation, resulting in release of DM1-containing cytotoxic catabolites (primarily lysine-MCC-DM1).⁷

3.0 POLICY QUESTION

Should targeted therapies i.e. trastuzumab (tzmb), pertuzumab (pzmb) and lapatinib (lpnb) in combination with chemotherapy be used as a neoadjuvant treatment for HER2-positive early and locally advanced breast cancer in Ministry of Health facilities?



4.0 OBJECTIVE

4.1 To conduct a systematic review:

- I. To assess the effectiveness and safety of trastuzumab, pertuzumab, lapatinib in combination with chemotherapy in neoadjuvant setting for patient with HER2-positive breast cancer.
- II. To determine whether to use one or dual targeted therapies in combination with chemotherapy in neoadjuvant setting for HER2-positive breast cancer.
- III. To evaluate the cost-effectiveness of trastuzumab, pertuzumab, lapatinib in combination with chemotherapy for HER2-positive breast cancer in neoadjuvant setting.
- IV. To assess the organisational or societal implication related to the use of trastuzumab, pertuzumab, lapatinib in neoadjuvant setting for HER2-positive breast cancer.

PART A- SYSTEMATIC REVIEW OF LITERATURE

1.1 METHODS

5.1.1 SEARCHING

Search Strategy

Electronic databases were searched through the Ovid interface:

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R)-1946 to March 26, 2021. Google Scholar was used to search for additional web-based materials and information. Additional articles were identified from reviewing the references of retrieved articles. Last search was conducted on 5th of August 2021. Search was limited to articles in English and in human. Several search terms were used such as; *breast neoplasms, mammary cancer, neoadjuvant therapy, trastuzumab, pertuzumab, lapatinib, targeted therapy*. Appendix 3 shows the detailed search strategies.

5.1.2 STUDY SELECTION

Three reviewers (AS, MAR and AA) independently screened the titles and abstracts against the inclusion and exclusion criteria as shown below and evaluated the selected full-text articles for final article selection.



Inclusion criteria

a	Population	<ul style="list-style-type: none"> ○ Adult patients with HER2-positive breast cancer, early breast cancer and locally advanced breast cancer
b	Intervention	<p>Targeted therapies:</p> <ul style="list-style-type: none"> -Monoclonal antibodies such as trastuzumab, trastuzumab biosimilar and pertuzumab -Kinase inhibitors: lapatinib (monotherapy or combination with chemotherapy: taxane-based, anthracyclines, cyclophosphamide, carboplatin) ○ chemotherapy + dual targeted therapy ○ chemotherapy + single targeted therapy
c	Comparator	<ul style="list-style-type: none"> ○ chemotherapy + single targeted therapy ○ chemotherapy only
d	Outcomes	<p>Primary Outcomes:</p> <ul style="list-style-type: none"> ○ Pathological complete response (defined as no residual invasive tumour in both the breast and the axilla: i.e. ypT0/is pN0). ○ Progression-free survival ○ Number of patients had progressed ○ Disease-free survival/Relapse-free survival ○ Event-free survival ○ Overall survival <p>Secondary outcomes:</p> <ul style="list-style-type: none"> ○ Conserving surgery rates/Conservative breast surgery (for early breast cancer) <p>Safety</p> <ul style="list-style-type: none"> ○ Adverse events (any grade 3-4 adverse event) <p>Economic impacts</p> <ul style="list-style-type: none"> ○ Cost effectiveness analysis ○ Cost utility analysis ○ Cost benefit analysis ○ Cost analysis ○ Any other measure of economic outcomes <p>Organisational issues</p> <ul style="list-style-type: none"> ○ Length of hospital stay (LOS) ○ Hospital Admission ○ Day care <p>Social implication</p> <ul style="list-style-type: none"> ○ Preferences ○ Tolerability ○ Satisfaction
e	Study design	<p>HTA reports, systematic review with network meta-analysis, systematic review with meta-analysis, randomised controlled trial (RCT), observational study and economic evaluation studies.</p>
f	English full text articles	



Exclusion criteria

- a. Study design: animal study, laboratory study, narrative review, editorials, and letter to the editors.
- b. Non English full text article.

Based on the above inclusion and exclusion criteria, study selection will be carried out independently by three reviewers. Disagreement will be resolved by discussion.

5.1.3 CRITICAL APPRAISAL OF LITERATURE/ ASSESSMENT OF RISK OF BIAS

The risk of bias or quality assessment (methodology quality) of all retrieved literatures will be assessed by three reviewers depending on the type of the study design; using the relevant checklist of National Collaborating Centre for Methods and Tools (ROBIS) for Systematic Review, revised Cochrane assessing risk-of-bias tool (RoB 2) for Randomised Controlled Trials and Critical Appraisal Skill Programme (CASP) checklist for cohort and economic studies.

5.1.4 ANALYSIS AND SYNTHESIS OF EVIDENCE

Methods of analysis/synthesis

Data on the effectiveness, safety and outcomes of using targeted therapies were presented in tabulated format with narrative summaries. Meta-analysis using RevMan 5.0 was conducted for this Health Technology Assessment for selected outcomes namely pathological complete response (pCR) rate and safety data. The data was pooled when heterogeneity, I^2 was less than 75% (heterogeneity more than 75% is considerable heterogeneity).¹⁶ Risk ratio (RR), Odds ratio (OR) were calculated using fixed-effect model with 95% Confidence Interval (CI). Statistical significance was set at $p < 0.05$ for all outcomes.

6.0 RESULTS

6.1 SELECTION OF INCLUDED ARTICLES

A total of 1019 records were identified through Ovid interface and 12 records were identified from other sources (references of retrieved articles). All the records were screened and 915 records were excluded. Of these, 85 relevant abstracts were retrieved in full text. After applying inclusion and exclusion criteria, 66 articles were excluded with reasons (Figure 2).

There were 19 studies included in this review: two systematic review (SR) and network meta-analysis (NMA), nine randomised controlled trials (RCTs), three cohort studies, one cross-sectional study and four economic analyses.





All studies included were published in English language between 2012 and 2021 and were mostly conducted in Japan, China, Italy, Poland, South Korea, Russia, Taipei, Taiwan, Spain, Pakistan, United States (US), United Kingdom (UK), Belgium, Germany, Switzerland, France, Spain, Ukraine and India. The selection of the studies was shown on Figure 2. The studies were excluded due to irrelevant study design (n=10), irrelevant population (n=8), irrelevant intervention (n=9), irrelevant outcome (n=8) as well as those already included in the systematic reviews (n=32). The excluded studies are listed in Appendix 5.

Descriptions of 19 full-text articles included in qualitative synthesis are presented in Table 1, Table 2 and Table 3. Table 2 represents articles included in quantitative analysis (meta-analysis) which involved trials using Pertuzumab plus Trastuzumab. The selection of the studies was shown on Figure 2. The SR was reported following PRISMA checklist.

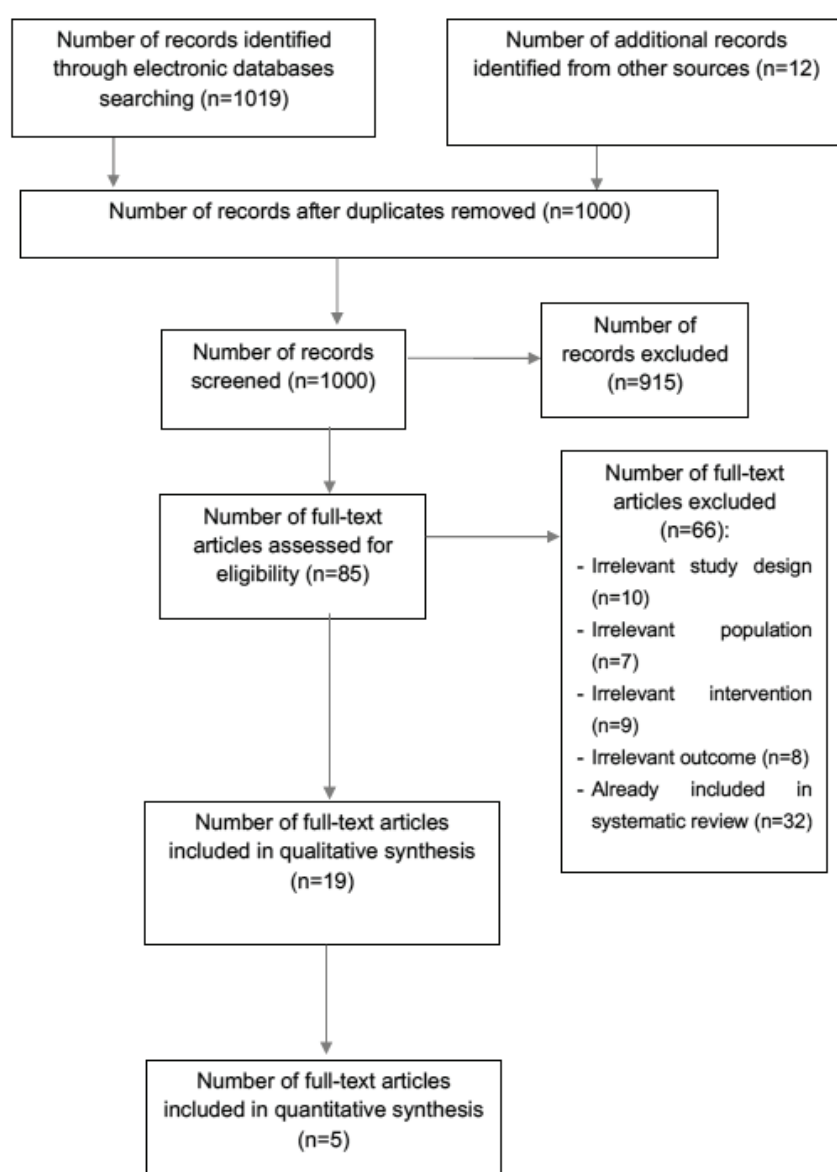


Figure 2: Flow chart of study selection

Table 1. Description of the included studies: types of breast cancer, number of patients, intervention and comparison and outcome measures.

Study	Studies included/ Types of breast cancer	Number of patients (n)	Intervention & Comparison	Outcome measures
Systematic Review (SR) with Network Meta-Analysis (NMA)				
Zhang et al. (2021)	Stebbing, 2017 (NCT021611)	n=549	CT-P6 (Biosimilar) vs Trastuzumab	<ul style="list-style-type: none"> • Pathological complete response rate • Adverse events: neutropoemia, diarrhoea, febrile neutropoemia, hepatotoxicity • Pathological complete response rate • Adverse events: neutropoemia, diarrhoea, febrile neutropoemia, hepatotoxicity
Nakashoji et al. (2018)	Baselga, 2012 (NeolITTO)	n=455	Trastuzumab + Lapatinib + Chemotherapy vs Lapatinib + Chemotherapy vs Trastuzumab + Chemotherapy	<ul style="list-style-type: none"> • Pathological complete response rate • Adverse events: neutropoemia, diarrhoea, febrile neutropoemia, hepatotoxicity
	Carey, 2016 (CALGB 40601)	n=305		
	Bonnefoi, 2015 (EORTC)	n=128		
	Guarneri, 2012 (CHER-LOB)	n=121		
Gianni et al. (2016)	Holmes, 2013 (LPT 109096)	n=100	Lapatinib + Chemotherapy vs Trastuzumab + Chemotherapy	<ul style="list-style-type: none"> • Adverse events: neutropoemia, diarrhoea, febrile neutropoemia, hepatotoxicity
	Robidoux, 2013 (NSABP B-41)	n=529		
Randomised Controlled Trials (RCTs)	Hurvitz, 2020 (TRIO-USB07)	n=128	Lapatinib + Chemotherapy vs Trastuzumab + Chemotherapy	<ul style="list-style-type: none"> • Pathological complete response rate • Adverse events: neutropoemia, diarrhoea, febrile neutropoemia, hepatotoxicity
	Urtch, 2012 (GeparQuinto)	n=615		
Randomised Controlled Trials (RCTs)	Alba, 2014 (GEICAM)	n=102	Trastuzumab Chemotherapy vs Chemotherapy (FEC+ Pacli+cyclo+doce)	<ul style="list-style-type: none"> • Pathological complete response rate • Adverse events: neutropoemia, diarrhoea, febrile neutropoemia, hepatotoxicity
	Buzdar, 2013 (ACOSOG Z1041)	n=282		
	Gianni, 2010 (NOAH)	n=235		
Randomised Controlled Trials (RCTs)	Pierga, 2010 (REMAUGUS)	n=120	Trastuzumab + Docetaxel vs Docetaxel	<ul style="list-style-type: none"> • Pathological complete response rate • Safety
	Steger, 2013 (ABCSSG-24)	n=93		
Gianni et al. (2012)	Locally advanced breast cancer	n=417	Pertuzumab+Trastuzumab +Docetaxel vs Trastuzumab + Docetaxel	<ul style="list-style-type: none"> • Pathological complete response rate • Safety
Gianni et al. (2016)	Locally advanced breast cancer	n=417	Pertuzumab+Trastuzumab +Docetaxel vs Trastuzumab + Docetaxel	<ul style="list-style-type: none"> • Progression-free survival • Disease-free survival • Tolerability • Adverse events



Table 2. Description of the included studies: types of primary tumour, number of patients, intervention and comparison and outcome measures.

Study	Studies included/ Types of breast cancer	Number of patients	Intervention & Comparison	Outcome measures
Randomised Controlled Trials (RCTs)				
Shao et al. (2020)	PEONY, early and locally advanced breast cancer	n=329	Pertuzumab+Trastuzumab +Docetaxel vs Trastuzumab + Docetaxel	<ul style="list-style-type: none"> • Pathological complete response rate • Adverse event(s)
Fernandez-Martinez et al. (2020)	CALGB 40601 Alliance, locally advanced breast cancer Stage II and III HER2-positive breast cancer	n=305	Lapatinib Trastuzumab, Paclitaxel	<ul style="list-style-type: none"> • Relapse-free survival • Death/Overall survival
Huober et al. (2019)	NeoALTO study (BIG 1-06), early breast cancer, patients with operable, unilateral, non-inflammatory	n=455	Lapatinib Trastuzumab, Paclitaxel	<ul style="list-style-type: none"> • Event-free survival • Overall survival
Buzdar et al. (2019)	ACOSOG Z1041 (Alliance) operable breast cancer, invasive breast cancer with 3+ IHC	n=282 (sequential vs concurrent)	Trastuzumab + FEC + Paclitaxel vs FEC + Placitaxel	<ul style="list-style-type: none"> • Pathological complete response rate • Disease-free survival/Event-free survival • Adverse event(s)
Untch et al. (2018)	GeparQuinto (G5) study IHC 3+, in situ hybridization (ratio \geq 2.0), tumour lesions size of \geq 2cm	n=620	EC+ Lapatinib vs EC + Trastuzumab	<ul style="list-style-type: none"> • Disease-free survival/Event-free survival • Adverse event(s)
Stebbing et al. (2021)	NCT 02162667 stage I–IIa operable HER2-positive breast cancer	n=549	CT-P6 Biosimilar vs Trastuzumab	<ul style="list-style-type: none"> • Pathological complete response rate • Disease-free survival • Overall survival • Adverse event(s) • Event-free survival • Overall survival • Adverse event(s)
Jackisch et al.	HannaH study, early breast cancer	n=596	SC Trastuzumab vs IV Trastuzumab	<ul style="list-style-type: none"> • Pathological complete response rate • Disease-free survival • Overall survival • Adverse event(s) • Event-free survival • Overall survival • Adverse event(s)
Pivot et al.	Randomized, two-cohort PrefHer study	n=488	SC Trastuzumab single-use injection device (SID) IV Trastuzumab	<ul style="list-style-type: none"> • Preferences



Table 3. Description of the included studies: types of primary tumour, number of patients, intervention and comparison and outcome measures.

Study	Studies included/ Types of breast cancer	Number of patients	Intervention & Comparison	Outcome measures
Observational study				
Sheikh et al. (2019)	Locally advanced breast cancer Immunohistochemical (IHC) stain of 3+ or FISH positive	n=131	Trastuzumab +Taxane vs Taxane	<ul style="list-style-type: none"> • Pathological complete response rate • Breast conservation • Toxicity
Murthy et al. (2018)	Locally advanced breast cancer	n=977	Pertuzumab + Trastuzumab +Paclitaxel/Docetaxel+ FEC/ (Doxorubicin+ Carboplatin)	<ul style="list-style-type: none"> • Pathological complete response rate • Breast conservation • Toxicity
Hussain et al. (2018)	Locally advanced breast cancer	n=45	Pertuzumab+ Trastuzumab + Docetaxel + Carboplatin vs Trastuzumab + Docetaxel + Carboplatin	<ul style="list-style-type: none"> • Safety
Economic and Social studies				
Hassett et al. (2020)	stage II-III HER2-positive cancer	NA	1)Tzmb+Taxol 2)TDM-1+Pzmb 3)Pzmb+tzmb+docetaxel+carboplatin 4)taxol+ tzmb+ pzmb then doxorubicin+ cyclophosphamide 5)taxol + tzmb + pzmb S1 & S2: DDAC-THP, S3: THP, S4: HP, S5: TCHP	<ul style="list-style-type: none"> • Cost-effectiveness analysis (CEA)
Kunst et al. (2020)	Locally advanced breast cancer	NA	1) Pzmb + tzmb + docetaxel 2) Trastuzumab + docetaxel	<ul style="list-style-type: none"> • Cost-effectiveness analysis (CEA)
Squires et al. (2018)	Locally advanced (including inflammatory) breast cancer and women with high-risk early- stage breast cancer (classified as T2/3 or N1)	n=214	1) Pzmb + tzmb + docetaxel 2) Trastuzumab + docetaxel	<ul style="list-style-type: none"> • Single Technology Appraisal by NICE
Lee et al. (2016)	HER2+ Early Breast Cancer	NA	1) SC trastuzumab 2) IV trastuzumab	<ul style="list-style-type: none"> • Cost-minimisation analysis
Cross-sectional study				
Pivot et al. (2014)	HER2-positive early breast Cancer	n=245	SC Trastuzumab via single-used injection device VS IV Trastuzumab	<ul style="list-style-type: none"> • patients' preferences

Notes: DDAC: dose-dense anthracycline/cyclophosphamide plus, THP: paclitaxel (T), trastuzumab (H) pertuzumab (P), TCHP: docetaxel (T) carboplatin (C) plus HP



6.2 QUALITY ASSESSMENT/ RISK OF BIAS

Three reviewers (AS, MAR and AAAR) independently appraised and assessed risk of bias of relevant articles using Risk of Bias in Systematic reviews (ROBIS) for Systematic Review, Risk of Bias (RoB) 2 for Randomised Controlled Trials and Critical Appraisal Skill Programme (CASP) checklist for cohort and economic studies.¹⁵⁻¹⁷ Review authors' judgements involved answering pre-specified questions and discrepancies were resolved by consensus.

Assessment for Systematic Review (SR) using ROBIS¹⁵

Two SR were included in this assessment and the risk of bias was shown in Table 3. All studies were judged to have overall low risk of bias.

Review	Phase 2				Phase 3
	STUDY ELIGIBILITY CRITERIA	IDENTIFICATION AND SELECTION OF STUDIES	DATA COLLECTION AND STUDY APPRAISAL	SYNTHESIS AND FINDINGS	RISK OF BIAS IN THE REVIEW
Zhang et al. 2021	+	+	+	+	+
Nakashoji et al. 2018	+	+	+	+	+




-  High risk
-  Unclear
-  Low risk bias

Table 3: Summary of risk of bias assessment for systematic review using ROBIS



Assessment for Randomised Control Trial (RCT) using Revised Cochrane Risk of Bias Tool (RoB 2)¹⁶

Nine RCTs were included in this assessment and the risk of bias assessment was as shown in figure 4. All studies were judged to have overall low risk of bias.

	Risk of bias domains					Overall
	D1	D2	D3	D4	D5	
Gianni et al. 2012	+	+	+	+	+	+
Gianni et al. 2016	+	+	+	+	+	+
Shao et al. 2019	+	+	+	+	+	+
ernandez-Mertinez et al. 2020	+	+	+	+	+	+
Huober et al. 2019	+	+	+	+	+	+
Buzdar et al. 2018	+	+	+	+	+	+
Untch et al. 2018	+	+	+	+	+	+
Stebbing et al. 2021	+	+	+	+	+	+
Jackish et al. 2016	+	+	+	+	+	+

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
+ Low

Table 4: Summary of risk of bias assessment for randomised controlled trials using risk of bias 2 (ROB 2)

Assessment for Cohort Study Using Critical Appraisal Skills Programme (CASP) Checklist¹⁷

The cohort studies were assessed using the CASP checklist. Three articles were included in this appraisal (Table 5). Hussain et al. was judged as 'can't tell' for criteria 'outcome accurately measured' because common side effect such as neutropaenia were not reported in the paper.

Study	Criteria assessed				
	SELECTION OF COHORT	EXPOSURE ACCURATELY MEASURED	OUTCOME ACCURATELY MEASURED	CONFOUNDING FACTORS	FOLLOW-UP OF SUBJECTS
Murthy et al., 2018	yes	yes	yes	yes	yes
Hussain et al. 2018	yes	yes	can't tell	yes	yes
Sheikh et al. 2019	yes	yes	yes	yes	yes

Table 5: Summary of risk of bias assessment for cohort study using CASP Checklist



Assessment for Economic Evaluation Studies using Critical Appraisal Skills Programme (CASP) Checklist¹⁷

Three cost-effectiveness analyses were included in this assessment and were summarised in Table 6. Only one study (Lee et al.) was assessed as 'can't tell' for two domains. Two studies (Kunst et al. and Lee et al.) were assessed as 'no' for one domain because the discounting rate was not mentioned in the articles.

Criteria assessed	Study		
	Hassett et al. 2020	Kunst et al. 2020	Lee et al. 2016
A well-define question posed?	yes	yes	yes
Comprehensive description of competing alternative given?	yes	yes	yes
Effectiveness established?	yes	yes	yes
Effects of intervention identified, measured and valued appropriately?	yes	yes	yes
All important and relevant resources required and health outcome costs for each alternative identified, measured in appropriate units and valued credibly?	yes	yes	can't tell
Costs and consequences adjusted for different times at which they occurred (discounting)?	no	yes	no
Results of the evaluation?	yes	yes	yes
Incremental analysis of the consequences and costs of alternatives performed?	yes	yes	can't tell
Sensitivity analysis performed?	yes	yes	yes

Table 6: Summary of quality assessment for economic studies using CASP checklist

6.3 EFFICACY/ EFFECTIVENESS

This review included 14 studies on the effectiveness of targeted therapies in combination with neoadjuvant chemotherapy for HER2-positive breast cancer. These studies comprised of two SR with NMA, nine RCTs and three cohort studies. The results were reported based on outcomes as follow; pathologic complete response (pCR), progression free survival (PFS), number of patients who had progressed or died, disease-free survival (DFS)/relapse-free survival (RFS), event-free survival (EFS), adverse events and overall survival (OS). For each outcome, results were presented based on five strategies; combination





6.3.1 Pathological Complete Response (pCR) rate

Two SR with NMA, three RCTs and one observational study reported on this outcome that included all five comparisons of intervention. In general, the results from Zhang et al (2021) who did a network meta-analysis of all interventions demonstrated the percentage of best treatment used for HER2-positive breast cancer.^{18, level I} The ranking of all regimes from their outcomes was based on the surface under the cumulative ranking curve (SUCRA), which value from 0% to 100%. A higher SUCRA value was associated with a higher pCR rate and a lower dropout rate or less toxicity (Table 7).

Interventions/experimental arms	Zhang et al. Percentage (%)	Nakashoji et al. Percentage (%)
Chemotherapy (without A)+trastuzumab +pertuzumab	89.8	NA
Chemotherapy (A) + trastuzumab+ pertuzumab	84.9	NA
Chemotherapy (without A)+ trasztuzumab +lapatinib	72.8	79
Chemotherapy (without A)+ trastuzumab biosimilar	71.7	NA
Chemotherapy (A) + trastuzumab + lapatinib	68.6	79
Chemotherapy (A) + trastuzumab biosimilar	62.1	NA
Mono chemotherapy+ trastuzumab +pertuzumab	47.7	85
Mono chemotherapy+ trastuzumab +lapatinib	37	79
Trastuzumab + pertuzumab	3.6	NA
Trastuzumab + Lapatinib	NA	32
Chemotherapy (with or without A) + Trastuzumab	67.7 (1 arm)	70
Chemotherapy + Pertuzumab	13.5 (1 arm)	41
Chemotherapy + Lapatinib	35.1(comb) & 6.1 (mono)	49

Notes: A= anthracyclines

Table 7. Ranking for the pathological complete response for experimental arms (Zhang et al 2021 and Nakashoji et al 2018)

Combination of Pertuzumab, Trastuzumab and Chemotherapy versus Trastuzumab and Chemotherapy

a) Combination chemotherapy (with or without anthracyclines)

A systematic review with network meta-analysis by Zhang et al (2021) includes 39 articles from 36 trials that involved 10379 patients.^{18, level I} Databases were searched up to November 2020 focusing on pathologic complete response in patients with HER2-positive early breast cancer. They did an indirect meta-analysis that compared the combination of pertuzumab, trastuzumab and chemotherapy versus combination of trastuzumab and chemotherapy showed a significant increase in complete response rate for group with anthracyclines [Odds ratio (OR) 24.71 (95% confidence interval (CI) 1.57 to 118.8)] and non-significant increase without anthracyclines [OR 7.74 (95% CI 0.32 to 40.88)]

favouring combination dual-targeted therapy. A NMA ranked was performed based on the surface under the cumulative ranking curve (SUCRA), the results revealed that dual-targeted therapy was significantly better than single-targeted therapy and combination chemotherapy was significantly better than mono chemotherapy, $p < 0.05$ (Table 7).

b) Mono chemotherapy

Three out of five studies reported on the outcome of mono chemotherapy either using docetaxel or paclitaxel.¹⁹⁻²¹ Gianni et al.¹⁹, level II-1 Shao et al.²⁰, level II-1 and Murthy et al.²¹, level II-11 conducted studies to compare the combination of pertuzumab, trastuzumab and docetaxel/paclitaxel with combination of trastuzumab and docetaxel/paclitaxel in early and locally advanced HER2 positive breast cancer patients. We pooled the data from RCTs on this outcome and the result showed that combination of pertuzumab, trastuzumab and docetaxel/paclitaxel significantly increased pathological complete response (pCR) rate with OR 2.33 (95% CI 1.57 to 3.47) compared with trastuzumab and docetaxel. When we included observational study, the rate was better in combination of pertuzumab, trastuzumab and docetaxel with OR 2.99 (95% CI 2.17 to 4.13) compared with combination of trastuzumab and docetaxel only (Figure 4).

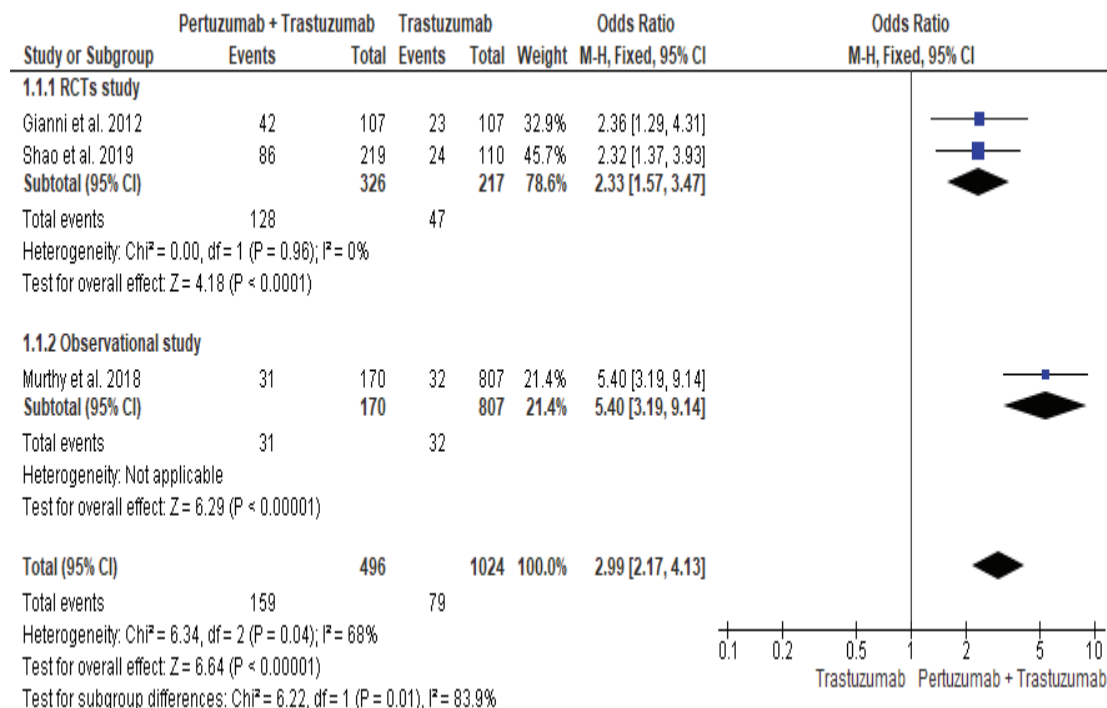
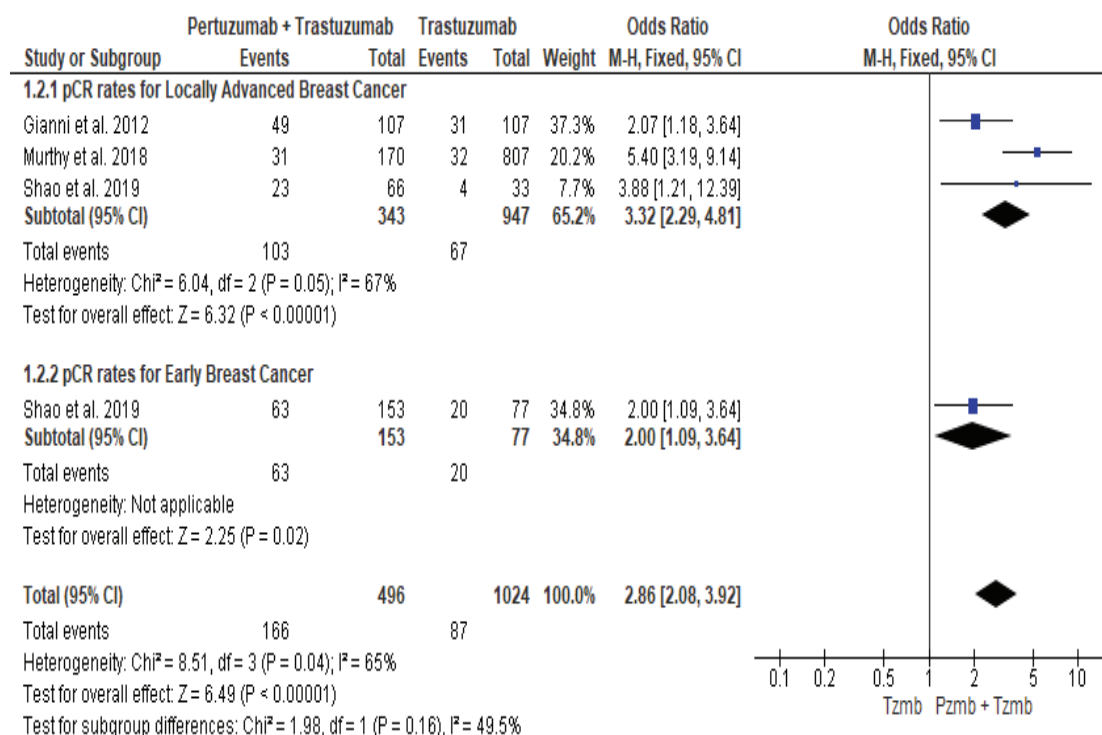


Figure 4. Pertuzumab, Trastuzumab and Docetaxel versus Trastuzumab and Docetaxel; Outcome: Total pathological complete response rate



We did a subgroup meta-analysis according to early breast cancer and locally advanced breast cancer, the pooled data showed significant increase in pCR for both subgroups with the treatment of pertuzumab, trastuzumab and docetaxel



than the treatment of trastuzumab and docetaxel (Figure 5).

Figure 5. Pertuzumab, Trastuzumab and Docetaxel versus Trastuzumab and Docetaxel; Outcome: Total pathological complete response rate; Subgroup: Locally advanced and early BC

Combination of Lapatinib, Trastuzumab and Chemotherapy versus Lapatinib and Chemotherapy or Trastuzumab and Chemotherapy

a) Combination chemotherapy (with or without anthracyclines)

Zhang et al (2021) in their SR with NMA did a direct meta-analysis that compared the combination of lapatinib, trastuzumab and chemotherapy versus combination of lapatinib and chemotherapy.^{18, level I} Dual-targeted therapy significantly increased the pCR rate with anthracyclines (OR 2.15 95% CI 1.42 to 3.13) and without anthracyclines (docetaxel plus carboplatin: OR 3.88 95% CI 1.22 to 9.63) compared with combination of lapatinib and chemotherapy. The network meta-analysis ranked of pCR rate also showed that combination without anthracycline was higher which is 72.8% (combination chemotherapy), followed by combination with anthracyclines (68.6%) and mono chemotherapy (37%) (Table 7).^{18, level I}

However, the combination of chemotherapy with or without anthracyclines, lapatinib and trastuzumab resulted in not statistically significant difference in pCR rate when compared with combination of chemotherapy and trastuzumab only, OR 1.37 (95% CI 0.47 to 3.21) without anthracyclines: docetaxel plus carboplatin; OR 1.39 (95% CI 0.93 to 2.02) with anthracyclines.^{18, level I}

b) Mono chemotherapy

Result from pooled meta-analysis in Zhang et al. showed that combination of mono chemotherapy (paclitaxel), lapatinib and trastuzumab significantly increased the pCR rate, OR 3.33 (95% CI 1.94 to 5.37)] compared with mono chemotherapy and lapatinib only.^{18, level I} Combination of mono chemotherapy, lapatinib and trastuzumab significantly increased pCR rate when compared with mono chemotherapy and trastuzumab only [OR 1.83 (95% CI 1.12 to 2.82)].

Combination of Trastuzumab and Chemotherapy versus Chemotherapy only

a) Combination chemotherapy (with or without anthracyclines)

Nakashoji et al (2018) conducted a SR with direct MA and NMA to evaluate the effectiveness of addition of trastuzumab to chemotherapy.^{22, level I} Overall; thirteen studies that enrolled 3184 patients were included. Five studies with a total of 537 patients were reported on combination trastuzumab and chemotherapy (with or without anthracyclines) resulted in significant increase in pCR [OR 2.32 (95% CI 1.49 to 3.62)] than chemotherapy alone.

In the meta-analysis by Zhang et al, a pooled results showed a significant increase in pCR rate for groups with anthracyclines, OR 2.28 (95% CI 1.5 to 3.39) and without anthracyclines, OR 3.12 (95% CI 1.9 to 4.8) indirect meta-analysis, compared with chemotherapy alone groups.^{18, level I}

Sheikh et al. conducted a cohort study in 2019 to compare the pCR in 131 patients with locally advanced breast cancer receiving trastuzumab plus taxane-based chemotherapy with those receiving chemotherapy alone.^{23, level II-2} The pCR of the patients who received trastuzumab in the neoadjuvant setting was significantly higher (n=32) 50% than the reference group (n=16) 23.9%. This difference was statistically significant with a p-value of 0.002 (<0.05).^{22, level I}

Combination Trastuzumab and Chemotherapy versus Lapatinib and Chemotherapy

a) Combination chemotherapy (with or without anthracyclines)

In a SR and NMA conducted by Zhang et al, the pooled results of direct meta-analysis comparing combination of trastuzumab and chemotherapy with combination of lapatinib and chemotherapy, showed that combination of trastuzumab and chemotherapy (with anthracyclines) significantly increase pCR compared to combination of lapatinib and chemotherapy (with anthracyclines)



with OR 1.56 (95% CI 1.13 to 2.11).^{18, level I} While in their indirect comparison, there was no significant difference in the pCR rate between combination of lapatinib and chemotherapy (without anthracyclines) and trastuzumab and chemotherapy (without anthracyclines) OR 0.43 (95% CI 0.12 to 1.12).^{18, level I}

Trastuzumab Biosimilar and Chemotherapy versus Trastuzumab and Chemotherapy

a) Combination chemotherapy (with or without anthracyclines)

Zhang et al in their SR and NMA did a direct meta-analysis that compared the combination of trastuzumab biosimilar and chemotherapy (with anthracyclines) versus combination of trastuzumab and chemotherapy (with anthracyclines).^{18, level I} The analysis showed there was no significant difference between these two groups OR 1.21 (95% CI 0.91 to 1.56). The network meta-analysis ranked of pCR rate also showed that combination without anthracycline was higher (71.7%) than the combination with anthracyclines (62.1%) (Table 7).^{18, level I}

6.3.2 Progression-Free Survival (PFS)

Two RCTs reported on this outcome that included two comparisons of intervention that involved pertuzumab and trastuzumab biosimilar.

Combination of Pertuzumab, Trastuzumab and Chemotherapy versus Trastuzumab and Docetaxel/ Pertuzumab and Trastuzumab/ Pertuzumab and Chemotherapy

a) Combination chemotherapy (with or without anthracyclines)

Gianni et al (2016) conducted a secondary/post-hoc analysis of randomised open label of NeoSphere trial to evaluate the five-year progression-free survival, disease-free survival and safety.^{24, level II-1} About 417 locally advanced breast cancer patients from 59 centers in 16 countries from December 2007 to December 2009 were randomised to receive either combination of pertuzumab, trastuzumab and chemotherapy (docetaxel) (n=107) or combination of trastuzumab and docetaxel (n=107) or combination of pertuzumab and trastuzumab (n=107) or pertuzumab and docetaxel (n=96). The five-year progression-free survival rates in combination of pertuzumab, trastuzumab and docetaxel group was not statistically significant difference [86% (95% CI 77 to 91)] than in trastuzumab and docetaxel group [81% (95% CI 71 to 87)] with hazard ratio (HR) of 0.69 (95% CI 0.34 to 1.40). There was no significant difference for PFS rate in pertuzumab and trastuzumab group when compared with combination of pertuzumab, trastuzumab and docetaxel group which was 73% (95% CI 64 to 81) with HR of 1.25 (95% CI 0.68 to 2.30). There is a significant difference with the combination of pertuzumab and docetaxel [73% (95% CI 63 to 81)] when compared with pertuzumab, trastuzumab and docetaxel group with HR of 2.05 (95% CI 1.07 to 3.93).^{24, level II-1}



Combination of Trastuzumab Biosimilar and Chemotherapy versus Combination of Trastuzumab and Chemotherapy

a) *Combination chemotherapy (with or without anthracyclines)*

Stebbing et al. (2021) conducted a phase III trial to evaluate the efficacy and safety data following neoadjuvant therapy for patients with HER2-positive early breast cancer after up to three years' follow-up.^{25, level II-1} The estimated hazard ratio (HR) were not statistically significantly different between combination of CT-P6 (trastuzumab biosimilar) and chemotherapy (with anthracyclines) group and combination of trastuzumab reference and chemotherapy (with anthracyclines) group which was 1.31 (95% CI 0.86 to 2.01) for progression-free survival. They also found that patients who achieved total pathological complete response (for all groups) had longer progression-free survival [85% (95% CI 76 to 91)] compared with patients who did not [76% (95% CI 71 to 81)]. However, the difference was not statistically significant with HR of 0.54 (95% CI 0.29 to 1.00).^{25, level II-1}

6.3.3 Disease-Free Survival (DFS)/ Relapse-Free Survival (RFS)

Five RCTs reported on this outcome that included all five comparisons of interventions.

Combination of Pertuzumab, Trastuzumab and Chemotherapy versus Combination of Trastuzumab and Chemotherapy

a) *Mono chemotherapy*

In 2016, NeoSphere RCT conducted by Gianni et al. analysed disease-free survival in patients who had surgery and the treatment given was divided into four groups.^{24, level II-1} They found that disease-free survival results were consistent with progression-free survival that was highest in the group that received combination of pertuzumab, trastuzumab and chemotherapy (docetaxel) [84% (95% CI 72 to 91)], followed by combination of trastuzumab and docetaxel [81% (95% CI: 72 to 88)], combination pertuzumab and trastuzumab [80% (95% CI 70 to 86)] and combination of pertuzumab and docetaxel [75% (95% CI 64 to 83)].^{24, level II-1}

Combination of Lapatinib, Trastuzumab and Chemotherapy versus Lapatinib and Chemotherapy / Trastuzumab and Chemotherapy

a) *Mono chemotherapy*

Fernandez-Martinez et al. 2020 conducted a secondary or post-hoc analysis of RCTs (CALGB 40601 Alliance trial) from December 2008 to February 2015 for locally advanced breast cancer.^{26, level II-1} Three hundred five patients were randomly allocated to groups: combination of lapatinib, trastuzumab and





chemotherapy (paclitaxel) (n=118), combination of trastuzumab and paclitaxel (n=120) and combination of lapatinib and paclitaxel (n=67). They found at more than seven years of follow-up, relapse-free survival events were highest in dual-targeted group which was 93% (95% CI 88 to 98) for combination of lapatinib, trastuzumab and paclitaxel, followed by 79% (95% CI 71 to 87) for combination of trastuzumab and paclitaxel and 69% (95% CI 58 to 82) for combination of lapatinib and paclitaxel.^{26, level II-1}

Combination of Trastuzumab and Chemotherapy versus Chemotherapy only

a) Combination chemotherapy (with or without anthracyclines)

Buzdar et al. (2019) in their ACOSOG trial compared the combination of trastuzumab and chemotherapy (with anthracyclines) through sequential arm and concurrent arm for treatment of operable HER2-positive breast cancer patients.^{27, level II-1} They were enrolled from September 2007 to December 2011 from 36 centers in the continental United States and Puerto Rico. Hundred thirty-eight patients were randomised to receive anthracycline (fluorouracil, epirubicin and cyclophosphamide (FEC)) every three weeks for 12 weeks followed by combination of paclitaxel and trastuzumab (sequential arm), while another 142 patients received paclitaxel with trastuzumab weekly for 12 weeks followed by FEC every three weeks with weekly trastuzumab for 12 weeks (concurrent arm). The treatment between the two groups did not differ significantly in DFS with HR 1.02 (95% CI 0.56 to 1.83).^{27, level II-1}

Trastuzumab and Chemotherapy versus Lapatinib and Chemotherapy

a) Combination chemotherapy (with or without anthracyclines)

GeparQuinto trial was conducted in 2018 reported disease-free survival rates did not differ significantly between patients treated with trastuzumab and chemotherapy (with anthracyclines) and lapatinib and chemotherapy (with anthracyclines) with HR 1.04 (95% CI 0.73 to 1.49).^{28, level II-1}

Trastuzumab Biosimilar and Chemotherapy versus Trastuzumab and Chemotherapy

a) Combination chemotherapy (with or without anthracyclines)

In the RCT conducted by Stebbing et al. in 2021, they reported disease-free survival in their secondary analysis of NCT 02162667 trial and found it was similar between trastuzumab biosimilar (CT-P6: 0.83, 95% CI 0.77–0.87) and trastuzumab (0.83, 95% CI 0.76–0.88) in terms of the three-year rate.^{25, level II-1} The estimated hazard ratio was 1.23 (95% CI 0.78 to 1.93) for trastuzumab biosimilar (CT-P6) and chemotherapy (docetaxel with anthracyclines) versus trastuzumab reference and chemotherapy (docetaxel with anthracyclines).^{25, level}

II-1

6.3.4 Number of Patients Had Progressed/Died

One RCT reported on this outcome that involved pertuzumab and trastuzumab.

Combination of Pertuzumab, Trastuzumab and Chemotherapy versus Trastuzumab and Chemotherapy

a) *Mono chemotherapy*

Gianni et al in their NeoSphere trial, found at clinical cut off five-year analysis, the number of patients who had progressed or died were 16% in patients who received combination of pertuzumab, trastuzumab and docetaxel (n=17), 18% in the group receiving of trastuzumab and docetaxel (n=19), 25% in the group on pertuzumab and trastuzumab (n=24) and 25% in the group on pertuzumab plus docetaxel (n=27).^{24, level II-1}.

6.3.5 Event-free survival (EFS)

Two RCTs reported on this outcome that involved lapatinib and trastuzumab

Combination of Lapatinib, Trastuzumab and Chemotherapy versus Lapatinib and Chemotherapy / Trastuzumab and Chemotherapy

a) *Mono chemotherapy*

Huober et al (2019) reported the updated results of the 455 patients enrolled in the NeoALTTO trial from 2008 to 2010.^{29, level II-1} The six-year EFS rates were highest in dual-targeted group, lapatinib, trastuzumab and chemotherapy (paclitaxel) (74%) followed by lapatinib and paclitaxel (67%) and trastuzumab and paclitaxel (67%). The estimated hazard ratio for group who received combination of lapatinib, paclitaxel versus trastuzumab, paclitaxel was not statistically significant [0.98% (95% CI 0.64 to 1.51, p=0.56)] than the group who received combination of lapatinib, trastuzumab and paclitaxel versus trastuzumab and paclitaxel [0.81% (95% CI 0.52 to 1.26, p=0.35)].^{29, level II-1}

Combination of Trastuzumab and Chemotherapy (comparison between intravenous or subcutaneous trastuzumab)

a) *Combination chemotherapy (with or without anthracyclines)*

In the open label RCT (HannaH trial) conducted by Jackish et al., they reported associations between pCR and event-free survival involving 596 HER2-positive early breast cancer patients.^{30, level II-1} Patients were randomised to receive intravenous (IV) or subcutaneous (SC) trastuzumab and combination of chemotherapy (docetaxel with anthracyclines). They used Cox regression to assess associations between pCR and EFS while EFS rates per subgroup were estimated using the Kaplan Meier method. They found that there was





no significant difference in the 3-year event-free survival between IV and SC groups (73% versus 76%) with HR 0.95 (95% CI 0.69 to 1.3). In their exploratory analyses, they found that patients who achieved total pCR had more than 60% reduction in the risk of an EFS event compared with those who did not with HR 0.38 (95% CI 0.22 to 0.65) in the SC arm and HR 0.32 (95% CI 0.18 to 0.60) in the IV arm.^{30, level II-1}

6.3.6 Overall survival/death

Four RCTs reported on this outcome that involved lapatinib, trastuzumab and trastuzumab biosimilar

Combination of Lapatinib, Trastuzumab and Chemotherapy versus Combination of Lapatinib and Chemotherapy / Trastuzumab and Chemotherapy

a) Mono chemotherapy

In RCT conducted by Fernandez-Martinez et al. (CALGB 40601 Alliance), a median follow-up of seven years and a comprehensive exploratory analysis testing on overall survival found patients treated with combination of lapatinib, trastuzumab and chemotherapy (paclitaxel) group had a significant improvement in overall survival compared with trastuzumab and chemotherapy (paclitaxel) [HR 0.34 (95% CI 0.12 to 0.94) p=0.037].^{26, level II-1} The seven years OS rates was higher in lapatinib and trastuzumab and paclitaxel (96%) followed by combination of trastuzumab and paclitaxel (88%) and combination of lapatinib and paclitaxel (84%) with corresponding four death (3.4%) occurred in combination of lapatinib, trastuzumab and paclitaxel, nine death (13.4%) occurred in combination of lapatinib and paclitaxel and 14 deaths (11.7%) occurred in trastuzumab plus paclitaxel.^{26, level II-1}

Another RCT conducted by Huober et al in 2019, where they did the secondary analysis in the updated NeoALTTO trial found the six-year overall survival rates were highest (85%) in patients treated with combination of lapatinib, trastuzumab and chemotherapy (paclitaxel) followed by combination of lapatinib and paclitaxel (82%) group and combination of trastuzumab and paclitaxel (79%) group.^{29, level II-1} However the differences were not statistically significant in combination of lapatinib, trastuzumab and paclitaxel group as compared with combination of trastuzumab and paclitaxel group [HR 0.72% (95% CI 0.41 to 1.27), p=0.26] and when combination of lapatinib and paclitaxel compared with combination of trastuzumab and paclitaxel group [HR 0.85% (95% CI 0.49 to 1.46) p=0.56].^{29, level II-1}

Combination of Trastuzumab and Chemotherapy versus Chemotherapy only

a) *Combination chemotherapy (with or without anthracyclines)*

Buzdar et al. (2019), in their RCT analysed the six-year overall survival between sequential arm and concurrent arm of trastuzumab and chemotherapy group (with anthracyclines) in patients with operable HER2-positive breast cancer.^{27, level II-1} They found that overall survival did not differ significantly between the two treatment arms [HR 1.17 (95% CI 0.48 to 2.88)].^{27, level II-1}

Combination of Trastuzumab Biosimilar and Chemotherapy versus Combination of Trastuzumab and Chemotherapy

a) *Combination chemotherapy (with or without anthracyclines)*

Stebbing et al. (2021) in an RCT found the estimated three-year overall survival rate was not statistically significant difference between combination of trastuzumab biosimilar (CT-P6) and chemotherapy and chemotherapy only with HR of 1.10 (95% CI 0.57 to 2.13).^{25, level II-1}

6.3.7 Breast Conservation

Sheikh et al. in their analysis, found that breast conservation was possible in 57 (43.51%) patients in total and 51.56% (n=33) in patients getting combination of trastuzumab and chemotherapy preoperatively as compared to 35.82% (n=24) in patients who received chemotherapy alone (p-value= 0.69, not statistically significant, but still a considerable number of patients had a less extensive surgery).^{23, level II-2}

6.3.8 Subtype analysis: Hormone receptor-positive and hormone receptor-negative

Gianni et al. (2012) did an advance analysis comparing hormone receptor-positive and hormone receptor-negative in their NeoSphere trial.^{19, level II-1} Pathological complete response (pCR) were noted higher in patients with hormone receptor-negative tumours [36 of 57 (63.2%)] than in patients with hormone receptor-positive who received combination of pertuzumab, trastuzumab and chemotherapy [13/50 (26%)]. In the group who received pertuzumab and trastuzumab only, 15 of 55 (27.3%) patients with hormone receptor-negative tumours had complete eradication of the tumour in the breast, compared to 3 of 51 (5.9%) patients in patients with hormone receptor-positive tumours (Table 8).^{19, level II-}





Intervention	Hormone receptor-positive	Hormone receptor-negative
Pertuzumab + trastuzumab + docetaxel	13/50 (26.0%) (95% CI 14.6-40.3)	36/57 (63.2%) (95% CI 49.3-75.6)
Trastuzumab + docetaxel	10/50 (20.0%) (95% CI 10.0-33.7)	21/57 (36.8%) (95% CI 24.4-50.7)
Pertuzumab + trastuzumab	3/51 (5.9%) (95% CI 1.2-16.2)	15/55 (27.3%) (95% CI 16.1-41.0)
Pertuzumab + docetaxel	8/46 (17.4%) (95% CI 7.8-31.4)	15/50 (30%) (95% CI 17.9-44.6)

Table 8. Pathological complete responses according to subtype hormone analysis¹⁹

Murthy et al. (2018) in their observational study, when they did a univariate analysis within the pertuzumab and trastuzumab group, they found the pCR rates were lower for hormone receptor-positive compared to hormone receptor-negative (51% versus 71%) (OR 0.42; 95% CI 0.22 to 0.81; $p=0.0082$).²¹, level II-2

Huober et al. (2019) did a further analysis and found that the pCR rates were higher in all three arms of the NeoALTTO trial for the hormone receptor-negative compared to those in the hormone receptor-positive cohort.²⁹, level II-1 The survival advantage of achieving a pCR was limited to the hormone receptor-negative cohort (HR 0.35, 95% CI 0.16 to 0.70; $p=0.005$). In the hormone receptor-negative cohort, the six-year EFS rate was higher in the combination of lapatinib, trastuzumab and paclitaxel group (74%) than in the combination of lapatinib and paclitaxel group (61%) and the combination of trastuzumab and paclitaxel (63%). However the differences between the groups was not statistically significant (Lapatinib, trastuzumab and paclitaxel versus trastuzumab and paclitaxel: HR 0.81 95% CI 0.44 to 1.51; $p=0.52$); lapatinib and paclitaxel versus trastuzumab and paclitaxel: HR 1.09 95% CI 0.61 to 1.95; $p=0.76$). There were also no significant differences across the three treatment groups when OS was analysed by the hormone receptor status (Lapatinib and trastuzumab versus trastuzumab and paclitaxel: HR 0.72 95% CI 0.41 to 1.27; $p=0.26$); lapatinib and paclitaxel versus trastuzumab and paclitaxel: HR 0.85 95% CI 0.49 to 1.46; $p=0.56$).²⁹, level II-1

In an analysis by Untch et al. (2018), patients who achieved pCR had statistically significantly better DFS and OS ($p=0.002$ and 0.002 , respectively) compared with those without pCR in patient with hormone receptor-negative.²⁸, level II-1 No statistically significant difference in all treatment arms were observed in patients with hormone receptor-positive tumours who achieved pCR compared with those without pCR. No difference was observed in all treatment arms for outcome DFS and DDFS with hormone receptor-positive patients. However, OS in patients treated with combination of lapatinib and trastuzumab was significantly better when compared with those treated with trastuzumab alone (HR 0.32, 95% CI 0.12 to 0.87; test for interaction, $p=0.033$).²⁸, level II-1

Jackish et al. (2016) in HannaH trial, did an exploratory analysis and found there was no significant difference in EFS among both hormone receptor-positive (HR 0.86, 95% CI 0.54 to 1.38) and hormone receptor-negative (HR 1.04, 95%

CI 0.68 to 1.59). In addition, three-year EFS rates were higher in hormone receptor-positive disease compared to hormone receptor-negative disease/unknown oestrogen receptor status for both subcutaneous and intravenous trastuzumab: 79% and 73% in the subcutaneous arm and 76% and 71% in the intravenous arm.^{30, level II-1}

6.4 SAFETY

The use of targeted therapies has been approved by U.S. Food and Drug Administration (FDA) for the following indications:³¹

- Herceptin (chemical name: trastuzumab) was approved by US FDA to treat HER2-positive breast cancer that is either early-stage or advanced-stage/metastatic:
 - to treat metastatic HER2-positive breast cancer to stop the cancer from growing
 - to treat earlier stages of HER2-positive breast cancer, either as part of a regimen with chemotherapy or alone after a chemotherapy regimen that includes an anthracycline, to reduce the risk of the breast cancer coming back (recurrence)
 - in combination with pertuzumab and docetaxel before surgery to treat HER2-positive, early-stage (the cancer must be larger than 2 cm or cancer must be in the lymph nodes), inflammatory, or locally advanced-stage breast cancer with a high risk of metastasizing or becoming fatal
 - in combination with Perjeta and chemotherapy after surgery to treat HER2-positive, early-stage breast cancer with a high risk of recurrence
- Perjeta (chemical name: pertuzumab) has been approved by FDA on September 2013 for use in combination with trastuzumab and docetaxel (Taxotere) as neoadjuvant treatment of HER2-positive, locally advanced, inflammatory, or early-stage breast cancer patients.
- Seven biosimilars of trastuzumab (Herzuma, Hertraz, Zuhera, Ogivri, Ontruzant, Trazimera, Kanjinti) have been approved since December 2017 to treat HER2-overexpressed breast cancer. All biosimilars of trastuzumab have demonstrated efficacy and safety outcomes bioequivalent to those of the standard trastuzumab

Adverse events

The adverse events of HER2 targeted drugs are often mild, but some can be serious. The monoclonal antibodies can sometimes cause heart damage during or after treatment. This can lead to congestive heart failure. For most



(but not all) women, this effect lasts a short time and gets better when the drug is stopped. The risk of heart problems is higher when these drugs are given with certain chemo drugs that also can cause heart damage, such as doxorubicin (Adriamycin) and epirubicin (Ellence).⁶⁻⁷

A SR and NMA conducted by Zhang et al. (2021) found that pertuzumab is associated with high incidence of neutropaenia either with or without anthracycline. In addition, lapatinib lead to a high incidence of diarrhoea in nearly 30% of patients (Table 8).^{18, level I}

Interventions	neutropaenia	diarrhoea	hepatotoxicity	febrile neutropaenia
Pzmb + tzmb + comb chemo (A)	53.68%	8.99%	3.81%	11.72%
Pzmb + tzmb + comb chemo (without A)	44.10%	15.28%	3.29%	9.48%
Pzmb + tzmb + mono chemo	40.49%	5.61%	NA	8.41%
Lpnb + tzmb + comb chemo (A)	23.01%	26.1%	4.41%	6.19%
Lpnb+ tzmb+ comb chemo (without A)	13.79%	27.59%	NA	NA
Lpnb + tzmb + mono chemo	8.55%	21.05%	10.53%	NA
Pzmb + tzmb	0.93%	NA	NA Cardiac disorder, LEVF decreased ≥10% : 0.93%	NA
Biosimilar + comb chemo (A)	4.40%	NA	NA	NA

Notes: A= anthracyclines, Lpnb= lapatinib, Tzmb=trastuzumab, Pzmb=pertuzumab, comb=combination

Table 9. Most frequent WHO grade 3-5 adverse events in each experimental arm in SR with NMA by Zhang et al.¹⁸

Another SR with NMA conducted by Nakashoji et al. (2018) evaluated the number of patients who had grade 3 or 4 adverse events.^{22, level I} The adverse events were graded according to the National Cancer Institute Common Terminology Criteria (NCI-CTC) version 4.0. Diarrhoea was reported in 10 studies, neutropaenia was reported in 11 studies of which 10 reported as grade 3 and 4 events, cardiac events were reported in 12 studies, skin disorder was reported in 10 studies and all of them reported as grade 3 and 4 events. They found that most adverse events occurred with chemotherapy and lapatinib. Lapatinib-containing treatment arms showed significantly less treatment completion with more incidents of diarrhoea and skin disorders compared with trastuzumab plus chemotherapy. However, combination of trastuzumab plus pertuzumab had significantly lower incidents of neutropaenia compared with the chemotherapy-containing arms. The incidence of cardiac events did not show any statistically significant differences between all treatment arms.^{22, level I}



They estimated the value of surface under the cumulative ranking (SUCRA) line for each treatment arm (which was a simple numerical summary to supplement the graphical display of cumulative ranking) (Table 9).^{22, level I}

Diarrhoea	Neutropaenia	Cardiac event	Skin disorders
Lapatinib + trastuzumab + chemotherapy = 0.93	Lapatinib + chemotherapy = 0.85	Pertuzumab + trastuzumab + chemotherapy = 0.84	Lapatinib + chemotherapy = 0.96
Lapatinib + chemotherapy = 0.8	Lapatinib + trastuzumab + chemotherapy = 0.73	Trastuzumab + chemotherapy = 0.66	Lapatinib + trastuzumab + chemotherapy = 0.81
Chemotherapy = 0.71	Pertuzumab + chemotherapy = 0.58	-	-

Table 10. Rank according to the types of adverse events for all interventions²²

Combination of Pertuzumab, Trastuzumab and Chemotherapy versus Trastuzumab and Chemotherapy

a) Mono chemotherapy

Two RCTs (Gianni, 2016; Shao, 2020) and one cohort study (Hussain, 2018) reported the data.^{20,24,32} However not all adverse events data were provided from these three studies. Pooled results from our meta-analysis for combination of pertuzumab, trastuzumab and chemotherapy (docetaxel) showed a significantly higher incidence of diarrhoea in patients treated with combination of pertuzumab, trastuzumab and docetaxel compared to patients treated with combination of trastuzumab and docetaxel with OR 2.90 (95% CI 1.73 to 4.88). There were no significant difference in total number of serious adverse events with OR 1.31 (95% CI 0.80 to 2.13), neutropaenia OR 0.93 (0.65, 1.33), febrile neutropaenia OR 1.23 (95% CI 0.51 to 2.97), and leucopaenia OR 0.43 (0.16, 1.18) (Figure 6).^{20,24,32} There was no significant difference in the adverse events when compared to combination of trastuzumab and chemotherapy except incidence of diarrhoea.

Combination of Lapatinib, Trastuzumab and Chemotherapy versus Combination of Lapatinib and Chemotherapy or Trastuzumab and Chemotherapy

In a review by Nakashoji et al., they found that combination of lapatinib, trastuzumab and chemotherapy had significantly higher incidents of diarrhoea [OR 14.36 (95% CI 7.84 to 26.32)] and skin disorders [OR 4.11 (95% CI 1.78 to 9.51)] when compared with combination of trastuzumab and chemotherapy.^{22, level I}

^I There was no statistically significant difference in incidence of neutropaenia and cardiac events between the two groups: combination of lapatinib, trastuzumab





and chemotherapy versus combination of trastuzumab and chemotherapy [neutropaenia; OR 1.37 (95% CI 0.89 to 2.10), cardiac events; OR 1.31 (95% CI 0.33 to 5.26)].^{22, level I}

Comparing combination of lapatinib and chemotherapy versus combination of lapatinib, trastuzumab and chemotherapy, they found no significant difference between these two groups in the occurrence of diarrhoea OR 1.23 (95% CI 0.85 to 1.78), neutropaenia: OR 0.80 (95% CI 0.54 to 1.21), cardiac events: OR 0.94 (95% CI 0.22 to 3.99) and skin disorder: OR 0.76 (95% CI 0.44 to 1.30).

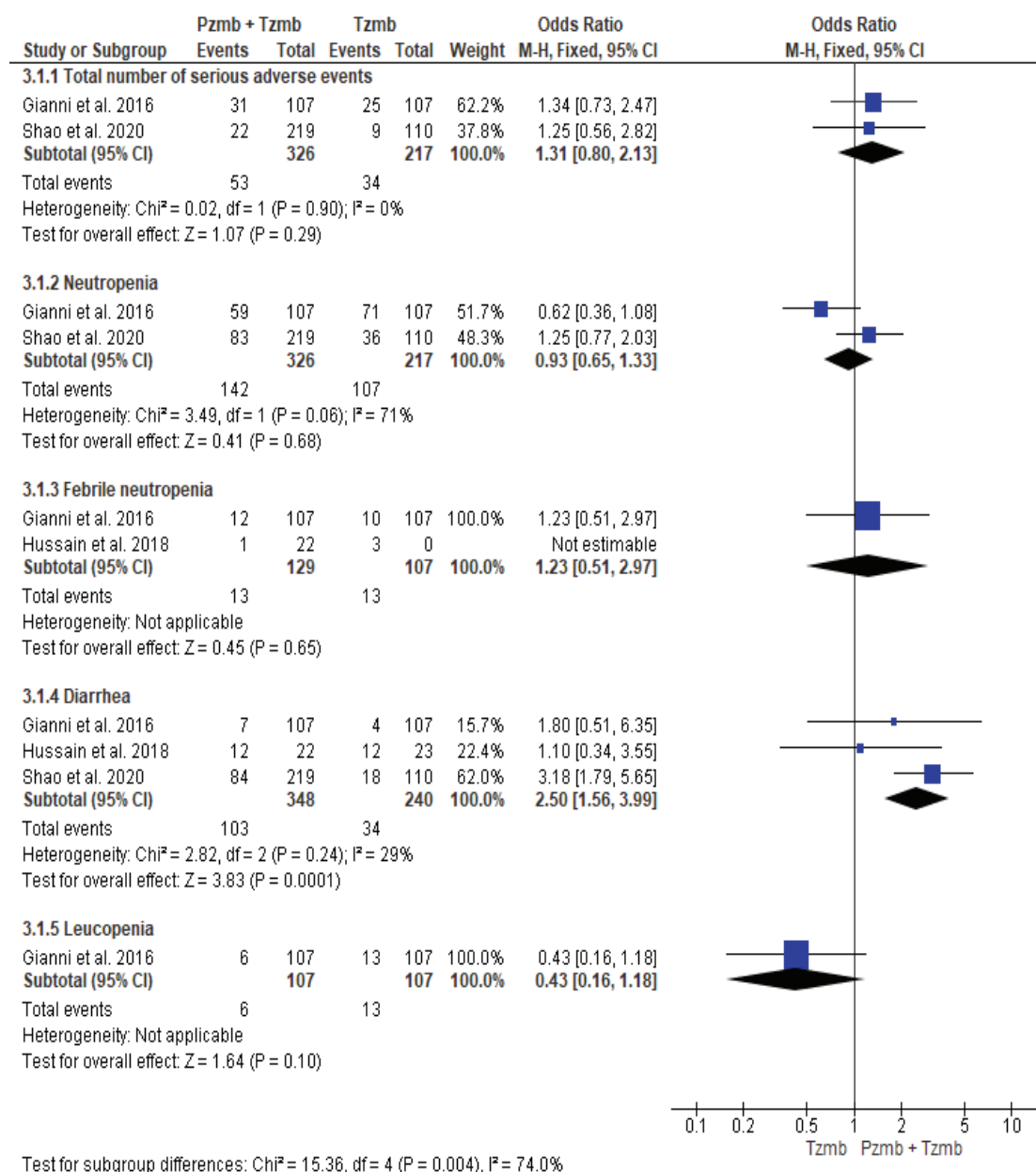


Figure 6. Combination of Pertuzumab, Trastuzumab and Chemotherapy versus Trastuzumab and Chemotherapy; Outcome: Adverse events

Combination of Trastuzumab and Chemotherapy versus Chemotherapy only

SR with NMA conducted by Nakashoji et al. published in 2018 included five studies comparing combination of trastuzumab and chemotherapy group with chemotherapy alone found that there were no significant difference in all main adverse events that include diarrhoea (OR 0.24 95% CI 0.03 to 2.17), neutropaenia (OR 1.28 95% CI 0.33 to 4.29), cardiac events (OR 1.33 95% CI 0.70 to 2.53) and skin disorder (OR 0.55 95% CI 0.18 to 1.72).^{22, level I}

In a cohort study conducted by Sheikh et al., they found that by adding trastuzumab, there were no major differences in the toxicity profiles of both groups. A major concern with the addition of trastuzumab was the drop in ejection fraction. However, they found that the incident was almost equal in both groups with no major differences. No patient developed symptomatic heart failure and none had to stop trastuzumab before completing the planned therapy.^{23, level II-2}

Combination of Trastuzumab and Chemotherapy versus Combination of Lapatinib and Chemotherapy

Nakashoji et al. in their meta-analysis comparing combination of lapatinib and chemotherapy with combination of trastuzumab and chemotherapy found there was a significant increase in the occurrence of diarrhoea (OR 8.56 95% CI 5.33 to 13.75) and skin disorder, OR 7.04 (95% CI 3.35 to 14.80) in lapatinib containing arm. However, there was no significant difference in terms of neutropaenia (OR 1.59 95% CI 0.87 to 2.91) and cardiac events, OR 0.78 (95% CI 0.52 to 1.15).^{22, level I}

Combination of Trastuzumab Biosimilar and Chemotherapy versus Trastuzumab and Chemotherapy

In SR with NMA conducted by Zhang et al., they included one biosimilar study that compared combination of trastuzumab biosimilar (CT-P6) and chemotherapy (with anthracyclines) with combination of trastuzumab and chemotherapy (with anthracyclines) (Stebbing et al).^{18, level I} According to the WHO grade 3-5 side effects, the occurrence of neutropaenia in biosimilar group was 4.4% (Table 9). In detail analysis by Stebbing et al., they found that adverse events were comparable between groups for cardiac disorders [CT-P6: 22 (8.1%) patients; trastuzumab: 24 (8.6%) patients), febrile neutropaenia [four (1%) versus one (<1%)] and neutropaenia [one (<1%) versus two (1%)]. Grade 3 or worse treatment-related adverse events occurred in 17 of 271 patients (6%) in the CT-P6 group versus 23 of 278 patients (8%) in the reference trastuzumab group; the most frequently reported adverse event was neutropaenia; ten (4%) versus 14 (5%), respectively. In general, they found that CT-P6 was well tolerated, with comparable safety and immunogenicity to trastuzumab.^{24, level I}



6.5 ECONOMIC IMPLICATION/COST-EFFECTIVENESS

Four articles related to the cost implication of targeted therapies in combination with neoadjuvant chemotherapy for the treatments of HER2-positive breast cancer were included in this review; two cost-effectiveness analysis (Hassett et al. and Kunst et al.), one single technology appraisal by NICE (Squires et al.) and one cost-minimisation analysis (Lee et al.).

Hassett et al. (2020) in a cost-effectiveness analysis conducted in United State of America (USA) from a payer's perspective, developed a decision-analytic model for patients with stage II-III HER2-positive cancer that incorporated utilities based on toxicity and recurrence.³² They separately modelled hormone receptor-negative (HR-) and positive (HR+) disease and calculated quality-adjusted life years (QALYs) and costs through five years. Simulated patients received one of the following neoadjuvant treatments: three regimens (TCHP: docetaxel, carboplatin, trastuzumab, pertuzumab; THP + AC: taxol, trastuzumab, pertuzumab then doxorubicin and cyclophosphamide; THP: taxol, trastuzumab, pertuzumab) and two de-escalated regimens (TH: taxol plus trastuzumab; TDM-1 plus pertuzumab) followed by adjuvant treatment based on pathologic response.³² Among the treatment strategies, mono chemotherapy (THP) was more effective and less costly compared with combination chemotherapy (TCHP or THP + AC) for both hormone receptor-positive and hormone receptor-negative. For each treatment strategy, HR- cancers had slightly higher QALYs relative to their HR+ because of the greater likelihood of pCR with neoadjuvant therapy. When de-escalated strategies were included, combination of TH became the most cost-effective option. For HR-negative cancer, combination of TH had 0.003 fewer QALYs than combination of THP but was less costly by \$55,831, resulting in an incremental cost-effectiveness ratio of over US \$18million/QALY for THP, above any threshold. For HR-positive cancer, treatment with TH dominated the THP strategy. Sensitivity analysis demonstrated that adding of adjuvant TCHP in patients who received neoadjuvant TH but did not achieve pCR has increased the costs and decreased the QALYs of the neoadjuvant TH strategy with US \$198 688 and 4.66 QALYs for HR-negative cancers and US \$234 203 and 4.58 QALYs for HR-positive cancers.³²

Kunst et al. (2020) performed a cost-effectiveness analysis with selection of various neoadjuvant followed by adjuvant treatment strategies for patients with HER2-positive breast cancer from a health care payer perspective in the USA.³³ They developed a decision-analytic model and simulated patients receiving five different neoadjuvant followed by adjuvant treatment strategies (Table 11). The decision tree included five different treatment strategies and distributed patients into one of the Markov model with four main health states that include recurrence free, local recurrence, distant recurrence, and death which simulated lifetime costs and quality-adjusted life-years (QALYs) associated with neoadjuvant-adjuvant regimen combinations by applying 3% discounting rate.³⁴



Strategy	Neoadjuvant treatment	Stage	Adjuvant treatment
1	DDAC/THP	residual pCR	Trastuzumab Trastuzumab
2	DDAC/THP	residual pCR	TDM1 Trastuzumab
3	THP	residual pCR	DDAC/TDM1 Trastuzumab
4	HP	residual pCR	DDAC/THP + TDM1 Trastuzumab
5	TCHP	residual pCR	TDM1 Trastuzumab

Notes: DDAC; dose-dense anthracycline/cyclophosphamide, T: paclitaxel, H: trastuzumab, P: pertuzumab

They found that strategy 3 was associated with the highest health benefits (10.73 QALYs) and lowest costs (US \$415 833) and dominated all other strategies. Strategy 5 was the next highest health benefits of 10.66 QALYs and strategy 4 was associated with the third highest health benefits of 10.31 QALYs. However, strategy 5 (US \$489 449) and strategy 4 (US \$518 859) were associated with increased costs compared with strategy 3. Strategy 1 was associated with the least health benefits (9.67 QALYs) and the third lowest costs (US \$479 226). Strategy 2 was associated with the second lowest health benefits (10.22 QALYs) and the second lowest costs (US \$452 034).³⁴

Squires et al. conducted a review on clinical and cost-effectiveness data submitted by manufacturer as part of NICE Single Technology Appraisal Perspective in 2018. The clinical data submitted by company that were based on a phase II, randomised, open-label, active controlled study (NeoSphere trial).³⁵ They also did a cohort-level state transition approach based on six health states which include event free, locoregional recurrence, remission, metastatic not progressed, metastatic progressed and death. The assessment was from NHS and Personal Social Services perspectives with costs and health outcomes were discounted at 3.5% per year. The probabilistic incremental cost-effectiveness ratio was estimated to be £20,104 per quality-adjusted life-year gained for pertuzumab alongside trastuzumab and docetaxel compared with trastuzumab and docetaxel, which was revised to £21,869 per quality-adjusted life-year gained following the clarification process. The Evidence Review Group corrected an error in the digitisation of the survivor functions and modified the clinically inappropriate assumption that recurrence is zero after seven years. The Evidence Review Group's (ERG) probabilistic base case was £23,962 per quality-adjusted life-year gained. Similarly, the ERG's deterministic base-case ICER is estimated to be £23,467 per QALY gained.³⁵

Lee et al. (2016) conducted a cost-minimisation analysis to investigate cost-savings of subcutaneous (SC) compared to intravenous (IV) trastuzumab in a middle-income Asian country.³⁵ They performed a local adaptation of a mathematical model developed by Roche, Switzerland, the Herceptin cost-





minimisation model (version 1.2). The model was adapted with adjustments for differences in practices and costs in the Ministry of Health. The costs incurred per patient for the full one-year course of treatment with IV and SC trastuzumab were taken into consideration. This model was previously utilised in two other cost-minimisation analysis of SC trastuzumab in England and Scotland. They obtained the data used to populate the CMA model from various sources including official statistics, price lists and estimates from 22 healthcare personnel at four MOH hospitals. Additionally, information on treatment practices, drugs and consumables were obtained from four participating MOH hospitals, namely: Penang General Hospital, Sarawak General Hospital, Likas Hospital and Sultan Ismail Hospital. All four hospitals were the main public sector cancer treatment centres in their respective states with oncology departments and in-house pharmacy units for cytotoxic drug reconstitution (CDR).³⁶

The analysis was performed from two perspectives (MOH and societal). Analysis for MOH which include these cost categories: healthcare professional time's cost, drug cost and consumables cost, while analysis from societal perspectives included the same costs identified in the MOH perspective with addition of patient time costs which were measured by the human capital approach. The SC trastuzumab treatment resulted in cost savings to the MOH of MYR 7561 per patient compared to IV trastuzumab treatment. From the societal perspective, the cost of IV and SC trastuzumab was MYR 87627 and MYR 79806 per patient respectively, with patient time costs making up 0.5% of IV cost and 0.3% of SC cost. The used of SC trastuzumab generated a cost savings to society of MYR 7820 per patient.³⁶

6.6 ORGANISATIONAL

Guidelines / Recommendations

Neoadjuvant therapy is the treatment of choice for patients with inflammatory breast cancer or those with unresectable or locally advanced disease at presentation whose disease may be rendered resectable with neoadjuvant treatment. Nevertheless, guidelines and recommendation by several organisations have suggested the option of targeted therapies in combination with chemotherapy in this population.

The American Society of Clinical Oncology Guideline (ASCO) in 2021 developed recommendations concerning optimal neoadjuvant therapy for invasive breast cancer including chemotherapy and targeted therapies as below: ³⁷

“Neoadjuvant systemic therapy may be offered to reduce the extent of surgery (BCS and axillary lymph node dissection). Chemotherapy in combination with targeted therapy as a neoadjuvant therapy may be offered for HR-positive disease. The choice of therapy with the use of anthracycline and taxane or non-anthracycline-based regimen with trastuzumab was recommended to patients with node-positive or high-risk node-negative, HER2-positive disease. Pertuzumab may also be used with trastuzumab in the neoadjuvant setting.” ³⁷

National Comprehensive Cancer Network (NCCN) in their clinical guideline

published in 2020 recommended the choices of HER2-targeted therapy that treats HER2-positive breast cancer include HER2 antibodies such as trastuzumab and pertuzumab, HER2 inhibitors such as lapatinib and neratinib and HER2 conjugates such as ado-trastuzumab emtansine and fam-trastuzumab deruxtecan-nxki.³⁸ The preferred option for this population were doxorubicin and cyclophosphamide followed by paclitaxel with trastuzumab, doxorubicin and cyclophosphamide followed by paclitaxel with trastuzumab and pertuzumab, paclitaxel with trastuzumab, combination of docetaxel, carboplatin and trastuzumab, combination of docetaxel, carboplatin, trastuzumab and pertuzumab. However, if there is no residual disease after preoperative therapy, it is preferable to complete HER-2 targeted therapy with trastuzumab alone or with pertuzumab up to one year. For patients with residual disease after preoperative therapy, ado-trastuzumab emtansine alone is recommended, but if it is discontinued due to toxicity, trastuzumab alone or with pertuzumab is recommended to complete the treatment up to one year.³⁸

European Society for Medical Oncology (ESMO) guideline on metastatic breast cancer in 2020 stated that anti-HER2 therapy should be offered early as first line therapy to all patients with HER2-positive advanced breast cancer, except in the presence of contraindications to the use of such therapy.³⁹ The choice of the anti-HER2 agent will depend on country-specific availability, the specific anti-HER2 therapy previously administered and the relapse-free interval. The optimal sequence of all available anti-HER2 therapies is currently unknown. Combination of chemotherapy plus trastuzumab is superior to combination of chemotherapy and lapatinib in terms of PFS and OS in the first line setting for HER2-positive advanced breast cancer previously treated or untreated with trastuzumab. However, for the standard first line therapy for patients previously untreated with anti-HER2 therapy was the combination of chemotherapy plus trastuzumab plus pertuzumab because it has proven to be superior to combination of chemotherapy and trastuzumab in terms of OS for this population.³⁹

Malaysian Clinical Practice Guidelines (CPG) on Management of Breast Cancer (third edition) published in 2019 recommended combination of chemotherapy and trastuzumab-based therapy to patients with HER2-positive breast cancer who require neoadjuvant therapy.⁶ However, addition of pertuzumab as dual HER2 blockade may be considered in high risk patients.⁶

6.7 SOCIAL/ ETHICAL / LEGAL

A cross-sectional study by Pivot et al. conducted in France (PrefHer) to assess patient preference, healthcare professional satisfaction and safety data pooled from cohort 1 and also cohort 2, towards intravenous (IV) trastuzumab and subcutaneous (SC) trastuzumab where SC trastuzumab was delivered via hand-held syringe. Four hundred eighty eight patients were randomised to receive four adjuvant cycles of 600 mg fixed-dose SC trastuzumab (n=245) followed by four cycles of standard IV trastuzumab (n=243) or vice versa. The



primary endpoint was overall preference proportions for SC. or IV assessed by patient interviews in the evaluable intention to treat population.^{40, level II-3}

The analysis was done using two-sided test showed that SC trastuzumab was preferred by 415/467 patients 98.9%; 95% CI 85.7 to 91.6; $p < 0.0001$) compared to IV trastuzumab that was preferred by 45/467 patients (9.6%; 95% CI 7 to 13), while 7/467 indicated no preference (1.5%; 95% CI 1 to 3).^{40, level II-3}

The results were consistent in both study arms when SC changed to IV arm, 89.8% of patients (211/235, 95% CI 85.2–93.3) preferred SC, 8.9% (21/235, 95% CI 5.6–13.3) preferred IV, and 1.3% (3/235, 95% CI 0.3–3.7) had no preference; IV changed to SC arm, 87.9% of patients (204/232, 95% CI 83.0–91.8) preferred SC, 10.3% (24/232, 95% CI 6.7–15.0) preferred IV, and 1.7% (4/232, 95% CI 0.5–4.4) had no preference.^{40, level II-3}

The two main reasons that patients gave for preferring SC when asked in an open-ended question were that it saved time and that it resulted in less pain or discomfort or side effects. 60.6% of patient (283/467 patients) reported that SC was the least painful, where as 17.3% (81/467) preferred IV, 22.1% (103/467) reported no preference. They also reported that SC caused less bother from bruising [41.1% (192/467) versus 16.1% (75/467); 42.8% (200/467) reported no difference] and SC also cause less irritation to the injection site [33.0% (154/467) versus 14.6% (68/467); 52.5% (245/467) reported no difference].^{40, level II-3}

No evidence retrieved on ethical and legal issues.



7.0 ECONOMIC EVALUATION

7.1 OBJECTIVE

The general objective of this economic evaluation was to assess the cost-effectiveness of additional targeted therapy in the neoadjuvant treatment of high risk early HER2-positive breast cancer patients.

The specific objective was to calculate the incremental cost-effectiveness ratio (ICER) between single and dual targeted therapy (Trastuzumab and Pertuzumab/ Trastuzumab respectively) with standard neoadjuvant chemotherapy for early HER2-positive breast cancer patients with high risk of recurrence.

7.2 METHODS

A hybrid model (Decision tree and Markov cohort simulation) was developed using Microsoft 365 Excel Workbook® to estimate the lifetime costs and quality adjusted life years (QALYs) of using targeted agents in combination with neoadjuvant chemotherapy in early HER2+ breast cancer. This type of model was chosen for its ability to extrapolate efficacy data from short-term clinical trials in early HER2+ breast cancer to longer term cost-effectiveness results.

Based on the systematic review and meta-analysis conducted in this HTA report earlier, the most efficacious with no substantial differences in tolerability was the trastuzumab (biosimilar) plus pertuzumab based dual targeted therapy with combination chemotherapy.^{18,20,22,41} Taking the current practice and availability of drugs available in MOHMF, the single targeted therapy assessed was the trastuzumab biosimilar and chemotherapy; whereas the dual targeted therapy assessed was the pertuzumab-trastuzumab combination. A hypothetical cohort of high-risk stage II/ III HER2-positive breast cancer patients were simulated in three strategies: -

- i) Standard six cycles of neoadjuvant chemotherapy
- ii) Addition of single targeted therapy with chemotherapy given concurrently 3-weekly intravenously - Trastuzumab biosimilar
- iii) Addition of dual targeted therapy with chemotherapy given concurrently 3-weekly intravenously- Pertuzumab/ Trastuzumab

Model Structure

The model structure was constructed with reference to other published studies^{33-34,44} and in consultation with an expert committee consisting of multidisciplinary experts namely clinical oncologists, breast and endocrine surgeons, pathologist, radiologist, health economists, public health physicians and pharmacists. This economic evaluation was designed from the Ministry of Health (MOH) perspective.

The simulated model clinical pathway is as follow:

- i. Patient cohort that enters the model are diagnosed with stage II node positive, stage III node negative HER2 positive breast cancer.
- ii. The patients receive six cycles of 3-weekly neoadjuvant therapy,
 - i. Chemotherapy only,
 - ii. Single targeted therapy [(IV Trastuzumab 8mg/kg loading



- dose (LD) then 6mg/kg maintenance dose (MD)) + (3 EC, 3 Doxetaxel)], or
- iii. Dual targeted therapy [(IV Trastuzumab 8mg/kg LD then 6mg/kg MD + IV Pertuzumab 840mg LD then 420mg MD) + (3 EC, 3 Doxetaxel)] before surgery.
 - iii. After surgery, all patients (regardless of those who achieve pathological complete response or had residual disease, all receive 9 cycles of 3-weekly IV Trastuzumab biosimilar 6mg/kg for 6 months.
 - iv. Patients are in the treated and disease-free state until they experience recurrence, metastasis, or death.
 - v. The health outcome and economic impact related to drug-induced complications were not included as the addition of targeted therapy to neoadjuvant chemotherapy did not increase the toxicities.^{20,22}
 - vi. Patients who had recurrence state can move to metastasis state or die.
 - vii. All patients undertook surveillance follow-up in surgical and oncology specialists clinic which was 3-monthly in the first 2 years, 6-monthly in year 3-5, and then annually thereafter.
 - viii. Long term effectiveness was measured by the Event free survival (EFS), Disease free survival (DFS) and Progression free survival (PFS).

The model decision analyses were projected to lifetime horizon (20 years) and the transition cycle was one year. Half cycle correction was performed to increase the applicability.

Model Estimation

The epidemiological and disease-related data were obtained from local sources of data whenever available, or literature review when local data was not available.

a. Effectiveness Data

The effectiveness parameters in this study were obtained from published clinical trials as shown in **Table 12**. The main outcomes from these clinical trials were the proportion of population who achieved pathological complete response. And later outcomes were the disease-free survival, event free survival, and progression free survival.



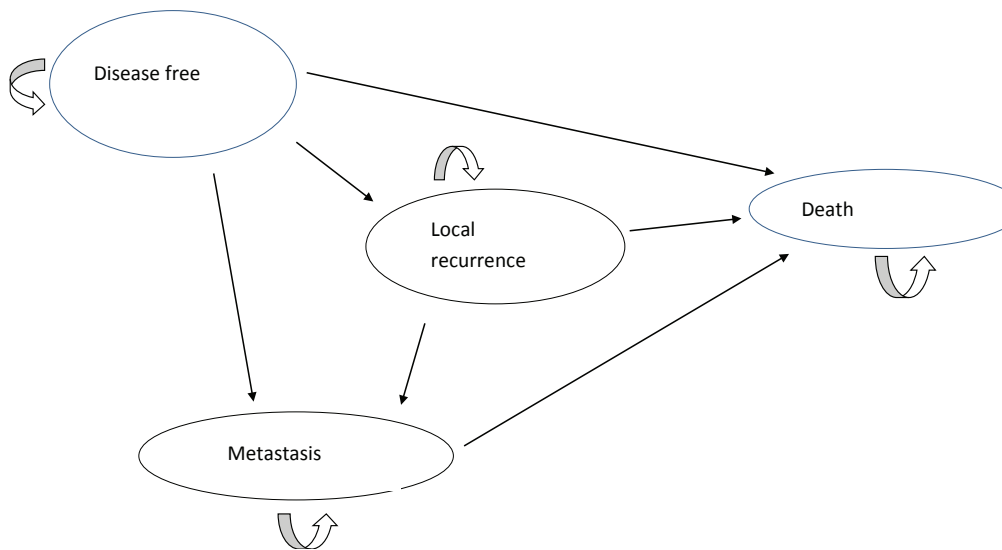


Figure 7. Decision Tree of three strategy arms of neoadjuvant therapy in high risk early HER2 breast cancer patients.

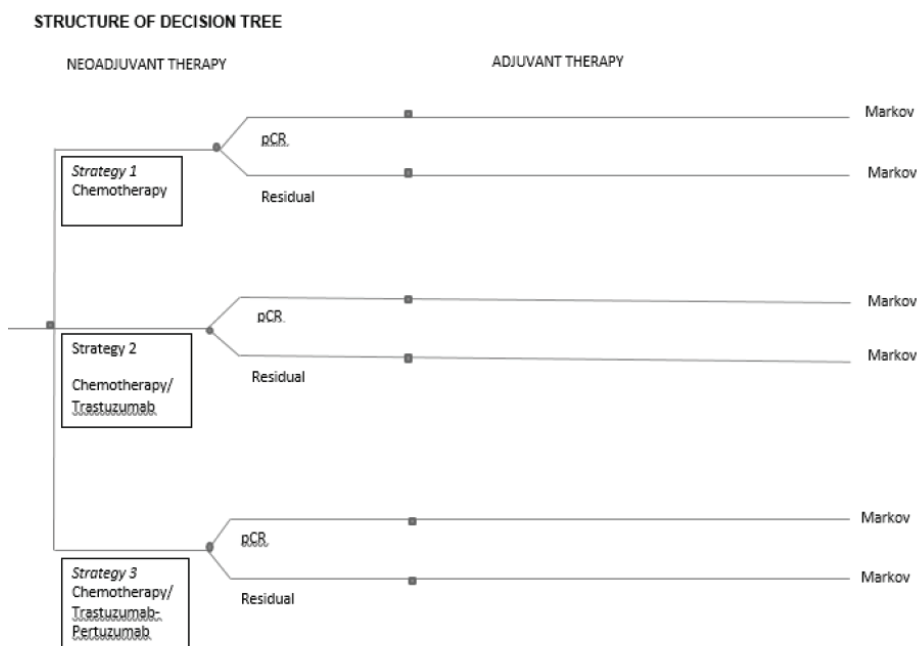


Figure 8. Markov Model of high risk early HER2 breast cancer patients after undergoing initial neoadjuvant systemic therapy, definitive surgery and adjuvant therapy.

Transitional probabilities among different states were derived primarily from the efficacy results of the phase 3 clinical trial comparing neoadjuvant chemotherapy and Neoadjuvant trastuzumab-chemotherapy and comparing Neoadjuvant pertuzumab-trastuzumab-chemotherapy and Neoadjuvant trastuzumab-chemotherapy.



Table 12. Effectiveness data

Parameter		Reference
Probability of death due to breast cancer	0.143	45,46
Annual rate of all-cause mortality for Malaysian	Age specific	47
Chemotherapy (CT)		
pCR rate (%)	19%	48
5 year EFS (pCR)	54.8%	49
5 year EFS (No pCR)	43.3%	49
CT + trastuzumab		
pCR rate (%)	29%	19
5 year DFS (pCR)	81% (95% CI: 72-88)	24
5 year PFS	81% (95% CI: 71-87)	35
5 Year EFS (No PCR)	57.5%	49
CT + Trastuzumab + Pertuzumab		
pCR rate (%)	45.8%	19
5 year DFS (pCR)	84% (95% CI: 72-91)	24
5 year PFS	86% (95% CI: 77-91)	35
5 year EFS (No PCR)	63% (95% CI 43-78)	50
Annual rate of recurrence (Year 5-9)	0.049	52
Annual rate of recurrence (Year 10-14)	0.035	52
Annual rate of recurrence (Year ≥ 15)	0.027	52

Notes: pCR: Pathological complete response; EFS: Event free survival; DFS: Disease free survival; PFS: Progression free survival

b. Utility Data

Health-related quality of life was incorporated into the economic evaluation using estimated utility values from the published economic evaluation and health related quality of life studies. The utility values from Buendia et al. were derived from published literature. Utilities for the recurrence health state represented in the model were obtained from a EQ-5D self classifier and direct time trade-off (TTO) exercise by Lidgren et al. All the utility values incorporated in the model were as shown in Table 13.



Health states	Base-case value	95%CI	Reference
Disease free	0.847	0.807 – 0.886	51
Recurrence	0.779	0.745 – 0.811	53
Metastasis	0.484	0.426 – 0.542	51

Table 13. Utility inputs

c. Resources and Cost Data

The costs used in this analysis were based on MOH Consumer Price Guide from Pharmaceutical Services Program, published literature using local data and personal communication with oncology pharmacists from MOH Hospitals. Direct medical costs included were cost of drugs, cost of procedures such as IV administration of drugs, cost of recurrence related management, cost of specialist clinic follow-ups and cost of metastasis related management. All costs are expressed in Malaysian Ringgit (MYR) for year 2020. All results were presented as incremental cost-effectiveness ratio (ICER).

Sensitivity Analysis

Deterministic sensitivity analysis was performed as one-way sensitivity analysis to determine which variables, when changed, in key model inputs would have a substantial impact on the model results. Input parameters were varied over a specified range or using values of reported upper and lower limit of 95% confidence or probability interval. Input parameters tested in sensitivity analyses were:

- Annual discounting rate (0-5%)
- Transition probability of recurrence among patients with dual targeted therapy (per cycle)
- Utility values for recurrence state
- Cost reduction of dual targeted therapy (range: 25% to 75%)
- Reduction of neoadjuvant therapy cycles (range: 4-5 cycles)

Assumptions

The following key assumptions were used in this model:

- i. All health states are mutually exclusive, the patient will not be other health states while in one health states.
- ii. Patients entered the model at average age of 50 years old. All patients in all arms underwent cardiac assessments before treatment. All patients underwent definitive surgery.
- iii. Patients could suffer only one recurrence; any subsequent recurrence were distant.



- iv. All deaths by breast cancer occur in women with distant recurrence.
- v. The additional targeted therapies did not incur additional toxicities which were significantly more than chemotherapy.^{20,22} All adverse events were fully reversible.
- vi. Chemotherapy, radiotherapy, endocrine therapy, and post-treatment follow-up protocol are assumed to be identical in all groups.
- vii. The cost and effectiveness of chemotherapy is assumed to be the same regardless of regime.
- viii. The probabilities of recurrence from year 5 onwards is attributed to the response to adjuvant trastuzumab.

7.3 RESULTS

Base-Case Analysis

The main outcome of the decision-analytic model were discounted costs and QALY associated with the two intervention strategies, estimated incremental costs and incremental QALYs, and then the calculated incremental cost-effectiveness ratios (ICERs).

The results of this hybrid model reflected the incremental cost-effectiveness ratios if HER2 targeted therapy (3-weekly trastuzumab and 3-weekly pertuzumab/trastuzumab) were used in addition of neoadjuvant chemotherapy in treatment of high risk early HER2 positive breast cancer patients. The base case results of the evaluated strategies were presented in **Table 14**. The mean total discounted cost and QALY per patient receiving 3-weekly trastuzumab biosimilar with neoadjuvant chemotherapy was MYR 36,006.33 and 6.43 respectively, while for 3-weekly Pertuzumab/Trastuzumab added to neoadjuvant chemotherapy was MYR 100,114.38 and 6.66. For standard neoadjuvant chemotherapy group in which no targeted therapy was given, the mean discounted cost and QALY was MYR 27,298.41 and 5.90 respectively.

The base case analysis indicated that the deterministic ICER for addition of 3-weekly trastuzumab to neoadjuvant chemotherapy was **MYR 16,471.59 per QALY gained**. Over the lifetime of the patient cohort (20 years), there was a cost increase of MYR 8,707.92 and a benefit of 0.53 QALYs per patient when 3-weekly trastuzumab biosimilar in addition to chemotherapy was given as neoadjuvant therapy in high risk early HER2 positive breast cancer patients compared with neoadjuvant chemotherapy alone. The ICER for addition of 3-weekly dual targeted agent (Pertuzumab/Trastuzumab) to neoadjuvant chemotherapy was MYR 72,815.97 with slightly higher incremental QALY gained of 0.76 compared with neoadjuvant chemotherapy alone.



Strategies	Total cost per patient	Total QALY per patient	Increment. Cost	Increment. QALY	ICER (compared to standard care)
Chemotherapy	MYR 27,298.41	5.90			Standard care
Addition of Single Targeted therapy	MYR 36,006.33	6.43	MYR 8,707.92	0.53	MYR 16,471.59
Addition of Dual Targeted Therapy	MYR 100,114.38	6.66	MYR 72,815.97	0.76	MYR 96,013.20

Table 14. Incremental cost-effectiveness ratios (ICERs) for base-case

Among the two intervention options, addition of single targeted therapy was the most cost-effective option with a much lower ICER compared to addition of dual targeted therapy. This estimate considers that the biosimilar drug and the originator drug is of the same effectiveness, and the current available option in Malaysian public hospitals.

Sensitivity Analysis

One-way sensitivity analysis was performed around key model parameters including discounting rate, clinical parameters, and utility parameters. Different feasible scenarios of neoadjuvant therapy where cost parameters for addition of dual targeted therapy may differ were also explored. The findings from the different scenario analyses were presented in **Table 15**. Results of the sensitivity analysis was plotted as tornado diagram (**Figure 9 and Figure 10**) to illustrate the differences in ICERs obtained given the range of parameter estimates were tested.

Table 15. Scenario analysis of key model parameters

a) Addition of Single targeted therapy

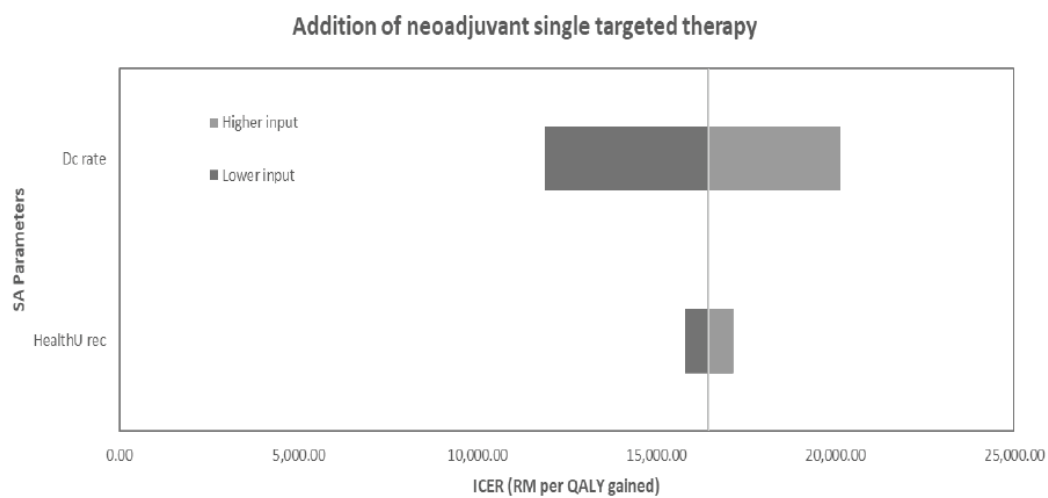
Parameters	Range	ICER of single targeted therapy
BASE CASE ICER		MYR 16,471.00
Number of neoadjuvant therapy cycles	4	MYR 10,796.90
	5	MYR 13,634.24





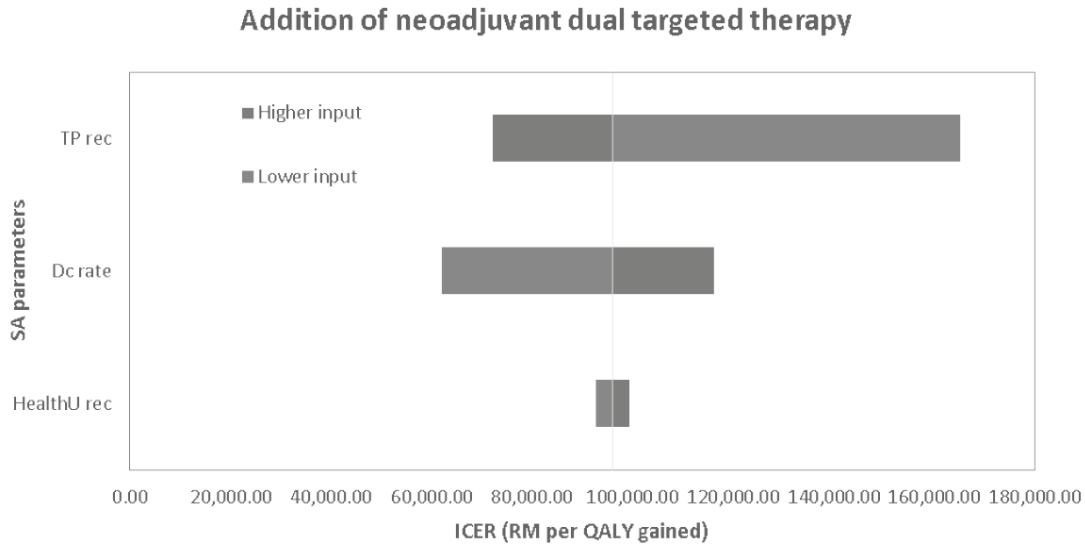
b) Addition of Dual targeted therapy

Parameters	Range	ICER of dual targeted therapy
BASE CASE ICER		MYR 96,013.20
Number of neoadjuvant therapy cycles	4	MYR 76,893.89
	5	MYR 82,168.18
Cost reduction of Pertuzumab-Trastuzumab (Herceptin) combo	25%	MYR 60,302.38
	50%	MYR 47,555.63
	75%	MYR 23,326.84



Notes: Dc rate: Discount rate; HealthU rec: Health Utility value of recurrence state

Figure 9. Tornado diagram of addition of neoadjuvant trastuzumab biosimilar to chemotherapy (one-way sensitivity analysis)



Notes: TP rec: transition probability of recurrence in dual targeted therapy arm; Dc rate: Discount rate; HealthU rec: Health Utility value of recurrence state

Figure 10. Tornado diagram of addition of neoadjuvant Pertuzumab/Trastuzumab to chemotherapy (one-way sensitivity analysis)

By varying the input parameters, the estimated ICERs ranged from a lower bound of MYR 10,796.90 per QALY gained to an upper bound of MYR 20,144.54 when comparing addition of single targeted therapy to standard neoadjuvant therapy; and a lower bound of MYR 23,326.84 per QALY gained to an upper bound of MYR 165,173.36 when comparing addition of dual targeted therapy to standard neoadjuvant therapy.

From the sensitivity analysis, the most sensitive input parameter in this model was the total cost of drugs. Transition probability of recurrence in dual targeted therapy and discounting rate had moderate impact on the ICER as shown in the tornado diagram.

8.0 DISCUSSION

Findings

This review included two SR with NMA, nine RCTs and three cohort studies to assess effectiveness and safety of trastuzumab, pertuzumab, lapatinib with chemotherapy that was grouped into five group of interventions either:

- single-targeted therapy
- dual-targeted therapy
- combination of chemotherapy with anthracyclines group
- combination of chemotherapy without anthracyclines group

We evaluated nine outcomes measure that included: pathological complete response (pCR), progression free survival (PFS), disease-free survival (DFS)/ relapse free survival (RFS), number of patients had progressed, event-free survival (EFS), overall survival (OS), breast conservation, subgroup analysis of hormone receptor-positive and hormone receptor-negative and adverse events.

In general, we found that targeted therapies whether as dual-targeted or single-targeted therapy produced favourable and improved outcomes in HER2-positive early and locally advanced breast cancer patients. This finding is in agreement with three SR with MA (Chen et al. 2019, Clavarezza et al. 2016 and Hicks et al. 2015).⁵⁴⁻⁵⁶ From 19 studies included to assess the effectiveness, safety, organisational, societal and cost-effectiveness in our review, the dual targeted therapy which is the combination of pertuzumab and trastuzumab with combination of chemotherapy (with or without anthracyclines) was the most effective treatment in terms of pCR rate, PFS, DFS and OS as compared to single-targeted therapy or mono chemotherapy. However, based on the cost effectiveness analysis, the ICER for dual targeted therapy was beyond the threshold. Sensitivity analysis showed that the drug price as the most sensitive determinant and reduction of the drug price up to 50% could be cost-effective.

Several international guidelines such as the ASCO, NCCN and ESMO also recommend the used of combination of trastuzumab with chemotherapy in neoadjuvant setting and should be offered early as first line therapy for HER2-positive breast cancer population. Pertuzumab and lapatinib were also included in the list. While for societal issues, patients were preferred the used of subcutaneous trastuzumab than intravenous trastuzumab because it saved time and they experienced less pain and less discomfort experienced.

Dual-targeted therapy versus Single-targeted therapy

In terms of effectiveness, evidence showed that the dual-targeted therapy (pertuzumab and trastuzumab followed by lapatinib and trastuzumab) resulted among the highest pCR either with or without anthracyclines compared to single-targeted therapy. The result also indicated that combination chemotherapy was significantly better than mono chemotherapy. Interestingly, combination of trastuzumab biosimilar plus chemotherapy (with or without anthracyclines)



resulted in higher pCR rates than combination of pertuzumab plus trastuzumab plus mono chemotherapy. The results of this review was consistent with two SR with NMA where they found that by adding anthracycline to chemotherapy might not improve the pCR outcome, while dual-targeted therapy without chemotherapy and chemotherapy alone were both associated with the worst pCR percentages.^{18, 19}

The five-year and seven-year PFS rate was higher in dual-targeted therapy, combination of pertuzumab plus trastuzumab and lapatinib plus trastuzumab than single-targeted therapy, pertuzumab or lapatinib or trastuzumab (plus mono chemotherapy) and was lowest in intervention without chemotherapy (pertuzumab plus trastuzumab plus docetaxel versus pertuzumab plus trastuzumab).²⁴ The results were similar between trastuzumab biosimilar and trastuzumab (plus anthracyclines).²⁵ These results were consistent with DFS where dual-targeted therapy (pertuzumab plus trastuzumab plus docetaxel and lapatinib plus trastuzumab plus paclitaxel) were the highest events among the others.²⁴ However, DFS rates were not significant different between single-targeted therapy using either with trastuzumab, lapatinib or trastuzumab biosimilar in combination with chemotherapy.^{25,28} The six-year EFS rates were highest in dual-targeted therapy (lapatinib plus trastuzumab plus paclitaxel) than single-targeted therapy (lapatinib or trastuzumab) and no different in EFS between SC trastuzumab and IV trastuzumab.^{29,30} The seven-year analysis on OS showed better result with dual-targeted therapy (trastuzumab plus lapatinib) when compared with single-targeted therapy (trastuzumab, lapatinib).^{26,29} However the result of OS did not differ between trastuzumab versus chemotherapy alone and trastuzumab biosimilar.^{25,27}

The evidence showed that addition of pertuzumab was associated with high incidence of neutropaenia and occurrence of diarrhoea was high with lapatinib treatment.^{18,22} These results were consistent in all studies. Our pooled meta-analysis showed the higher incidence of diarrhoea with combination of pertuzumab and trastuzumab than trastuzumab alone. However there were no differences in number of serious adverse events, neutropaenia, febrile neutropaenia and leucopaenia between these two groups.^{20,24,32} This was in line with the PEONY trial findings in 2020.²⁰ In addition, one SR with NMA found that lapatinib-chemotherapy arms significantly cause diarrhoea and skin disorders among all treatments while no difference in the incidence of cardiac events.²² While biosimilar trastuzumab was comparable to trastuzumab in safety profile.¹⁸ The other study in 2018 that assessed the potential of trastuzumab biosimilar also reported that incidence of all-causality, grade 3 to 4 treatment-emergent adverse events was comparable between PF-05280014 (potential trastuzumab biosimilar) plus docetaxel and carboplatin versus trastuzumab reference product (Herceptin) plus docetaxel and carboplatin (38.1% vs 45.5%).⁴⁴





Subtype analysis: hormone receptor-positive and hormone receptor-negative

Several studies did a further subtype-analysis to compare the effectiveness between hormone receptor-positive and hormone receptor-negative.^{19,21,28,29} Two RCTs and one cohort study found that pCR were higher in patients with hormone receptor-negative than patients with hormone receptor-positive for treatment of pertuzumab plus trastuzumab plus docetaxel, lapatinib plus trastuzumab plus paclitaxel. However, the EFS, OS results were not significantly different between these two subtype groups.^{19,21,29,30} These results were in agreement with another trial in 2018 that evaluated the impact of hormone receptor status on the efficacy of HER2-targeted treatment. They found that hormone receptor-negative had greater benefit of pCR than hormone receptor-positive patients.⁴³

In terms of treatment sequence, our current practice in MOH facilities followed the sequential types of treatment where anthracyclines were given first followed by trastuzumab. This is to reduce the toxicity events among patients if the treatment was given concurrently.

Economic evaluation

Based on cost-effectiveness analyses reviewed, mono chemotherapy (pertuzumab plus trastuzumab plus taxol) showed the highest health benefits (10.73 QALYs) and lowest cost (US \$ 415 833) compared to other strategies; combination chemotherapy (taxol plus carboplatin plus pertuzumab plus trastuzumab or taxol plus pertuzumab plus trastuzumab plus anthracyclines). However, de-escalated strategies found that combination of trastuzumab plus taxol became the most cost-effective option in both HR-positive and HR-negative patients. One cost-minimisation analysis found that SC trastuzumab treatment resulted in cost savings to the MOH of MYR7561 per patient compared to IV trastuzumab treatment while it generated a cost savings of MYR7820 per patient to the society.

Strengths and Limitation

The main strength of this review is the degree of rigour in the conduct of the review. The searching methods and screening of the articles were comprehensive. The quality of the 14 studies and meta-analyses included in this review were of high quality and judged as low risk of bias.

This systematic review has several limitations. This review has been prioritized to include selected targeted therapy of different types which were trastuzumab, pertuzumab, lapatinib and trastuzumab biosimilar despite other drugs used in this population because these are the available drugs in Ministry of Health Medicines Formulary (MOHMF), Malaysia.

A few outcomes in the SR with NMA whereby there were no control group to the combination treatment were not included. Ongoing trials including nine registered in PROSPERO, an international prospective register of systematic reviews that related to this topic were not included in this review. Attempts have been made to contact the authors, however, the studies were still ongoing and have not been published yet.

One of the main limitations of this economic evaluation was the use of trial-based clinical parameters (pCR rates, transition probability, long term survival, utility values) from other countries due to lack of local data. The ICER could be under- or overestimated. It was also difficult to obtain head-to-head trials with the exact protocol. Therefore, the ICER should be interpreted cautiously. However, the most suitable parameters were carefully selected based on the similarity of clinical pathways and practices, representativeness of population and the best availability of data. Several assumptions have been used in accordance with other published literatures and expert consultations.

Among the different strategies studied, Hassett et al had similar finding. The addition of single targeted therapy (trastuzumab) to neoadjuvant chemotherapy (taxol) was the most cost-effective strategy especially when de-escalation strategy was included.³³ This is consistent with the economic evaluation results in our selected population.

Although there are many targeted therapies and chemotherapy regimens for the treatment of early HER2-positive breast cancer, Pertuzumab and Trastuzumab are the currently available targeted therapies for use for selected patients in MOH hospitals. Therefore, the evaluation of the other targeted therapies such as lapatinib, neratinib and trastuzumab emtansine was not included in the objective of this economic evaluation. Definition of one Malaysian GDP per capita per QALY gained is MYR 43,475. Based on one-way sensitivity analysis performed, these components have shown to be sensitive parameters for ICER estimation: discount rate, recurrence state transition probability values, and cost of targeted therapies.





9.0 CONCLUSIONS

Based on the above review, there was sufficient fair to good level of evidence retrieved on targeted therapies in combination with neoadjuvant chemotherapy for HER2-positive breast cancer. Evidence demonstrated targeted therapy improved the pathologic complete response rates in HER2-positive early and locally advanced breast cancer population particularly with the treatment of dual-targeted therapy. Dual targeted therapy with pertuzumab and trastuzumab in combination with chemotherapy (with or without anthracyclines) was the most effective treatment in terms of pCR rate, PFS, DFS and OS as compared to single-targeted therapy or mono chemotherapy.

In terms of safety, grade 3 to 5 treatment-related side effects were significantly higher in patients who received pertuzumab (neutropaenia), lapatinib (diarrhoea and skin disorders) and chemotherapy with commonly reported side effects of diarrhoea and skin disorders. For incidence of cardiac events, there was no significant difference observed in all treatment arms. Trastuzumab biosimilar had comparable side-effects to trastuzumab.

From the decision analytic modelling that has been conducted, addition of six cycles of neoadjuvant trastuzumab biosimilar was the most cost-effective strategy for high-risk early breast cancer with HER2 positive, yielding an ICER of MYR 16,471.59 per QALY gained. Addition of neoadjuvant Pertuzumab/Trastuzumab on top of standard neoadjuvant chemotherapy yielded an ICER of MYR 96,013.20 per QALY gained. If the suggested cost-effectiveness threshold of ≤ 1 GDP per capita per QALY gained for Malaysia is taken into consideration, addition of single targeted therapy may be the most cost-effective strategy.

10.0 RECOMMENDATION

Targeted therapy in combination with chemotherapy is recommended to be used in early and locally advanced breast cancer. Combination of chemotherapy plus trastuzumab biosimilar is the most cost-effective option for Malaysian population.

However, dual-targeted therapy may be used to achieve the highest effectiveness treatment, if cost reduction of the dual targeted therapy of at least 50% could be negotiated.

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APPENDIX 1: HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES/ DIAGNOSTIC STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

- I** Evidence obtained from at least one properly designed randomised controlled trial.
- II-1** Evidence obtained from well-designed controlled trials without randomisation.
- II-2** Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.
- II-3** Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
- III** Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)



APPENDIX 2: HEALTH TECHNOLOGY ASSESSMENT PROTOCOL

HEALTH TECHNOLOGY ASSESSMENT (HTA) PROTOCOL: TARGETED THERAPIES IN COMBINATION WITH NEOADJUVANT CHEMOTHERAPY FOR THE TREATMENT OF HER2-POSITIVE BREAST CANCER AND ECONOMIC EVALUATION

1. BACKGROUND INFORMATION

Breast cancer is the most prevalent type of malignancy in females, a heterogeneous disease which can be divided into several subtypes.¹ Based on the severity of breast cancer disease, it is broadly categorised into three groups which are early breast cancer (EBC), locally advanced breast cancer (LABC) and metastatic breast cancer (MBC).¹ Human epidermal growth factor receptor 2 (HER2) is a growth-promoting protein on the outside of all breast cells. About 15-20% women with breast cancer have overexpression of HER2 and called as HER2-positive.^{1,2} HER2-positive is an aggressive subtype that exhibits unique epidemiological, clinical and prognostic differences with poor response to standard chemotherapy regimens compared with HER2-negative.²⁻³ In addition, HER2 may become positive from initially negative tumours over time especially after treatment of endocrine targeting therapy oestrogen receptor (ER).¹

Breast cancer is the commonest cancer in Malaysia with the prevalence of 19% among Malaysian as revealed in the Malaysian National Cancer Registry Report (2012-2016). The new cases of breast cancer had increased from 32.1% (2007-2011) to 34.1% (2012-2016) of overall cancer among women.⁴ The incidence started to increase at the age of 25 and peak at the age of 60 to 64 years. The incidence was highest among Chinese (40.7 per 100,000) followed by Indian (38.1 per 100,000) and Malay (31.5 per 100,000).⁴

In general, the overall survival rates of breast cancer have improved even though it varies worldwide due to improvement in medical care and availability of more effective treatment. Majority of them are diagnosed at an earlier and localised stage.⁵ In many countries, the five-year survival rate for women diagnosed with stage one or two breast cancer is 80 to 90%.⁵ According to Malaysian Clinical Practice Guideline (CPG), early breast cancer include stage I, stage IIA and stage IIB while locally advanced breast cancer includes stage III.⁶ In 2012-2016, the percentage of women in Malaysia diagnosed with breast cancer at stage one was 17.5%, stage two was 34.5% and stage three was 25.2%. Hence, approximately more than third-quarter of breast cancer patients was likely included in the early and locally advanced breast cancer population (77.2%).⁴

The treatment of breast cancer generally depends on the stage of disease and characteristics of the tumour which involves surgery, chemotherapy, radiotherapy and hormonal therapy.¹⁻² Neoadjuvant therapy in breast cancer



refers to the administration of treatment with the intent of down staging the tumour and improve operability and surgical outcomes.⁶ Half of HER2-positive breast cancers are ER-positive but they generally have lower ER levels and many have p53 alterations.¹ Current Malaysian practice for management of EBC include neoadjuvant chemotherapy only while management of LABC include neoadjuvant chemotherapy and anti-HER2 therapy for operable and inoperable conditions. These tumours have higher proliferation rates, extra aneuploidy and are associated with poorer patient prognosis. The poor outcome is improved with appropriate chemotherapy combined with the HER2-targeting drug.¹ Pathological complete response (pCR) have been achieved in 75% patients with metastatic HER2-positive breast cancer, hence improved their prognosis.² Despite the achievements, however, the persisting high toll of deaths resulting from HER2-positive breast cancer calls for continued intensive clinical research of newer therapies and combinations.⁷

Targeted Therapies

Targeted drugs are designed to precisely identify and block the growth and spread of specific cancer cells which are different from chemotherapy drugs that attack all growing cells including cancer cells.⁸ Four types of targeted therapies used for treatment of HER2-positive breast cancer are monoclonal antibodies, small molecule tyrosine kinase inhibitors, antibody-drugs conjugates and other emerging anti-HER2.⁸

a) Monoclonal antibodies

Monoclonal antibodies are immune system proteins (antibodies) that are designed to attach to the HER2 protein on cancer cells, which can help stop the cells from growing.⁷ Monoclonal antibody approved by FDA for breast cancer include trastuzumab, pertuzumab and bevacizumab.⁹ Trastuzumab (Herceptin®) was the first monoclonal antibody drugs against the extracellular domain of HER2 approved by United States Food and drug Administration (US FDA) which is well-tolerated in patients with little toxicity followed by pertuzumab (Perjeta®).⁹ Trastuzumab biosimilars that have been approved by FDA were Hertraz, Zuhera, Herzuma, Kanjinti, Ogivri, Ontruzant and Trazimera.¹⁰ Even though previous studies have proved the tolerable therapeutic efficacy of trastuzumab, some HER2-positive breast cancer patients showed intrinsic or acquired resistance to it.⁸ Hence, research on developing anti-HER2 agents are still on-going.⁸ Later, the combination of pertuzumab with trastuzumab and docetaxel was approved by US FDA on September 2013 as neoadjuvant treatment of patients with HER2-positive for early-stage breast cancer, locally advanced or inflammatory.⁹

b) Tyrosine Kinase Inhibitors

Tyrosine kinase inhibitor (TKI) is a group of drugs which interrupts the HER2 and epidermal growth factor receptor (EGFR) pathways by disrupting the signal transduction pathways of protein kinases through several modes of inhibition.¹¹ Kinase inhibitors are either irreversible or reversible. The irreversible kinase inhibitors tend to covalently bind and block the ATP site resulting in irreversible inhibition. The reversible kinase inhibitors can further subdivide into four major



subtypes based on the confirmation of the binding pocket as well as the DFG motif. Tyrosine kinase enzymes (TKs) can be categorized into receptor tyrosine kinases (RTKs), non-receptor tyrosine kinases (NRTKs), and a small group of dual-specificity kinases (DSK) which can phosphorylate serine, threonine, and tyrosine residues. Lapatinib (Tykerb®) is the second US FDA approved HER2 targeted drug after trastuzumab.⁷ In addition, FDA approved TKIs for breast cancer also include afatinib, neratinib and tucatinib (which targets HER1 and HER2), have substantial efficacy in the treatment of HER2-positive breast cancer.¹¹⁻¹²

a) Antibody drugs conjugates (ADCs)

Antibody drug conjugates (ADCs) are highly targeted biopharmaceuticals drugs which a potent small molecule is linked to an antibody. Trastuzumab–emtansine (T-DM1) is an antibody drug conjugate of trastuzumab combined with an anti-microtubule cytotoxic chemical agent, emtansine.⁷ In advanced-stage disease, randomized trials suggest that the antibody drug conjugate, trastuzumab-DM1 and pertuzumab, may have superior efficacy or add to the efficacy of trastuzumab-based therapy.⁷

In Ministry of Health Drug Formulary, Malaysia (FUKKM), trastuzumab injection was approved in **adjuvant setting** only for patients with HER2-positive, over-expressed by FISH (Fluorescence in situ hybridization) and high risk group (>30% lifetime risk but no known genetic variant).¹³ Both drugs (pertuzumab and lapatinib) were registered under National Pharmaceutical Regulatory Agency (NPRA) but not included in the FUKKM.¹³⁻¹⁴ Pertuzumab injection was indicated for **neoadjuvant treatment** of patients with **HER2-positive, locally advanced, inflammatory, or early stage breast cancer** (either >2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer and indicated in combination with trastuzumab and docetaxel for patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for metastatic breast cancer.¹⁴ While, lapatinib was indicated in combination with capecitabine for the treatment of patients with **advanced or metastatic breast cancer** whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab or in combination with letrozole for the treatment of postmenopausal women with **hormone receptor-positive metastatic breast cancer**.¹⁴ As these agents may play an important role in neoadjuvant therapy setting, their effectiveness and economic implications need to be assessed. This HTA was requested by Clinical Oncologist, Hospital Kuala Lumpur (HKL).



2. POLICY QUESTION

Should targeted therapies i.e. trastuzumab (T), pertuzumab (P) and lapatinib (L) in combination with chemotherapy be used as a neoadjuvant treatment for HER2-positive early and locally breast cancer in Ministry of Health facilities?

3. OBJECTIVES

- 3.1. To conduct a systematic review:
 - i. To assess the effectiveness and safety of T, P, L in combination with chemotherapy in neoadjuvant setting for patient with HER2-positive breast cancer.
 - ii. To determine whether to use one or dual targeted therapies in combination with chemotherapy in neoadjuvant setting for HER2-positive breast cancer.
 - iii. To evaluate the cost-effectiveness of T, P, L in combination with chemotherapy for HER2-positive breast cancer in neoadjuvant setting.
 - iv. To assess the organisational or societal implication related to the use of T, P, L in neoadjuvant setting for HER2-positive breast cancer.

4. METHODS

4.1. Search Strategy

Electronic database will be searched for published literatures pertaining to the use of targeted therapies in neoadjuvant setting

4.1.1 Databases as follows: MEDLINE, EBM Reviews-Cochrane Database of Systematic Review, EBM-Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-Health Technology Assessment, EBM Reviews-DARE, EBM Reviews-NHS Economic Evaluation Database and Embase through the Ovid interface will be searched. Searches will also be conducted in PubMed, Horizon Scanning database, INAHTA database, and FDA database.

4.1.2 Additional literatures will be identified from the references of the retrieved articles.



4.1.3 General search engine will also be used to get additional web-based materials and information.

4.1.5 The search strategy will be included in the appendix.

4.2 Inclusion and exclusion criteria

4.2.1. Inclusion criteria

- a. Population: Adult patients with HER2-positive breast cancer, early breast cancer and locally advanced breast cancer
- b. Intervention: Targeted therapies: Monoclonal antibodies such as trastuzumab, trastuzumab biosimilar and pertuzumab
Kinase inhibitors: lapatinib (Combination with chemotherapy: docetaxel, doxorubicin, paclitaxel)
- c. Comparators: chemotherapy only and single therapy + chemotherapy
- d. Outcome: **Effectiveness:**
Primary Outcomes:
i. Pathological complete response (defined as no residual invasive tumour in both the breast and the axilla: i.e. ypT0/is pN0).
ii. Progression free survival/ Overall survival

Secondary outcomes:
i. Conserving surgery rates/Conservative breast surgery (for early breast cancer)
ii. Quality of life

Safety:
Adverse events (any grade 3-4 adverse event)
Organisational: (e.g. hospital admission, length of stay, day care)
Social: (e.g. patient satisfaction, compliance)
Cost-effectiveness, cost-benefit, cost-utility
- e. Study design: HTA reports, Systematic Review, Randomised Controlled Trials (RCT) and economic evaluation studies.
- f. English full text articles



4.2.2. Exclusion criteria

- a. Study design: Non-randomised controlled trials, animal study, laboratory study, narrative review, editorials, and letter to the editors.
- b. Non English full text article.

Based on the above inclusion and exclusion criteria, study selection will be carried out independently by two reviewers. Disagreement will be resolved by discussion.

4.2 Critical Appraisal of Literature

The risk of bias (methodology quality) of all retrieved literatures will be assessed by three reviewers using the relevant checklist of National Collaborating Centre for Methods and Tools (ROBIS for Systematic Review), Cochrane assessing of bias tools by two reviewers depending on the type of the study design (RoB 2 for Randomised Controlled Trials) and Critical Appraisal Skill Programme (CASP) checklist for economic studies.

4.4 Analysis and Synthesis of Evidence

4.4.1 Data extraction strategy

The following data will be extracted:

- i. Details of methods and study population characteristics.
- ii. Details of intervention and comparators.
- iii. Details of individual outcomes for safety, effectiveness, cost implication, organisational and societal issues associated with the use of targeted therapies

Data will be extracted from selected studies by two reviewers using a pre-designed data extraction form and checked by another reviewer. Disagreements will be resolved by discussion.

4.4.2 Methods of analysis/synthesis

Data on the effectiveness, safety and cost implication of using targeted therapies will be presented in tabulated format with narrative summaries. Meta-analysis using RevMan 5.0 may be conducted for this Health Technology Assessment if possible.

5. REPORT WRITING





6. REFERENCES

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14. QUEST 3: Sistem pendaftaran produk & perlesenan Available at: <https://quest3plus.bpfk.gov.my/pmo2/detail.php?type=product&id=MAL13115219ARZ>



Early breast cancer definition (Huober et al., 2019)

- tumours of > 2cm by palpation or size of \geq 1cm by ultrasound
- histologically confirmed defined as IHC 3 +
- a FISH ratio of > 2.2
- in situ hybridization (ratio \geq 2.0)

Locally advanced breast cancer definition (Untch et al., 2018)

- stage cT4 or cT3
- clinically positive axillary nodes (cN+ for cT2 or pN_{SLN+} for cT1)

Types of chemotherapy registered in Malaysia used for treatment of breast cancer

Taxane-based	Docetaxel Paclitaxel
Anthracyclines	Doxorubicin Epirubicin
Alkylating Agents	Cyclophosphamide
Anti-metabolites	Capecitabine Gemcitabine Flurouracil (5-FU) Methotrexate
Microtubule inhibitors	Vinorelbine Eribulin
Platinum agents	Carboplatin Cisplatin



Dictionary

NIH, National Cancer Institute

Relapse-free survival (RFS)

In cancer, the length of time after primary treatment for a cancer ends that the patient survives without any signs or symptoms of that cancer. In a clinical trial, measuring the relapse-free survival is one way to see how well a new treatment works. It also called **DFS which is disease-free survival**.

Disease-free survival (DFS)

The time from the first date of no disease which was date of surgery to the first documentation of progressive disease or death.

Progression-free survival (PFS)

The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse. In a clinical trial, measuring the progression-free survival is one way to see how well a new treatment works.

Event-free survival (EFS)

In cancer, the length of time after primary treatment for a cancer ends that the patient remains free of certain complications or events that the treatment was intended to prevent or delay. These events may include the return of the cancer or the onset of certain symptoms, such as bone pain from cancer that has spread to the bone. In a clinical trial, measuring the event-free survival is one way to see how well a new treatment works.





Appendix 3: Search Strategy

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) <1946 to March 26, 2021>

Search Strategy:

-
- 1 BREAST NEOPLASMS/ (293769)
 - 2 breast cancer.tw. (282603)
 - 3 breast carcinoma*.tw. (30570)
 - 4 breast malignant neoplasm*.tw. (5)
 - 5 breast malignant tumor*.tw. (34)
 - 6 breast neoplasm*.tw. (1205)
 - 7 breast tumor*.tw. (20561)
 - 8 (cancer adj3 breast).tw. (294321)
 - 9 cancer*, mammary.tw. (135)
 - 10 carcinoma*, breast.tw. (724)
 - 11 (human mammary adj2 (carcinoma* or neoplasm*)).tw. (849)
 - 12 ((malignant neoplasm or malignant tumor) adj3 breast).tw. (118)
 - 13 mammary cancer*.tw. (3473)
 - 14 (human mammary adj2 (carcinoma* or neoplasm*)).tw. (849)
 - 15 (breast adj2 (neoplasm* or tumor*)).tw. (26579)
 - 16 NEOADJUVANT THERAPY/ (21974)
 - 17 (neoadjuvant adj2 (therapy* or treatment*)).tw. (11903)
 - 18 TRASTUZUMAB/ (7226)
 - 19 Herceptin.tw. (1903)
 - 20 Zuhera.tw. (0)
 - 21 trazimera.tw. (3)
 - 22 trastuzumab.tw. (10188)
 - 23 PERTUZUMAB/ (0)
 - 24 pertuzumab.tw. (1022)
 - 25 Perjeta.tw. (27)
 - 26 LAPATINIB/ (1608)
 - 27 lapatinib.tw. (2516)
 - 28 Tykerb.tw. (60)
 - 29 TARGETED THERAPY/ (30364)
 - 30 targeted therapy.tw. (23778)
 - 31 tageted therap*.tw. (1)
 - 32 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (398293)
 - 33 16 or 17 (28430)
 - 34 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 (63343)

- 35 32 and 33 and 34 (1019)
- 36 limit 35 to (english language and humans and yr="2015 -Current" and (meta analysis or randomized controlled trial or "systematic review")) (85)
- 37 from 36 keep 1-85 (85)
- 38 COST-BENEFIT ANALYSIS/ (83817)
- 39 marginal analys*.tw. (252)
- 40 (cost* adj3 benefit*).tw. (25251)
- 41 cost benefit.tw. (10438)
- 42 cost benefit data.tw. (17)
- 43 cost benefit analys*.tw. (4516)
- 44 cost effective*.tw. (143060)
- 45 cost effectiveness analys*.tw. (12301)
- 46 cost utility analysis.tw. (2555)
- 47 economic evaluation*.tw. (12432)
- 48 HEALTH CARE COSTS/ (40955)
- 49 healthcare cost*.tw. (12323)
- 50 health cost*.tw. (2793)
- 51 medical care cost*.tw. (931)
- 52 treatment cost*.tw. (8282)
- 53 Cost effective.tw. (99413)
- 54 "Costs and Cost Analysis"/ (49385)
- 55 affordability*.tw. (5158)
- 56 cost*.tw. (644691)
- 57 (cost adj1 (analy* or comparison* or measure*)).tw. (10426)
- 58 cost* adj3 cost analys*.tw. (7582)
- 59 pricing.tw. (5658)
- 60 cost minimization analysis.tw. (573)
- 61 ECONOMICS, HOSPITAL/ (11225)
- 62 hospital economic*.tw. (104)
- 63 ECONOMICS, MEDICAL/ (9126)
- 64 medical economic*.tw. (828)
- 65 economic.tw. (227501)
- 66 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 (882176)
- 67 35 and 66 (21)



Appendix 4: Evidence Table (INCLUDED STUDIES)

Evidence Table : Effectiveness and Safety

Question : Is targeted therapies in combination with neoadjuvant chemotherapy is effective and safe for HER2-positive breast cancer?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (if Applicable)	Outcome Measures/Effect Size	General Comments
1. Zhang J, Yu Y, Lin Y, Kang S, Lv X, Liu Y, Lin J, Wang J, Song C. Efficacy and safety of neoadjuvant therapy for HER2-positive early breast cancer: a network meta-analysis. <i>Ther Adv Med Oncol.</i> 2021 doi: 10.1177/17588359211006948.	<p>Systematic review (SR) of RCTs and Network Meta-analysis (NMA) (36/39 included for NMA)</p> <p>Aim To compare odds ratios (ORs) for pathologic complete response (PCR) and safety endpoints.</p> <p>Methods Data sources: The Cochrane Central Register of Controlled Trials, PubMed, Embase, and online abstracts from the American Society of Clinical Oncology and San Antonio Breast Cancer Symposium were searched up to November 2020.</p> <p>Selection criteria: (i) phase II or III randomised controlled trials that focused on neoadjuvant therapy for HER2-positive breast cancer, (ii) trials involved two or more treatment arms, (iii) the publication provided PCR rates for the experimental and control arms, and (iv) targeted therapy was administered to at least one arm. If multiple publications were derived from the same clinical study, only the latest result was included.</p>	I	<p>39 articles from 36 trials including 10,379 patients</p> <p>1 study chemo alone</p> <p>8 studies single therapy</p> <p>8 studies dual therapy</p> <p>2 studies TDM1</p> <p>2 studies trastu bio-similar</p> <p>Three steps:</p> <p>First steps: All treatment were divided into several arms according to the prescribed drugs. Since most of the patients withdrew from the trials due to intolerable toxicities, dropout rates were used as surrogate quantitative indicators for adverse events. Arm 10-Arm 17 & arm 20-arm 21 were included in this review.</p> <p>Second steps: arms receiving the same therapy strategy were gathered into one group, such as the dual-target therapy group or single-target therapy group, the combination chemotherapy group, or mono chemotherapy group, by adopting the pre specified criteria to include the treatment arms as the groups. Group 1-group 6 were included in this review.</p>	<p>targeted therapy</p> <p>Dual-target therapy compared with single-target therapy.</p> <p>Five T-DM1 in neoadjuvant therapy</p> <p>Five focused on trastuzumab biosimilars.</p> <p>24/36 studies in NMA</p> <p>11 studies direct comparison single vs dual</p> <p>4 studies comb chemo vs single chemo</p> <p>4 studies anthra vs without anthra</p>	<p>Single therapy, chemotherapy</p>	<p>NA searched up to November 2020.</p>	<p>Combination chemotherapies combined with dual-target therapy were ranked as the top two by SUCRA analysis:</p> <p>Ranked by NMA of the PCRs in experimental arms</p> <ol style="list-style-type: none"> 1. Com +trastuzumab +pertuzumab= 89.8% 2. Com (A) + trastu+ pertu = 84.9% 3. T-DM1+chem)= 81.9%-posterior-probability. 4. Com(A)+neratinib+trastu=79.6% 5. Com + trastu +lapatinib=72.8% 6. Com+ biosimilar=71.7% 7. Comb (A) + trastu + lapatinib= 68.6% 8. Comb+trastu=67.7% (4-arm) 9. Comb (A) + Bio=62.1% 10. Com(A)+neratinib=62% 11. Com(A)+trastu+ pertu= 56.8% (4-arm) 12. Mono +trastu +pertu= 47.7% 13. T-DM1+trastu)=43.7% 14. Mono+ trastu +lapatinib= 37% 15. Com(A)+lapatinib=35% (4-arm) 16. Com+lapatinib=28.9% (4-arm) 	<p>Included studies which related:</p> <p>Tzmb Biosimilar Stebbing (NCT 02162667)</p> <p>Tzmb + Lpnb Baselga (NeoALLITTO) Carey (CALGB) Bonnetoi (EORTC) Guarneri (CHER-LOB) Holmes (LPT109096) Robidoux (NSABP B-42) Hurvitz (Trio-US B07)</p>



Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristics	Intervention	Comparison	Length of Follow Up (if Applicable)	Outcome Measures/Effect Size	General Comments
	<p>Definition of outcomes: PCR was defined as the absence of residual invasive disease in both breast and axilla by pathological examination, according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual eighth edition.</p> <p>Statistical analysis: Bayesian NMA using Markov chain Monte Carlo methods in WinBUGS (version 1.4.3).² was used. The PCR data and adverse events were extracted from all studies included. These data were pooled in a separate NMA, and analysed in two steps: the first was to estimate the efficacy and safety outcome in experimental arms, and the second was to obtain the efficacy results in different strategy groups. The ranking of all regimens was based on the surface under the cumulative ranking curve (SUCRA). The SUCRA values ranged from 0% to 100%. A higher SUCRA value was associated with a higher PCR rate and a lower dropout rate. A comparison of PCR rates between HR-positive and HR-negative subgroups was made using the t-test. The risk of bias for each eligible study was assessed using the Cochrane Collaboration's Risk of Bias tool in Review Manager (version 5.3)</p>		<p>Third steps: direct comparisons were performed to evaluate the efficacy of the PCR between single target therapy and dual-target therapy, combination chemotherapy and single-agent anthracycline-containing and non-anthracycline therapy.</p>				<p>17. Chemo=23.6% († arm) 18. Mono+trastu=18.9% († arm) 19. Mono+pertu=13.5% († arm) 20. Mono+lapatinib=6.4% († arm) 21. Trastu + pertu=3.6%</p> <p>-Dual-target therapy alone without chemotherapy and chemotherapy alone without targeted therapy were both associated with the worst outcomes. -Dual-target therapy was significantly better than single-target therapy, p<0.05 -Combination chemotherapy was significantly better than single-agent chemotherapy, p<0.05 -Another comparison between the regimens with and without anthracycline indicated that adding anthracycline to chemotherapy might not improve the outcome</p> <p>Based on the rank order:</p> <ul style="list-style-type: none"> • trastuzumab+pervezumab • trastuzumab+TKI (lapatinib or neratinib) • as an irreversible TKI, neratinib > lapatinib • T-DM1 better > trastuzumab plus paclitaxel • trastuzumab biosimilars = trastuzumab <p>-dual-target therapy was significantly better than single-target therapy; -combination chemotherapy was significantly better than single-agent chemotherapy; -no significant difference was found between anthracycline-containing and non-anthracycline regimens.</p> <p>PCRs of direct comparison 11 studies compare dual-target vs single-target</p> <ul style="list-style-type: none"> ◦ Com (Doce+Carbo)+tzmb + lpbv vs Com + lpbv= 	<p>Included studies which related: Tzmb Biosimilar Stebbing (NCT 02162667)</p> <p>Tzmb + Lpbv Baselga (NeoALLTTO) Carey (CALGB) Bonneloi (EORTC) Guarnieri (CHER-LOB) Holmes (LPT109096) Robidoux (NSABP B-42) Hurvitz (Trio-US B07)</p>

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
	<p>Risk of Bias</p> <p>Overall risk of bias was low in all included trials. As most of the trials (29/36) adopted open-label designs, performance bias that did not affect the outcomes might exist. 7/36 trials did not analyse the outcomes in the intent-to-treat population, which might have led to attrition bias to a small extent. 19/36 trials described the method of randomisation, and only one had a high bias risk. Another trial showed a high risk of bias for allocation concealment. None of these trials showed a high risk of detection or reporting bias. However, there were other biases in 7 trials, mainly caused by high dropout rates. There was no obvious publication bias.</p>						<p>OR 3.88 (1.22-9.63)</p> <ul style="list-style-type: none"> o Com (Doce+Carbo)+tzmb + lpnrb vs Com + tzmb= <p>OR 1.06 (0.55-1.86)</p> <ul style="list-style-type: none"> o Com (A) + Tzmb + Lnpb vs Com (A) + tzmb= <p>OR 1.39 (0.93-2.02)</p> <ul style="list-style-type: none"> o Com (A) + Tzmb + Lnpb vs Com (A) + lpnrb= <p>OR 2.15 (1.42-3.13)</p> <ul style="list-style-type: none"> o Mono (Pacli) + tzmb + lpnrb vs Mono + tzmb= <p>OR: 1.83 (1.12-2.82)</p> <ul style="list-style-type: none"> o Mono (Pacli) + tzmb + lpnrb vs Mono + lpnrb= <p>OR: 3.33 (1.94-5.37)</p> <ul style="list-style-type: none"> o Com (A) + lpnrb vs com (A) tzmb= <p>OR 1.56 (1.13-2.11) Trastuzumab significantly increase pcr compared to lapatinib.</p> <ul style="list-style-type: none"> o Com (A) +Biosimilar vs Com (A) + Tzmb=OR 1.21 (0.91-1.56) <p>Safety</p> <p>Anthracycline, usually considered a hyperemetic drug that is associated with a high incidence of vomiting or nausea, slightly increased the incidence of cardiac disorders. Both lapatinib and neratinib lead to a high incidence of diarrhoea, especially neratinib, which caused diarrhoea in more than 30% of patients.</p> <ul style="list-style-type: none"> o Com + Tzmb + Lpnrb: <ul style="list-style-type: none"> o neutropoenia 13.79%, diarrhoea 27.59% o Com (A) + tzmb+ lpnrb: <ul style="list-style-type: none"> o neutropoenia 23.01%, diarrhoea 26.1%, hepatotoxicity 4.41% 	<p>Included studies which related:</p> <p>Tzmb Biosimilar</p> <p>Stebbing (NCT 02162667)</p> <p>Tzmb + Lpnrb</p> <p>Baselga (NeoALLTTO)</p> <p>Carey (CALGB)</p> <p>Bonnetal (EORTC)</p> <p>Guarnieri (CHER-LOB)</p> <p>Holmes (LPT109096)</p> <p>Robidoux (NSABP B-42)</p> <p>Hurvitz (Trio-US B07)</p>





Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (if Applicable)	Outcome Measures/Effect Size	General Comments
							<p>Com + tzmb + pzmb</p> <ul style="list-style-type: none"> o neutropaenia 44.10%, diarrhoea 15.28% <p>Com (A)+ tzmb + pzmb</p> <ul style="list-style-type: none"> o neutropaenia 53.68%, diarrhoea 8.99%, febrile neutropaenia 11.72% o Mono + tzmb + pzmb o neutropaenia 40.49%, febrile neutropaenia 8.41%, diarrhoea 5.61% <p>Mono + Tzmb + Lpnb:</p> <ul style="list-style-type: none"> o neutropaenia 8.55%, diarrhoea 21.05%, hepatotoxicity 10.53% <p>Tzmb+pzmb</p> <ul style="list-style-type: none"> o neutropaenia 0.93%, cardiac disorder, LVEF decreased $\geq 10\%$: 0.93% <p>Com (A) + Bio:</p> <ul style="list-style-type: none"> o neutropaenia 4.40% <p>Conclusion In summary, trastuzumab plus pertuzumab-based dual-target therapy with combination chemotherapy regimens showed the highest efficacy of all optional regimens. They also achieved the best balance between efficacy and toxicity. As our study showed that anthracycline could be replaced by carboplatin, we strongly recommended TCbHP as the preferred choice for neoadjuvant treatment of HER2-positive breast cancer</p>	

Evidence Table : Effectiveness and Safety
Question : Is targeted therapies in combination with neoadjuvant chemotherapy is effective and safe for HER2-positive breast cancer?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
2. Nakashoji A, Hayashida T, Yokoe T, Maeda H, Toyota T, Kikuchi M, Watanuki R, Nagayama A, Seki T, Takahashi M, Abe T, Kitagawa Y. The updated network meta-analysis of neoadjuvant therapy for HER2-positive breast cancer. <i>Cancer Treat Rev.</i> 2018 Jan;62:9-17. doi: 10.1016/j.ctrv.2017.10.009. Epub 2017 Oct 31. PMID: 29127857.	<p>Systematic review (SR) of RCTs and Meta-analysis (MA) also Network Meta-analysis (NMA) (13 studies)</p> <p>Aim To update our analysis based on the new clinical evidence available and further verify the effectiveness of dual-HER2 blockade. We also aimed to determine if more clinical studies of neoadjuvant HER2-positive breast cancer are required, and if so, which treatment regimens require additional studies the most.</p> <p>Methods Data sources: Searches were performed using MEDLINE and the Cochrane Central Register of Controlled Trials without any year and language restrictions, using the following keywords: Breast neoplasms AND Neoadjuvant therapy AND Antibodies, Monoclonal OR Receptor, erbB-2. The last search was updated in November 2016. In addition, the reference lists of all studies fulfilling the eligibility criteria were examined for other relevant articles missed by the electronic searches.</p>	I	<p>13 studies including 3184 patients</p> <p>5 Studies Trastu vs Chemo alone (n=537)</p> <p>5 Studies Trastu + Lapatinib vs Trastu vs Lapatinib (n=1513)</p> <p>2 Studies Trastu vs Lapatinib (n=717)</p> <p>1 Study Trastu + Pertu vs Trastu vs Pertu (n=417)</p>	<p>5 Studies CT + Trastu</p> <p>5 Studies CT+ Trastu + Lapatinib</p> <p>2 Studies CT + Trastu</p> <p>1 Study CT+ Trastu + Pertu</p>	<p>vs CT alone</p> <p>vs Trastu vs Lapatinib</p> <p>vs Lapatinib</p> <p>vs Trastu vs Pertu</p>	Up to November 2016	<p>Number of patients who received pCR CT vs CT + T: OR 2.32 (95% CI 1.49-3.62) CT + T vs CT + L: OR 0.62 (95% CI 0.48-0.81) CT + T vs CT + T + L: OR 1.67 (95% CI 1.30-2.14) CT + L vs CT + T + L: OR 2.34 (95% CI 1.76-3.10) CT + lpbm significantly achieved less pCR than CT + tzmb (OR = 0.62, 95% CI = 0.48-0.81, P=0.003).</p> <p>CT + tzmb + lpbm vs CT + tzmb resulted in a significant difference (OR = 2.38, 95% CI = 1.54-3.68, P < 0.0001).</p> <p>CT + lpbm vs CT + tzmb + lpbm which had shown a significant difference (OR = 2.34, 95% CI = 1.76-3.10, P < 0.00001).</p> <p>Number of patients who had grade 3 or 4 adverse events including diarrhoea, neutropaenia, and skin disorders. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria (NCI-CTC) version 4.0.</p> <ul style="list-style-type: none"> Diarrhoea was reported in 10 studies (chemo) and all of them reported grade 3 and 4 events based on NCI-CTC. Neutropaenia was reported in 11 studies (chemo) of which 10 reported grade 3 and 4 events. Cardiac events were reported in 12 studies (Pertuzumab less cardiac event) Skin disorder was reported in 10 studies (chemo) and all of them reported grade 3 and 4 events. <p>Mostly adverse events occurred with chemo and lapatinib</p> <ul style="list-style-type: none"> Lpbm-containing treatment arms showed significantly less treatment completion with more incidences of diarrhoea and skin disorders compared with CT + tzmb. 	





Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (if Applicable)	Outcome Measures/Effect Size	General Comments
	<p>Selection criteria: All randomized trials that compared at least two arms of different treatment regimens involving CT and/or anti-HER2 agents in HER2-positive breast cancer patients in the neoadjuvant settings were considered. All cytotoxic CT regimens were considered eligible for the meta-analysis. If multiple publications of the same trial were retrieved or if there was a case mixed between publications, only the most recent and informative publication was included.</p> <p>Definition of outcomes: pCR: defined as the absence of invasive residual cancer in the breast tissue and nodes (ypT0/is ypN0); non-invasive breast residuals were allowed. Secondary outcomes were the adverse events: cardiac events, including asymptomatic events, such as less than 50% left ventricular ejection fraction or a drop of at least 10% from baseline, and symptomatic events, such as congestive heart failure or cardiac deaths were reported separately. Overall survival (OS) and disease-free survival (DFS), were not analyzed because of insufficient data.</p>						<ul style="list-style-type: none"> Tzmb + pzmb had significantly lower incidences of neutropaenia compared with the CT-containing arms. The incidences of cardiac events did not show any statistically significant differences between the treatment arms (more in CT+T+P) <p>Network Meta-analyses dual anti-HER2 agents with CT resulted in significantly higher incidences of pCR than single agent (CT + tzmb + lpb vs CT + tzmb, OR = 1.58, 95% CI = 1.15–2.16, P=0.004) (CT + tzmb + pzmb vs CT + tzmb, OR = 2.36, 95% CI = 1.13–5.03, P = 0.01), whereas CT and CT + lpb resulted in significantly lower incidences of pCR compared with CT + tzmb.</p> <p>SUCRA rank Treatment rank (pCR + toxicity level)</p> <ol style="list-style-type: none"> CT+T+P= 0.97 CT + T +L=0.85 CT + T=0.62 CT + P=0.47 CT + L=0.32 T + P=0.16 CT=0.1 <p>pCR</p> <ol style="list-style-type: none"> CT +T + P= 0.85 CT + T +L=0.79 CT + T=0.70 CT + P=0.41 	

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	<p>Statistical analysis: The analysis model used was the multivariate random-effects Bayesian consistency model of Caldwell. We used the Wald-like test to evaluate inconsistencies in the whole study. Furthermore, we evaluated the ranking probability curve for each treatment by plotting the probability of each treatment having the highest rank. Estimating the surface under the cumulative ranking (SUCRA) line for each treatment is a simple numerical summary to supplement the graphical display of cumulative ranking.</p> <p>Direct comparisons and risk of bias assessment were calculated by the Review Manager (RevMan), Version 5.3. The Bayesian network meta-analyses and the node splitting method were performed using the WinBUGS version 14 (MRC Biostatistics Unit, Cambridge, UK). OR, heterogeneity, and inconsistency were calculated, and diagrams were made using the R version 3.3.2 (R Project for Statistical Computing, Vienna, Austria).</p> <p>Risk of Bias Using the Cochrane Collaboration risk of bias tool two independent reviewers (AN and TH) assessed all studies for appropriateness of allocation, blinding, management of incomplete outcome data and the completeness of reporting of outcomes.</p>					<p>5. CT + L=0.49</p> <p>6. T + lpnb=0.32</p> <p>7. CT=0.53</p> <p>Adverse event rank Diarrhoea 1. CT + Tzmb +Lpnb=0.93</p> <p>2. CT + Lpnb=0.8</p> <p>3. CT=0.71</p> <p>Neutropaenia 1. CT + Lpnb=0.85</p> <p>2. CT + Tzmb+L=0.73</p> <p>3. CT + Pzmb=0.58</p> <p>Cardiac Event 1. CT + Tzmb+ Pzmb=0.84</p> <p>2. CT + Tzmb=0.66</p> <p>Skin disorder 1. CT + Lpnb=0.96</p> <p>2. CT + Tzmb + Lpnb=0.81</p> <p>Conclusion CT + tzmb + pzmb had the highest probability of being the best treatment for pCR, though new pzmb related trials are required to fully determine the best dual-HER2 blockade regimen in neoadjuvant setting</p>		



Evidence Table : Effectiveness and Safety
Question : Is targeted therapies in combination with neoadjuvant chemotherapy is effective and safe for HER2-positive breast cancer?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (if Applicable)	Outcome Measures/Effect Size	General Comments
3. Gianni L, Pienkowski T, Im YH, Roman L, Tseng LM, Liu MC, Lluch A, Staroslawska E, de la Haba-Rodriguez J, Im SA, Pedrini JL, Poirier B, Morandi P, Semiglazov V, Sirmuninnimit V, Bianchi G, Szado T, Ráthayake J, Ross G, Valagussa P. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. <i>Lancet Oncol.</i> 2012 Jan;13(1):25-32. doi: 10.1016/S1473-2045(11)70336-9. Epub 2011 Dec 6. PMID: 22153890.	Randomised open label of NeoSphere trial Aim To investigate the combination of pertuzumab or trastuzumab, or both, with docetaxel and the combination of pertuzumab and trastuzumab without chemotherapy in the neoadjuvant setting. Methods Multicentre, open-label, phase 2 study, treatment-naïve women with HER2-positive breast cancer were randomly assigned (1:1:1) centrally and stratified by operable, locally advanced, and inflammatory breast cancer, and by hormone receptor expression to receive four neoadjuvant cycles of: trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg every 3 weeks) plus docetaxel (75 mg/m ² , escalating, if tolerated, to 100 mg/m ² every 3 weeks; group A) or pertuzumab (loading dose 840 mg, followed by 420 mg every 3 weeks) and trastuzumab plus docetaxel (group B) or pertuzumab and trastuzumab (group C) or pertuzumab plus docetaxel (group D).	II-1	417 patients from 59 centers in 16 countries from Dec 2007-Dec 2009; Locally advanced BC. HER2-positive, operable (T2-3, N0-1, M0), locally advanced (T2-3, N2-3, M0 or T4a-c, any N, M0), or inflammatory (T4d, any N, M0) breast cancer with primary tumours larger than 2 cm in diameter, were aged 18 years or older, and had not received any previous cancer therapy. Tumours had to be HER2 immunohistochemistry 3+ or 2+ and positive for fluorescence or chromogenic in-situ hybridisation. Other main inclusion criteria were: baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, baseline left ventricular ejection fraction (LVEF) of 55% or more, as measured by echocardiography or multiple acquisition (MUGA).	107 to group B pertuzumab + trastuzumab + docetaxel Procedures: Trastuzumab was given every 3 weeks at 8 mg/kg (cycle 1), followed by 6 mg/kg. The pertuzumab loading dose was 840 mg, followed by 420 mg every 3 weeks. Docetaxel was given at 75 mg/m ² escalating, if tolerated, to 100 mg/m ² every 3 weeks. After completion of neoadjuvant treatment (4 intravenous cycles), eligible patients underwent surgery and adjuvant FEC therapy (three cycles of fluorouracil 600 mg/m ² intravenously epirubicin 90 mg/m ² IV, and cyclophosphamide 600 mg/m ² IV every 3 weeks)	107 to group A, trastuzumab + docetaxel 96 to group D pertuzumab + docetaxel	2 years	pCR 3pCR and lymph-node negative at surgery: (European Medicines Agency and US FDA preferred definition of pCR) Tzmb+ Docetaxel: 23 (21.5%, 14.1-30.5) Pzmb+ Tzmb+ Docetaxel: 42 (39.3%, 30.0-49.2) Pzmb + tzmb: 12 (11.2%, 5.9-18.6) Pzmb+ Docetaxel: 17 (17.7%, 10.7-26.8) pCR and lymph-node positive at surgery: Tzmb+ Docetaxel: 8 (7.5%, 3.3-14.2) Pzmb+ Tzmb+ Docetaxel: 7 (6.5%, 2.7-13.0) Pzmb + tzmb: 6 (5.6%, 2.1-11.8) Pzmb+ Docetaxel: 6 (6.3%, 2.3-13.1) Subgroup analysis Fewer pathological complete responses were noted in tumours that were hormone receptor-positive . In patients with hormone receptor-negative tumours, pathological complete responses were noted in 36 of 57 women (63.2%) who received both anti-HER2 antibodies and chemotherapy in group B. In group C (without chemotherapy), 15 of 55 (27.3%) patients with hormone receptor-negative tumours had complete eradication of the tumour in the breast, which was a greater proportion than that achieved in patients with hormone receptor-positive tumours in all groups. Safety The most common adverse events of grade 3 or higher were neutropenia (57%, 61 of 107 women in group A, 44.9%, 48 of 107 in group B, 1%, one of 108 in group C, and 55.3%, 52 of 94 in group D), febrile neutropenia (eight, nine, none, and seven, respectively), and leucopenia (13, five, none, and seven, respectively). The number of serious adverse events was similar in groups A, B, and D (15-20 serious adverse events per group in 10-17% of patients) but lower in group C (four serious adverse events in 4% of patients).	



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	<p>Definition of the outcome: Primary endpoint was pathological complete response (pCR) in the breast (bpCR), defined in the study as absence of an invasive tumour in the breast irrespective of ductal carcinoma in-situ or nodal involvement, ypT0/Tis. Total pathological complete response was also reported, defined in the study as an absence of an invasive tumour in breast and lymph nodes irrespective of ductal carcinoma in-situ, ypT0/is ypN0.</p> <p>Statistical analysis: three comparisons (group A vs B, group A vs C, and group B vs D) using a two-sided Cochrane Mantel-Haenszel test at an alpha level of 0.2 (SAS version 8.2)</p>						<p>Conclusion Patients given pertuzumab and trastuzumab plus docetaxel (group B) had a significantly improved pathological complete response rate compared with those given trastuzumab plus docetaxel, without substantial differences in tolerability. Pertuzumab and trastuzumab without chemotherapy eradicated tumours in a proportion of women and showed a favourable safety profile.</p>	



Evidence Table : Effectiveness and Safety
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Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
4. Gianni L, Pienkowski T, Im YH, Tseng LM, Liu MC, Luch A, Staroslawska E, de la Haba-Rodriguez J, Im SA, Pedrini JL, Poirier B, Morandi P, Semiglazov V, Strimnimitz V, Bianchi GV, Magazzù D, McNally V, Douthwaite H, Ross G, Valagussa P. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. <i>Lancet Oncol.</i> 2016 Jun;17(6):791-800. doi: 10.1016/S1473-2045(16)00163-7. Epub 2016 May 11. PMID: 27179402.	<p>Secondary/post-hoc analysis of Randomised open label of NeoSphere trial</p> <p>Aim To report 5-year progression-free survival, disease-free survival, and safety of NeoSphere trial</p> <p>Methods multicentre, open-label, phase 2 randomised trial in hospitals and medical clinics, treatment-naïve adults with locally advanced, inflammatory, or early-stage HER2-positive breast cancer. Patients were randomly assigned (1:1:1:1) to receive four neoadjuvant cycles of trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg every 3 weeks) plus docetaxel (75 mg/m² every 3 weeks, increasing to 100 mg/m² from cycle 2 if tolerated; group A), pertuzumab (840 mg loading dose, followed by 420 mg every 3 weeks) and trastuzumab plus docetaxel (group B), pertuzumab and trastuzumab (group C), or pertuzumab and docetaxel (group D). After surgery, patients received three cycles of FEC (fluorouracil 600 mg/m², epirubicin 90 mg/m², and cyclophosphamide 600 mg/m²) every 3 weeks (patients in group C received four cycles of docetaxel prior to FEC), and trastuzumab 6 mg/kg every 3 weeks to complete 1 year's treatment (17 cycles in total). Randomisation was done by a central centre using dynamic allocation, stratified by operable, locally advanced, and inflammatory breast cancer, and by oestrogen and/or progesterone receptor positivity.</p>	II-1	<p>417 patients from 59 centers in 16 countries from Dec 2007-Dec 2009; Locally advanced BC.</p> <p>HER2-positive, operable (T2-3, N0-1, M0), locally advanced (T2-3, N2-3, M0 or T4a-c, any N, M0), or inflammatory (T4d, any N, M0) breast cancer with primary tumours larger than 2 cm in diameter, were aged 18 years or older, and had not received any previous cancer therapy. Tumours had to be HER2 immunohistochemistry 3+ or 2+ and positive for fluorescence or chromogenic in-situ hybridisation. Other main inclusion criteria were: baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, baseline left ventricular ejection fraction (LVEF) of 55% or more, as measured by echocardiography or multiple gated acquisition (MUGA).</p>	<p>107 to group B pertuzumab + trastuzumab + docetaxel</p> <p>Procedures: Trastuzumab was given every 3 weeks at 8 mg/kg (cycle 1), followed by 6 mg/kg. The pertuzumab loading dose was 840 mg, followed by 420 mg every 3 weeks. Docetaxel was given at 75 mg/m² escalating, if tolerated, to 100 mg/m² every 3 weeks. After completion of neoadjuvant treatment (4 intravenous cycles), eligible patients underwent surgery and adjuvant FEC therapy (three cycles of fluorouracil 600 mg/m² intravenously, epirubicin 90 mg/m² IV, and cyclophosphamide 600 mg/m² IV every 3 weeks)</p>	<p>107 to group A, trastuzumab + docetaxel</p> <p>107 to group C, pertuzumab + trastuzumab</p> <p>96 to group D pertuzumab + docetaxel</p>	5 years	<p>Progression-free Survival (PFS) 5-year progression-free survival rates were 81% (95% CI 71-87) for group A, 86% (77-91) for group B, 73% (64-81) for group C, 73% (63-81) for group D (hazard ratios 0.69 [95% CI 0.34-1.40] group B vs group A, 1.25 [0.68-2.30] group C vs group A, and 2.05 [1.07-3.93] group D vs group B).</p> <p>Disease-free survival were 81% (95% CI 72-88) for group A, 84% (72-91) for group B, 80% (70-86) for group C, 75% (64-83) for group D. The DFS hazard ratio for Arm B vs. Arm A was 0.60 (95% CI 0.28-1.27).</p> <p>Patients who achieved total pathological complete response (all groups combined) (85% [76-91]) had longer progression-free survival compared with patients who did not 76% [71-81] hazard ratio 0.54 [95% CI 0.29-1.00]).</p> <p>Tolerability was similar across groups (neoadjuvant and adjuvant treatment periods combined).</p> <p>Adverse events The number of patients with one or more serious adverse event was similar across groups (19-22 serious adverse events per group in 18-22% of patients).</p>	



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	<p>Statistical analysis: three comparisons (group A vs B, group A vs C, and group B vs D) using a two-sided Cochrane Mantel-Haenszel test at an alpha level of 0.2 (SAS version 8.2)</p>						<p>The most common grade 3 or worse adverse events:</p> <p>Neutropenia Pzmb+ Tzmb + Docetaxel 59 [55%] of 107 Tzmb + Docetaxel 71 [66%] of 107 patients Pzmb + Tzmb 40 [37%] of 108 Pzmb + Docetaxel 60 [64%] of 94</p> <p>Febrile neutropenia Pzmb+ Tzmb + Docetaxel 12 [11%] of 107 Tzmb + Docetaxel 10 [9%] of 107 patients Pzmb + Tzmb 5 [5%] of 108 Pzmb + Docetaxel 15 [16%] of 94</p> <p>Leucopenia Pzmb+ Tzmb + Docetaxel 6 [6%] of 107 Tzmb + Docetaxel 13 [12%] of 107 patients Pzmb + Tzmb 4 [4%] of 108 Pzmb + Docetaxel 8 [9%] of 94</p> <p>Conclusion Progression-free survival and disease-free survival at 5-year follow-up show large and overlapping CIs, but support the primary endpoint (pathological complete response) and suggest that neoadjuvant pertuzumab is beneficial when combined with trastuzumab and docetaxel.</p>	



Evidence Table : Effectiveness and Safety
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Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
5. Shao Z, Pang D, Yang H, et al. Efficacy, Safety, and Tolerability of Pertuzumab, Trastuzumab, and Docetaxel for Patients With Early or Locally Advanced ERBB2-Positive Breast Cancer in Asia: The PEONY Phase 3 Randomized Clinical Trial. JAMA Oncol. 2020;6(3):e193692. doi:10.1001/jamaoncol.2019.3692	<p>PEONY phase 3 Randomised Clinical Trial</p> <p>Aim To compare the efficacy, safety, and tolerability of adding pertuzumab to trastuzumab and docetaxel vs placebo, trastuzumab, and docetaxel in Asian patients with ERBB2-positive early or locally advanced breast cancer.</p> <p>Methods Multicenter, double-blind, placebo-controlled phase 3 trial enrolled 329 women with ERBB2-positive early (T2-3, N0-1, M0) or locally advanced breast cancer (T2-3, N2 or N3, M0; T4, any N, M0) and primary tumor larger than 2 cm from March 14, 2016, to March 13, 2017. Analysis of the primary end point was performed on an intention-to-treat basis.</p> <p>Statistical analysis: The 95% CIs for 1 sample binomial were calculated using the Clopper-Pearson method; approximate 95% CIs for differences between rates, using the Hauck-Anderson method. The 2-sided Cochran-Mantel-Haenszel test. Analyses were conducted using SAS version 9.4 (SAS Institute Inc).</p>	II-1	<p>329 patients from March 2016-March 2017, Early and Locally advanced BC.</p> <p>Adjuvant therapy: 3 cycles of IV fluorouracil, epirubicin, and cyclophosphamide followed by 13 cycles of the same IV anti-ERBB2 therapy (pertuzumab and trastuzumab or placebo and trastuzumab) for up to 1 year.</p>	<p>219 patients EBC: 153 LABC: 66</p> <p>4 cycles of: -IV pertuzumab (840-mg loading dose and 420-mg maintenance doses) + trastuzumab (9-mg/kg loading dose and 6-mg/kg maintenance doses), + docetaxel (75 mg/m²)</p>	<p>110 patients EBC: 77 LABC: 33</p> <p>4 cycles of: IV placebo, trastuzumab, and docetaxel every 3 weeks.</p>	1 year	<p>Outcomes of included studies</p> <p>Total pathologic PCR rates 39.3% (86 of 219) in the pertuzumab group 21.8% (24 of 110) in the placebo group (difference, 17.5% [95% CI, 6.9%-28.0%]; P = .001).</p> <p>Adverse Events Most common grade 3 or higher adverse events, there was a higher incidence of neutropenia in the pertuzumab group (83 of 218 [38.1%] vs 36 of 110 [32.7%]). Serious adverse events were reported in 10.1% of patients (22 of 218) in the pertuzumab group and 8.2% of patients (9 of 110) in the placebo group. Higher incidence of diarrhoea in pertuzumab gp (84 of 218 (38.5%) vs 18 of 110 (16.4%).</p> <p>Conclusion Treatment with pertuzumab, trastuzumab, and docetaxel resulted in a statistically significant improvement in the total pathologic complete response rate vs placebo, trastuzumab, and docetaxel for the neoadjuvant treatment of ERBB2-positive early or locally advanced breast cancer in Asian patients.</p>	



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6. Murthy RK, Raghavendra AS, Hess KR, Fujii T, Lim B, Barcenas CH, Zhang H, Chavez-MacGregor M, Mittendorf EA, Litton JK, Giordano SH, Thompson AM, Valero V, Moulder SL, Tripathy D, Jeno NT. Neoadjuvant Pertuzumab-containing Regimens Improve Pathologic Complete Response Rates in Stage II to III HER2+ neop-positive Breast Cancer: A Retrospective, Single Institution Experience. <i>Clin Breast Cancer</i> . 2018 Dec;18(6):e1283-e1288. doi: 10.1016/j.clbc.2018.07.008. Epub 2018 Jul 10. PMID: 30077429. (University of Texas MD Anderson Cancer center)	<p>Observational study of data in MD Anderson Cancer Center</p> <p>Aim To retrospectively determine the pathologic complete response (pCR) rate for trastuzumab and pertuzumab (HP)-containing regimens compared to trastuzumab (H)-containing regimens for stage II-III HER2+ BC.</p> <p>Methods Patients (n=977) with stage II-III HER2+ BC who received neoadjuvant HER2-targeted therapy from 2005 to 2016 and underwent definitive breast and axillary lymph node surgery were identified. pCR was defined as ypT0/is, ypN0.</p> <p>Selection criteria: A. prospectively maintained departmental database at The University of Texas MD Anderson Cancer Center was used to identify patients who received neoadjuvant HER2-targeted therapy, either trastuzumab alone or trastuzumab and pertuzumab, in combination with chemotherapy for stage II-III, histologically confirmed HER2+ invasive BC. All patients received HER2-targeted therapy as per routine clinical care at the time of treatment. This was followed by standard definitive breast and axillary lymph node surgery.</p>	II-III	977 patients from Jan 2005-Jan 2016, Locally advanced BC.	<p>170 patients Trastuzumab + Pertuzumab</p> <p>Trastuzumab (8 mg/kg loading dose followed by 6 mg/kg every 3 weeks or 4mg/kg loading dose followed by 2mg/kg every week)</p> <p>(3 regimens with anthracycline): TP+taxane+ either: (n=73/170)</p> <p>A. FEC</p> <p>5-Fluorouracil at 500 mg/m², Epirubicin at 100 mg/m², Cyclophosphamide at 500 mg/m² (FEC) every 3 weeks (4 cycles)</p> <p>B. FAC</p> <p>5-Fluorouracil at 500 mg/m², Doxorubicin at 50 mg/m², Cyclophosphamide at 500 mg/m² (FEC) every 3 weeks (4 cycles)</p> <p>C. AC</p> <p>Doxorubicin at 60 mg/m², Cyclophosphamide at 600 mg/m² (FEC) every 2/3 weeks (4 cycles)</p>	<p>807 patients Trastuzumab</p> <p>Trastuzumab (8 mg/kg loading dose followed by 6 mg/kg every 3 weeks or 4mg/kg loading dose followed by 2mg/kg every week)</p> <p>(3 regimens with anthracycline): T+ taxane + either</p> <p>A. FEC</p> <p>5-Fluorouracil at 500 mg/m², Epirubicin at 100 mg/m², Cyclophosphamide at 500 mg/m² (FEC) every 3 weeks (4 cycles)</p> <p>B. FAC</p> <p>5-Fluorouracil at 500 mg/m², Doxorubicin at 50 mg/m², Cyclophosphamide at 500 mg/m² (FEC) every 3 weeks (4 cycles)</p> <p>C. AC</p> <p>Doxorubicin at 60 mg/m², Cyclophosphamide at 600 mg/m² (FEC) every 2/3 weeks (4 cycles)</p>	11 years	<p>Outcomes of included studies</p> <p>pCR The pCR rate was higher for the HP group compared to the H group: 59% vs. 48%, odds ratio (OR) = 1.7 (95% CI=1.21, 2.37; p = 0.0021). After adjustment for clinically important factors (age, date of diagnosis, stage, tumor grade, nodal status, hormone receptor (HR) status, menopausal status, and chemotherapy backbone); adjusted OR=2.25 (95% CI = 1.08, 4.73, p = 0.032).</p> <p>The pCR rates for the HP group by chemotherapy : Trastuzumab + Pertuzumab group Taxane alone 74% Anthra-containing 62% C-containing 48%</p> <p>Trastuzumab group Taxane alone 48% Anthra-containing 49% C-containing 30%</p> <p>P was significantly more likely to be given to patients without A (40% vs. 10%, P<0.0001) and more likely to be given to patients with C (36% vs. 13%, P<0.001).</p> <p>Subgroup analysis In multivariate analysis, a significant predictor of pCR in both groups included HR status (HR->HR+) in a univariate analysis within the HP group, pCR rates were lower for HR+ compared to HR- (51% vs. 71%) (OR=0.42; 95% CI 0.22-0.81; p=0.0082).</p> <p>In a univariate analysis within the HP group, pCR rates were lower for HR+ compared to HR- (51% vs. 71%) (OR=0.42; 95% CI 0.22-0.81; p=0.0082).</p>	



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	<p>Statistical analysis: Univariate/multivariate regression and chi-squared test for comparing proportions was used for the statistical analysis. Statistical analysis was performed using (TIBCO Spotfire S+ 8.2 windows).</p>			<p>or (without anthracycline) D. Trastu + Pertu+ taxane alone (n=31/170) Pacitaxel (80 mg/m² every week) or Docetaxel (80 mg/m² every 3 week) E. Trastu + Pertu + taxane + Carbo (n=66/170) 6 cycles of Docetaxel at 75 mg/m² and Carboplatin every 3 weeks.</p>	<p>or (without anthracycline) D. Trastu + taxane alone Trastuzumab (8 mg/kg loading dose followed by 6 mg/kg every 3 weeks or 4mg/kg loading dose followed by 2mg/kg every week) or Pacitaxel (80 mg/m² every week) E. Trastu + taxane + Carbo 6 cycles of Docetaxel at 75 mg/m² and Carboplatin every 3 weeks.</p>		<p>Conclusion These results demonstrate that HP-containing regimens yield higher pCR rates compared to H-containing regimens in stage II-III HER2+ BC in clinical practice regardless of chemotherapy backbone</p>	

Evidence Table : Effectiveness and Safety
Question : Is targeted therapies in combination with neoadjuvant chemotherapy is effective and safe for HER2-positive breast cancer?

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7. Hussain N, Said ASA, Khan Z. Safety Assessment of Neoadjuvant Pertuzumab Combined with Trastuzumab in Nonmetastatic HER2-Positive Breast Cancer in Postmenopausal Elderly Women of South Asia. Int J Breast Cancer. 2018 Apr 19;2018:6106041. doi: 10.1155/2018/6106041. PMID: 29850259; PMCID: PMC5933036.	<p>Observational study in Pakistan</p> <p>Aim To evaluate the safety issues and adverse effects of using TCHP regimen (docelexel, carboplatin, trastuzumab, and pertuzumab) versus TCP regimen (docelexel, carboplatin, and trastuzumab) in older postmenopausal women with non-metastatic HER2-positive breast cancer.</p> <p>Methods The patient record database was accessed to identify all postmenopausal women in the Punjab Care hospital who were above 65 years old, with stages 1-3 HER2-positive breast cancer and treated with neoadjuvant TCHP and neoadjuvant TCP from 2013 till 2016.</p> <p>Statistical analysis: Package for Social Science (SPSS) Version 21 (SPSS Inc., Chicago IL, USA) was used for statistical analysis. The two treatment groups were compared using paired t-test and the calculated p value was considered to be significant if it was ≤ 0.05.</p>	II-11	From Dec 2013- Feb 2016, Locally advanced BC:	<p>22 Pertuzumab + Docelexel + Carboplatin</p> <p>trastuzumab (Herceptin, 8 mg/kg IV infusion over 90 minutes on the first day of every 21-day cycle which was adjusted to 6 mg/kg over 60 minutes on Cycle 2 and then adjusted to 6 mg/kg IV over 30 minutes on Cycles 3 through 6); pertuzumab (840 mg IV infusion over 60 minutes on Day 1 of Cycle 1 and, then, 420 mg IV infusion over 30 minutes on Day 1 of Cycles 2 (Carboplatin, IV infusion over 30 minutes on Day 1); and docelexel (75 mg/m² IV infusion over 60 minutes on day 1).</p>	<p>23 Trastuzumab + Docelexel + Carboplatin</p> <p>Patients receiving the TCP regimen (TCP group) received similar dosage and cycles of trastuzumab, carboplatin, and docelexel but did not receive pertuzumab.</p> <p>Duration of therapy was up to six months.</p> <p>Following surgery or mastectomy), both patient groups (TCH-P and TCP) continued every 3 weeks for a total of 52 weeks of therapy.</p>	3 years	<p>Outcomes of included studies</p> <p>Safety mild fatigue (36%-PTDC versus 34%-TDC) and diarrhoea (48%-PTDC versus 49%-TDC) were most common toxicities.</p> <p>Fever: (12%-PTDC versus 13%-TDC) was common.</p> <p>Anorexia: 16%-PTDC and 21%-TDC</p> <p>Febrile neutropaenia was higher in PTDC group 13% (3/23) versus 4.5% (1/22) in TDC group. Also 27.2% (6/22) of PTDC group was hospitalized for treatment related toxicities versus 21.7% (5/23) of TDC group. (refer table 2.)</p> <p>Conclusion Comparing neoadjuvant TCP and neoadjuvant TCH-P showed TCH-P regimen had an acceptable toxicity profile. Severe cardiac dysfunction was not observed. Using TCH-P regimen can be considered as relatively safe therapeutic option for elderly postmenopausal women with non-metastatic HER2-positive breast cancer.</p>																																																																																																																																																			
<p>Table 2. Reported side effects and toxicities associated with TCH versus TCP: The numbers reflect percentages of patients with recorded side effects. The numbers reflect percentages of patients with recorded mild, moderate, and severe side effects are correlated with CTCAE grade 1, grade 2, 3, and grade 4 side effects, respectively.</p> <table border="1"> <thead> <tr> <th rowspan="2">Side effect/toxicity</th> <th colspan="3">TCH group (n = 23)</th> <th colspan="3">TCP group (n = 22)</th> </tr> <tr> <th>Total (%)</th> <th>Mild (%)</th> <th>Moderate (%)</th> <th>Total (%)</th> <th>Mild (%)</th> <th>Severe (%)</th> </tr> </thead> <tbody> <tr> <td>General side effects</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Fatigue</td> <td>36</td> <td>34</td> <td>2</td> <td>2</td> <td>40</td> <td>36</td> </tr> <tr> <td>Fever</td> <td>14</td> <td>12</td> <td>1</td> <td>2</td> <td>16</td> <td>13</td> </tr> <tr> <td>Nausea</td> <td>21</td> <td>12</td> <td>8</td> <td>1</td> <td>22</td> <td>14</td> </tr> <tr> <td>Diarrhea</td> <td>5</td> <td>2</td> <td>2</td> <td>1</td> <td>8</td> <td>3</td> </tr> <tr> <td>Dry eyes</td> <td>5</td> <td>2</td> <td>2</td> <td>1</td> <td>8</td> <td>3</td> </tr> <tr> <td>Gastrointestinal symptoms</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Diarrhea</td> <td>54</td> <td>48</td> <td>4</td> <td>2</td> <td>55</td> <td>49</td> </tr> <tr> <td>Nausea</td> <td>8</td> <td>4</td> <td>2</td> <td>2</td> <td>7</td> <td>3</td> </tr> <tr> <td>Respiratory system side effects</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Cough</td> <td>9</td> <td>5</td> <td>2</td> <td>2</td> <td>8</td> <td>2</td> </tr> <tr> <td>Dermatological side effects</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Rash</td> <td>6</td> <td>3</td> <td>2</td> <td>1</td> <td>4</td> <td>2</td> </tr> <tr> <td>Neurological side effects</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Nyctalgias</td> <td>12</td> <td>6</td> <td>2</td> <td>4</td> <td>12</td> <td>5</td> </tr> <tr> <td>Neurological side effects</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Neuropathy</td> <td>4</td> <td>1</td> <td>2</td> <td>1</td> <td>3</td> <td>1</td> </tr> <tr> <td>Haematological side effects</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Febrile neutropaenia</td> <td>13</td> <td>2</td> <td>0</td> <td>1</td> <td>4</td> <td>3</td> </tr> </tbody> </table>									Side effect/toxicity	TCH group (n = 23)			TCP group (n = 22)			Total (%)	Mild (%)	Moderate (%)	Total (%)	Mild (%)	Severe (%)	General side effects							Fatigue	36	34	2	2	40	36	Fever	14	12	1	2	16	13	Nausea	21	12	8	1	22	14	Diarrhea	5	2	2	1	8	3	Dry eyes	5	2	2	1	8	3	Gastrointestinal symptoms							Diarrhea	54	48	4	2	55	49	Nausea	8	4	2	2	7	3	Respiratory system side effects							Cough	9	5	2	2	8	2	Dermatological side effects							Rash	6	3	2	1	4	2	Neurological side effects							Nyctalgias	12	6	2	4	12	5	Neurological side effects							Neuropathy	4	1	2	1	3	1	Haematological side effects							Febrile neutropaenia	13	2	0	1	4	3
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8. Fernandez-Martinez A, Krop IE. Survival, Pathologic Response, and Genomics in Neoadjuvant Phase III Trial of Paclitaxel-Trastuzumab With or Without Lapatinib in HER2-Positive Breast Cancer. 2020;38(35):4184-93.	<p>Secondary/post-hoc analysis of RCTs (CALGB 40601 Alliance trial)</p> <p>Aim To assessed whether dual versus single human epidermal growth factor receptor 2 (HER2)-targeting drugs added to neoadjuvant chemotherapy increased pathologic complete response (pCR). They reported relapse-free survival (RFS), overall survival (OS), and gene expression signatures that predict pCR and survival.</p> <p>Methods Three hundred five women with untreated stage II and III HER2-positive breast cancer were randomly assigned to receive weekly paclitaxel combined with trastuzumab plus lapatinib (THL), trastuzumab (TH), or lapatinib (TL). The primary end point was pCR, and secondary end points included RFS, OS and gene expression analyses. mRNA sequencing was performed on 264 pre-treatment samples.</p> <p>Selection criteria: Participants underwent four pre-treatment 16-gauge core biopsies for research. The CONSORT diagram (Data Supplement) shows the flow of participants from the intention-to-treat (ITT) population to the gene expression cohort. Patients with inadequate RNA quality were excluded from the final gene expression cohort, which consisted of 264 patients. All 264 patients signed an institutional review board-approved, protocol-specific informed consent document following federal and institutional guide lines. This document also included consent for biomarker research.</p>	II-1	<p>From Dec 2008- Feb 2015, Locally advanced BC: 305 women untreated stage II and III HER2-positive breast cancer receive paclitaxel (80 mg/m² trastuzumab (4 mg/kg loading dose followed by 2 mg/kg), lapatinib (1,500 mg/d), or both (Lapatinib 1,000 mg/d plus the same dose of trastuzumab) for 16 weeks.</p> <p>It was recommended that all patients receive dose-dense doxorubicin and cyclophosphamide and complete 1 year of trastuzumab adjuvantly.</p>	<p>118 Trastuzumab + lapatinib + paclitaxel (weekly)</p>	<p>120 Trastuzumab + paclitaxel (weekly)</p> <p>67 Lapatinib + paclitaxel(weekly)</p>	<p>40 months for PCR (~3years)</p> <p>90 months for RFS and OS (~7 years)</p>	<p>Outcomes of included studies</p> <p>PCR trastuzumab + lapatinib + paclitaxel arm: 57% (95% CI, 47% to 66%) Trastuzumab + paclitaxel arm: 45% (95% CI, 36% to 54%) Lapatinib + paclitaxel arm: 30% (95% CI, 19% to 42%) -Slightly different from the original pCR rates that were calculated using the pCR evaluable cohort (n=295). After surgery, as recommended by the protocol, 51% received doxorubicin + cyclophosphamide and 73% completed 1 year of trastuzumab. There was no imbalance by treatment arm in either the RNA sequencing and the ITT cohorts</p> <p>Relapse Free Survival Events were recorded in 16% of participants: Lapatinib + paclitaxel arm: 18 (26.9%) Trastuzumab + paclitaxel arm: 24 (20%) trastuzumab + lapatinib + paclitaxel arm: 8 (6.8%) with corresponding 7-year RFS rates of 69% (95% CI, 56% to 82%; TL), 79% (95% CI, 71% to 87%; TH), and 93% (95% CI, 88% to 98%; THL).</p> <p>-RFS difference between the THL and control TH arms was highly statistically significant (HR, 0.32; 95% CI, 0.14 to 0.71; P=0.005).</p> <p>Deaths /Overall Survival -9 deaths (13.4%) occurred in the TL arm, 14 (11.7%) in the TH group, and 4 (3.4%) in the THL group, with corresponding 7-year OS rates of 84% (TL), 88% (TH), and 96% (THL) -OS was significantly higher in the THL compared with the TH arm (HR, 0.34; 95% CI, 0.12 to 0.94; P=0.037). Neither receipt of adjuvant AC, nor whether the full year of adjuvant trastuzumab was completed, altered these relationships</p>	<p>Lapatinib was not been used in early breast cancer setting</p> <p>This trial is similar to NeoALTT0trial population but NeoALTT0 (84%) vs CALGB (76%) In event-free survival (non-sig)</p>



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	<p>Definition of outcomes: PCR was defined as no invasive tumor in the breast at surgery (ypT0/T1s). Secondary end points included Relapse Free Survival and Overall Survival. RFS was defined as the interval from surgery to ipsilateral invasive breast tumor recurrence, regional recurrence, distant recurrence, or death of any cause, whichever occurred first. Patients without an event were censored at the date of the last clinical assessment. OS was defined as the interval from random assignment to death or last follow-up.</p> <p>Statistical analysis: Clinical data collection and statistical analyses were conducted by the Alliance Statistics and Data Center.</p>						<p>Conclusion In CALGB 40601, dual HER2 blockade with lapatinib added to trastuzumab and chemotherapy demonstrated a significant effect on RFS and OS benefits compared with trastuzumab plus chemotherapy alone. Patients who achieved pCR had significantly better outcomes than patients with Residual Disease. However, most patients with RD did not experience relapse, and some pCR patients did experience relapse. Our genomic data suggest that future escalation and de-escalation strategies may benefit from integrating the information provided by clinical parameters, intrinsic subtype, and immune signatures to predict not only response, but also survival.</p> <p>There was a significant improvement in RFS and OS at 7 years with dual therapy in this trial, a surprising finding given that a large adjuvant trial, ALTO, which included a lower clinical risk but otherwise similar patient population, demonstrated only a modest and statistically nonsignificant effect (disease-free survival HR, 0.84) of adding lapatinib administered for a longer duration.</p>	



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9. Sheikh F, Nazir A, Yasmeen S, Badar F, Ahmad U, Siddiqui N. Pathologic Complete Response in HER2-Positive Breast Cancer Patients Receiving Trastuzumab in Neoadjuvant Setting. J Coll Physicians Surg Pak. 2019 Feb;29(2):159-163. Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore	Retrospective observational (cohort) study Aim To compare the pathological response in human epidermal growth factor receptor type 2 (HER-2) positive breast cancer patients getting neoadjuvant chemotherapy with or without trastuzumab. The secondary endpoints were to study the frequency of breast conservation in patients getting trastuzumab preoperatively along with chemotherapy irrespective of the PCR; and added toxicities and influence of other baseline characteristics. Methods The study was a retrospective, observational double-arm study. All patients receiving trastuzumab in neoadjuvant setting at Shaukat Khanum Memorial Cancer Hospital from 2008 to August 2016, fulfilling the inclusion criteria, were observed. Data sources: Medical records were reviewed from the computer based hospital information system	II-2	From 2008-2016, Locally advanced BC: 131 Patients were eligible for neoadjuvant trastuzumab, if they had HER2-positive breast cancer defined as immunohistochemical (IHC) stain of 3+ or FISH positive. The comparison group (n=67) included randomly selected equal number of HER2-positive breast cancer patients having similar tumor characteristics, getting neoadjuvant chemotherapy without trastuzumab. Patients received four cycles of trastuzumab 6mg/kg intravenously every 3 weeks, starting from a loading dose of 8mg/kg in the first cycle or 12 doses of 2mg/kg weekly with a loading dose of 4mg/kg in the first cycle concomitantly with taxane-based therapy.	67 chemotherapy	120 Trastuzumab + paclitaxel (weekly) 67 Lapatinib + paclitaxel(weekly)	8 years	Outcomes of included studies PCR The PCR of the patients who received trastuzumab in the neoadjuvant setting was (n=32) 50%, which was 26.1% higher than the reference group. (n=16) 23.9%. This difference was statistically significant with a p-value of 0.002 (<0.05) (double in comparison). Breast Conservation Breast conservation was possible in 57 (43.51%) patients in total and 51.56% (n=33) in patients getting trastuzumab preoperatively as compared to 35.82% (n=24) in patients who received chemotherapy alone (p-value= 0.69, not statistically significant, but still a considerable number of patients had a less extensive surgery) Toxicity Toxicities were documented according to National Cancer Institute Common Toxicity Criteria (version 4.0) grading of adverse events by reviewing the records in the computer-based Hospital Information System. By adding trastuzumab, there were no major differences in the toxicity profiles of both groups. The drop in ejection fraction, which is a major concern with the addition of trastuzumab, was also almost equal in both groups with no major differences. No patient developed symptomatic heart failure and none had to stop trastuzumab before completing the planned therapy.	Lapatinib was not been used in early breast cancer setting This trial is similar to NeoALTTOnial population but NeoALTTOn (84%) vs CALGB (76%) In event-free survival (non-sig)

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	<p>Definition of outcomes: Pathological complete response (pCR) was defined as no residual invasive or in situ residual tumor in breast tissue, or in the lymph nodes (ypT0 ypN0)</p> <p>Statistical analysis: Data was collected through the computer-based Hospital Information System (HIS). Statistical analysis was performed by using SPSS version 20. Bivariate analysis was done using Chi-square or Fisher exact test, wherever appropriate, to establish the association between two categorical variables with $p < 0.05$ considered as statistically significant.</p>						<p>Conclusion Combining trastuzumab with standard chemotherapy regimens in HER2-positive achieves significantly higher rate of pCR without clinically significant increased toxicity. Further studies with larger number of patients are required to demonstrate mechanisms leading to better responses in this population and whether this increased response can be translated into increased survival rates.</p>	



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10. Huober J, Holmes E, Basella J, de Azambuja E, Untch M, Fumegalli D, et al. Survival outcomes of the NeoALTO study (BIG 1-06): updated results of a randomised multicenter phase III neoadjuvant clinical trial in patients with HER2-positive primary breast cancer. European journal of cancer (Oxford, England:1990). 2019;118:169-177.	<p>Randomised Controlled Trial (BIG 1-06)</p> <p>NeoALTO study (BIG 1-06)</p> <p>Aim To report the updated outcome results of the 455 patients enrolled in the NeoALTO trial with regard to the secondary end-points EFS and OS</p> <p>Methods Patients randomly received Lapatinib 1500 mg/day, Trastuzumab 4 mg/kg followed by 2 mg/kg/wk or Lapatinib 1000 mg/day plus Trastuzumab for 6 weeks, followed by the assigned anti-HER2 treatment combined with paclitaxel (80 mg/m² once/wk). After surgery, patients received 3 cycles of fluorouracil, epirubicin and cyclophosphamide every 3 weeks. According to a protocol amendment in 2008, the lapatinib dose was reduced to 750 mg/day in combination with paclitaxel and trastuzumab because of toxicity (diarrhoea). The assigned anti-HER2 treatment was continued for 34 weeks thereafter. The primary end-point was pCR (ypT0is; for current analysis, it is ypT0is ypN0), and the secondary end-points were disease free survival/event-free survival (EFS) and Overall Survival.</p> <p>Selection of patients: The eligibility criteria included women with tumours of >2 cm and histologically confirmed HER2 + BC defined as IHC 3+ or a FISH ratio of >2.2. The HER2 status was assessed locally (after laboratory accreditation) or centrally (Vall D'Hebron Institute of Oncology).</p>	II-1	<p>From 2008-2010</p> <p>455 patients with patients with operable, unilateral, non-inflammatory, HER2-positive early breast cancer</p>	<p>152 Lapatinib + Trastuzumab + paclitaxel (weekly) 54 of 152 patients received reduced dose.</p>	<p>149 Trastuzumab + paclitaxel (weekly)</p> <p>154 Lapatinib + paclitaxel (weekly)</p>	<p>median follow-up of 6.7 years</p> <p>For OS, being in clinical (survival) follow-up at 30 weeks after randomisation was sufficient for inclusion,</p>	<p>Event-free survival (six-year rates) Lapatinib+ paclitaxel= 67% Trastuzumab+ paclitaxel=67% Lapatinib+ Trastuzumab + paclitaxel= 74%</p> <p>The differences were not significant HR: 0.98%, 95% CI: 0.64-1.51, p=0.56 (L vs T) HR: 0.81%, 95% CI: 0.52-1.26, p=0.35 (L+T vs T)</p> <p>Overall survival (6-Year) Lapatinib+ paclitaxel= 82% Trastuzumab+ paclitaxel=79% Lapatinib + Trastuzumab + paclitaxel= 85%</p> <p>The differences were not significant HR: 0.85%, 95% CI: 0.49-1.46, p=0.56 (L vs T) HR: 0.72%, 95% CI: 0.41-1.27, p=0.26 (L+T vs T)</p> <p>PCR-related to EFS and OS results Patients with a pCR had significantly higher 6-year EFS (77% vs 65%) than those without pCR, both overall (HR: 0.54, 95% CI, 0.34-0.82, P=0.005)</p> <p>significantly higher 6-year OS for those with pCR than those without pCR (89% vs 77%; HR, 0.43 [95% CI, 0.23-0.75; P=0.005])</p> <p>subtype analysis the pCR rates were higher in all three arms of the NeoALTO trial for the hormone receptor-negative than those in the hormone receptor-positive cohort. The survival advantage of achieving a pCR was limited to the hormone receptor-negative cohort (HR 0.35; 95% CI 0.16 to 0.70; p=0.005). In the hormone receptor-negative cohort, the six-year EFS rate was higher in the lapatinib plus trastuzumab plus paclitaxel group (74%) than in lapatinib plus paclitaxel group (61%) and trastuzumab plus paclitaxel group (63%). However the differences between the groups was not statistically significant</p>	

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	<p>Barcelona). Hormone receptors were locally tested and considered positive as per local guidelines. Left ventricular ejection fraction at baseline had to be $\geq 50\%$.</p> <p>Definition of outcomes:</p> <p>-pCR was defined as the absence of invasive tumour cells in the breast at the time of surgery.</p> <p>-EFS was defined as the time from randomisation to the first EFS event. For women who underwent breast cancer surgery, EFS events were defined as post-surgery breast cancer relapse, second primary malignancy or death without recurrence. For women who did not undergo breast cancer surgery, EFS events were death during clinical follow-up or non-completion of any neoadjuvant investigational product due to disease progression.</p> <p>Statistical analysis:</p> <p>Differences in EFS and OS between the trastuzumab group and each of the lapatinib-containing groups are described using HRs and 95% CIs with p-values from two-sided stratified log-rank tests, implemented as Wald tests from the Cox models. Tests of proportionality were. All 455 patients (i.e. the ITT population) were included in these analyses. Two-sided stratified log-rank tests of EFS/OS were implemented as Wald tests from the Cox model. Analyses were performed with SAS</p>						<p>(Lapatinib plus trastuzumab plus paclitaxel versus trastuzumab plus paclitaxel: HR 0.81 95% CI 0.44 to 1.51; p=0.52); lapatinib plus paclitaxel versus trastuzumab plus paclitaxel: HR 1.09 95% CI 0.61 to 1.95; p=0.76). There were also no significant differences across the three treatment groups when OS was analysed by the hormone receptor status (Lapatinib plus trastuzumab versus trastuzumab plus paclitaxel: HR 0.72 95% CI 0.41 to 1.27; p=0.26); lapatinib plus paclitaxel versus trastuzumab plus paclitaxel: HR 0.85 95% CI 0.49 to 1.46; p=0.56).</p> <p>Conclusion</p> <p>The NeoALTTO trial shows that achieving a pCR is important in HER2-positive disease and translates into a better EFS and OS. This association was more clearly seen in the hormone receptor-negative cohort and in patients assigned to the L+T arm. EFS and OS after 6 years did not significantly differ between the 3 treatment groups although L+T showed numerically higher EFS than T in the hormone receptor-negative group.</p>	



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11. Buzdar AU, Suman VJ, Meric-Bernstam F, Leitch AM, Ellis MJ, Boughey JC, Unzeitig GW, Royce ME, Hunt KK. Disease-Free and Overall Survival Among Patients With Operable HER2-Positive Breast Cancer Treated With Sequential vs Concurrent Chemotherapy: The ACOSOG Z1041 (Alliance) Randomized Clinical Trial. <i>JAMA Oncol.</i> 2019 Jan 1;15(1):45-50. doi: 10.1001/jamaoncol.2018.3691. PMID: 30193295; PMCID: PMC6331049.	<p>Randomised Controlled Trial of ACOSOG Z1041 (Alliance)</p> <p>Aim To assess DFS and OS for patients treated with sequential vs concurrent anthracycline plus trastuzumab</p> <p>Methods The ACOSOG Z1041 study was a randomized clinical trial that enrolled patients from September 15, 2007, to December 15, 2011, in 36 centers in the continental United States and Puerto Rico. The ACOSOG is now part of the Alliance for Clinical Trials in Oncology.</p> <p>Selection of patients: The study enrolled 282 women 18 years or older with invasive HER2-positive breast cancer (either 3+ by immunohistochemistry or amplification performed in the local laboratory where the patient was treated) who had adequate blood chemistry test results and a left ventricular ejection fraction of 55% or greater.</p> <p>Definition of outcomes: -pCR was defined as the absence of invasive tumour cells in the breast at the time of surgery. -DFS was defined as the time from randomization to the first of the following events: progression of disease during neoadjuvant therapy; local, regional, or distant recurrence; contralateral breast disease; other second invasive primary cancers; and death from any cause -OS was defined as the time from randomization to death from any cause or the last date of contact for surviving participants</p> <p>Statistical analysis: Kaplan-Meier Curves for diseases survival and overall survival</p>	II-1	<p>From September 2007-December 2011 in 36 centers in US and Puerto Rico</p> <p>282 HER2-positive breast operable cancer (invasive bc with 3+ IHC/ amplification by fluorescence in situ hybridization)</p>	<p>Sequential Arm 1: 138 received 500 mg/m² of fluorouracil, 75 mg/m² of epirubicin, and 500 mg/m² of cyclophosphamide (FEC) on day 1 of a 21-day cycle for 4 cycles, followed by four 21-day cycles of 80 mg/m² of paclitaxel + trastuzumab (4 mg/kg for subsequent doses) on days 1, 8, and 15.</p>	<p>Concurrent Arm 2: 142 received a dose of 80 mg/m² of paclitaxel + trastuzumab (4mg/kg initial dose; 2 mg/kg for subsequent doses) on days 1, 8, and 15 of a 21-day cycle for 4 cycles, followed by four 21-day cycles of FEC on day 1 and 2 mg/kg of trastuzumab on days 1, 8, and 15.</p>	4 years	<p>Outcomes of included studies</p> <p>PCR Proportion of patients who had pCR in the breast. Arm 1: 56.5% (95% CI 47.8–64.9) (76 of 138) Arm 2: 54.2% (95% CI 45.7–62.6) (77 of 142)</p> <p>Disease-free survival Did not differ significantly HR: 1.02, 95% CI: 0.56-1.83</p> <p>Overall survival (6-Year) Did not differ significantly HR: 1.17, 95% CI: 0.48-2.88</p> <p>Adverse effects No treatment-related deaths occurred. The most common severe toxic effects were: neutropaenia (35 [25.3%] of 138 patients in the sequential group vs 45 [31.7%] of 142 patients in the concurrent group) and fatigue (six [4.3%] vs 12 [8.5%]). Left ventricular ejection fraction dropped below the institutional lower limit of normal at week 12 in one (0.8%) of 130 patients who received sequential treatment and four (2.9%) of 137 patients who received concurrent treatment; by week 24, it had dropped below this limit in nine (7.1%) of 126 patients and in six (4.6%) of 130 patients, respectively.</p> <p>Conclusion pCR, DFS and OS (follow-up 5.1 year) did not differ with respect to concurrent or sequential administration of trastuzumab with FEC. Therefore, concurrent administration of trastuzumab with FEC was not found to offer additional clinical benefit and is not warranted.</p>	



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12. Untch M, von Minckwitz G, Gerber B, Schem C, Rezai M, Fasching PA, Tesch H, Eggermann H, Hänusch C, Huober J, Solbach C, Jackisch C, Kunz G, Bliohmer JU, Hauschild M, Fehm T, Nekhuda V, Loibl S, GBG and the AGO-B Study Group. Survival Analysis After Neoadjuvant Chemotherapy With Trastuzumab or Lapatinib in Patients With Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer in the GeparQuinto (G5) Study (GBG 44). J Clin Oncol. 2018 May 1;36(13):1308-1316.	<p>RCT on GeparQuinto (G5) Study (CBG 44)</p> <p>Aim To report results on long-term outcomes in patients with HER2-positive tumours from the GeparQuinto trial.</p> <p>Methods Patients were randomly assigned to receive either trastuzumab or lapatinib in addition to epirubicin (E) and cyclophosphamide (C), followed by docetaxel (T). Central random assignment was performed by dynamic allocation with the minimization method by Pocock in a 1-to-1 ratio. Minimization factors were participating site, ER/ PgR-status (ER and/or PgR positive v ER and PgR negative), and extent of disease (cT1-3 cN0-2 v T4 or N2) as described previously.</p> <p>Selection of patients: HER2 positive by: -immunohistochemistry (IHC 3+) -in situ hybridization (ratio ≥ 2.0) by the local pathologist. -tumour lesions size of ≥ 2 cm or a size of ≥ 1 cm in maximum diameter and measurable in two-dimensions, preferably by sonography.</p> <p>In the case of inflammatory disease, the clinical extent of inflammation was used as measurable lesion. Patients with locally advanced tumours stage cT4 or cT3, hormone receptor–negative tumours (estrogen receptor [ER] and progesterone receptor [PgR], 10%), or hormone receptor–positive tumours (ER and/or PgR < 10%) with clinically positive axillary nodes (cN+ for cT2 or pNSLN+ for cT1) were eligible.</p>	II-1	From November 2007-June 2010, 620 patients were enrolled in the HER2-positive cohort of the GeparQuinto study	<p>311 ECL-DL Epirubicin + Cyclophosphamide followed by (day 1, 3 weekly)</p> <p>Lapatinib 1,250 mg/day, starting on day 1 of the first cycle of EC until day 21 of the fourth cycle of docetaxel</p> <p>concomitantly with all chemotherapy cycles.</p> <p>The dose of lapatinib was reduced to 1,000 mg/day to improve tolerability</p>	<p>309 ECT-DT Epirubicin 90 mg/m² + Cyclophosphamide 600 mg/m² followed by (day 1, 3 weekly)</p> <p>Trastuzumab 6 mg/kg body weight IV every 3 weeks, starting with a loading dose of 8 mg/kg on day 1 of the first EC cycle + docetaxel (4 cycles) (100 mg/m², day 1, every 3 weeks).</p>	Median Follow-up of 55 months (0.2-79.9months) Results were at 3-year follow-up	<p>Outcomes of included studies</p> <p>Primary: PCR</p> <p>Secondary: Disease-free survival (DFS) Distant DFS (DDFS) Time to loco-regional relapse (TTLRR) Time to CNS metastases (TTCNSM) Overall survival (OS)</p> <p>There was no statistically significant difference for DFS, DDFS, OS, TTLRR, TTCNSM in patients who received neoadjuvant lapatinib followed by 12 months of adjuvant trastuzumab compared with neoadjuvant trastuzumab followed by 6 months of adjuvant trastuzumab</p> <p>DFS: HR, 1.04; 95% CI: 0.73-1.49, P = 0.808; DDFS: HR, 0.93; 95% CI: 0.45-1.28, P = 0.724; OS: HR, 0.76; 95% CI: 0.63-1.38, P = 0.297).</p> <p>patients with pCR (ypT0 ypN0) had statistically significant better DFS, DDFS, and OS compared with patients with residual disease (DFS: HR, 0.63; P = 0.042; DDFS: HR, 0.55; P = 0.021; OS: HR, 0.31; P = 0.004)</p> <p>Subgroup analysis of DFS and DDFS indicated no statistically significant difference between both treatment arms in patients who achieved pCR compared with those without pCR. No difference in OS rate was observed in patients with pCR compared with those without pCR in the lapatinib arm, whereas patients who were treated with trastuzumab and who achieved pCR experienced statistically significant better OS compared with those without pCR (HR, 0.15; P = .010)</p>	

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	<p>Definition of outcomes: pCR rate (ypT0 ypN0) after treatment with trastuzumab or lapatinib, administered concomitantly with neoadjuvant chemotherapy.</p> <p>All time-to-event end points were defined as the time (in months) from random assignment. Events for DFS were any invasive loco-regional (ipsilateral breast or local/regional lymph nodes) recurrence of disease, any invasive contralateral breast cancer, any distant recurrence of disease, any secondary malignancy, or death as a result of any cause, whichever occurred first. Progression during therapy was not counted as a DFS event. Events for DDFS were any distant recurrence of disease, any secondary malignancy, or death as a result of any cause, whichever occurred first. Events that were counted for TTLRR were any local or regional (ipsilateral breast [invasive or ductal carcinoma in situ] or local/regional lymph nodes) recurrence of disease, or any invasive contralateral breast cancer, whichever occurred first. Distant metastases, secondary malignancy, or death were considered competing risks. For TTCNSM, any CNS metastasis was an event. Other distant metastases, secondary malignancy, or death were considered competing risks. OS was defined as the time since random assignment until death as a result of any cause.</p> <p>Statistical analysis: Hazard ratio (HR) of 0.6 for DFS to the two-sided significance level of $\alpha = 0.05$. Median follow-up time was estimated using the inverse Kaplan-Meier method. Three-year event-free survival rates were estimated using the Kaplan-Meier product limit method, and treatment groups were compared using the log rank test. Cox proportional hazards regression models were used to estimate HR with 95% CI for DFS, DDFS, and OS. TTLRR and TTCNSM were analysed using the Fine-Gray competing-risk model.</p>						<p>Hormone receptor–negative tumors. DFS, DDFS, and OS were not different between the two treatment arms.</p> <p>Hormone receptor–positive tumors. no difference was observed for DFS and DDFS, whereas OS was a statistically significant better outcome for patients treated with lapatinib followed by trastuzumab compared with those treated with trastuzumab alone (HR, 0.32; test for interaction, $P = 0.033$).</p> <p>Hormone receptor–negative cohort. patients who achieved pCR had statistically significant better DFS, DDFS, and OS compared with those without pCR ($P = 0.002$, 0.005, and 0.002, respectively). No statistically significant difference was observed in patients with hormone receptor–positive tumors who achieved pCR compared with those without pCR.</p> <p>Patients with cT4 or cN3 disease who were treated with lapatinib had significantly improved DFS and DDFS compared with those treated with trastuzumab (DFS: HR, 0.46; test for interaction, $P = .010$; DDFS: HR, 0.44; test for interaction, $P = .027$), whereas OS remained unchanged.</p> <p>Adverse effects The required number of events for time-to-event end point analysis, including 58 deaths, was observed after a median follow up of 55 months (range, 0.2 months to 79.9 months)</p> <p>Conclusion pCR correlated with long-term outcome. In patients with hormone receptor–positive tumors, prolonged anti-HER2 treatment—neoadjuvant lapatinib for 6 months, followed by adjuvant trastuzumab for 12 months—significantly improved survival compared with anti-HER2 treatment with trastuzumab alone.</p>	

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	Univariable and multivariable Cox proportional hazards regressions were used for DFS, DDFS, and OS to adjust for the following factors, which included age. All statistical tests were two sided. No adjustment for multiple testing was done. Analyses were performed with SAS (SAS/STAT User's Guide, Version 9.2 and 9.4; SAS Institute, Cary, NC)							



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13. Stebbing J, Baranau YV, Banyash V, Manikhas A, Moiseyenko V, Dzagrntz G, Zhavrid E, Bolikh D, Pikel J, Eniu AE, Li RK, Tiangco B, Lee SJ, Kim S. Long-term efficacy and safety of CT-P6 versus trastuzumab in patients with HER2-positive early breast cancer: final results from a randomized phase III trial. <i>Breast Cancer Res Treat.</i> 2021 Aug;188(3):631-640. doi: 10.1007/s10549-021-06240-5. Epub 2021 Jun 20. PMID: 34148205; PMCID: PMC8272708.	<p>RCT phase III trial NCT 02162667 (CT-P6 Biosimilar)</p> <p>Aim To report updated safety and efficacy data of biosimilar CT-P6 and trastuzumab following neoadjuvant therapy for patients with human epidermal growth factor receptor-2 (HER2)-positive early breast cancer after up to 3 years' follow-up.</p> <p>Methods They recruited women aged 18 years or older with stage I–IIIA operable HER2-positive breast cancer from 112 centres in 23 countries. We randomly allocated patients 1:1 to receive neoadjuvant CT-P6 or reference trastuzumab intravenously. We stratified randomisation by clinical stage, receptor status, and country and used permuted blocks. We did surgery within 3–6 weeks of the final neoadjuvant study drug dose, followed by an adjuvant treatment period of up to 1 year. We monitored long-term safety and efficacy for 3 years after the last patient was enrolled. Participants and investigators were masked to treatment until study completion. The primary efficacy endpoint, analysed in the per-protocol population, was pathological complete response, assessed via specimens obtained during surgery, analysed by masked central review of local histopathology reports. The equivalence margin was –0.15 to 0.15</p>	II-1	<p>Between Aug 7, 2014, and May 6, 2016</p> <p>549 patients were recruited from 112 centers in 23 countries.</p>	<p>271 [49%] to CT-P6 IV (eight cycles, each lasting 3 weeks, for 24 weeks; 8 mg/kg on day 1 of cycle 1 and 6 mg/kg on day 1 of cycles 2–8) in conjunction with neoadjuvant docetaxel (75 mg/m² on day 1 of cycles 1–4) and FEC (fluorouracil [500 mg/m²], epirubicin [75 mg/m²], and cyclophosphamide [500 mg/m²], day 1 of cycles 5–8) therapy.</p>	<p>278 [51%] to Trastuzumab IV (eight cycles, each lasting 3 weeks, for 24 weeks; 8 mg/kg on day 1 of cycle 1 and 6 mg/kg on day 1 of cycles 2–8) in conjunction with neoadjuvant docetaxel (75 mg/m² on day 1 of cycles 1–4) and FEC (fluorouracil [500 mg/m²], epirubicin [75 mg/m²], and cyclophosphamide [500 mg/m²], day 1 of cycles 5–8) therapy</p>	Results were at 3-year follow-up	<p>Outcomes of included studies</p> <p>Primary: PCR A similar proportion of patients achieved pathological complete response with CT-P6 (116 [46.8%]; 95% CI 40.4–53.2) of 248 patients, and reference trastuzumab (129 [50.4%]; 44.1–56.7) of 256 patients)</p> <p>DFS and Overall Survival Estimated hazard ratios (HRs) and 3-year survival rates were similar between groups. Estimated HRs (95% confidence intervals) for CT-P6 versus trastuzumab were 1.23 (0.78–1.93) for DFS, 1.31 (0.86–2.01) for PFS, and 1.10 (0.57–2.13) for OS</p> <p>Adverse effects Safety findings were comparable between groups for the overall study and follow-up periods, including study drug-related cardiac disorders (CT-P6: 22 [8.1%] patients; trastuzumab: 24 [8.6%] patients [overall]) and decreases in left ventricular ejection fraction. Immunogenicity was similar between groups.</p>	
							<p>No difference between groups 19 (7%) of 271 patients in the CT-P6 group reported serious treatment-emergent adverse events versus 22 (8%) of 278 in the reference trastuzumab group; frequent (occurring in more than one patient) serious adverse events were febrile neutropaenia (four [1%] vs one [$<1\%$]) and neutropaenia (one [$<1\%$] vs two [1%]). Grade 3 or worse treatment-related adverse events occurred in 17 (6%) of 271 patients in the CT-P6 group versus 23 (8%) of 278 in the reference trastuzumab group. The most frequently reported adverse event was neutropaenia in ten (4%) versus 14 (5%).</p>	

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	<p>Selection of patients: Inclusion criteria were an Eastern Cooperative Oncology Group performance status score of 0 or 1; a normal left ventricular ejection fraction of at least 55%; adequate bone marrow, hepatic, and renal function; at least one measurable lesion; and known oestrogen and progesterone receptor status.</p> <p>Definition of outcomes: (DFS) defined as the interval between the date of breast surgery and disease progression, recurrence, or death from any cause; progression-free survival (PFS) defined as the interval between randomization and disease progression, recurrence, or death from any cause; and overall survival (OS) defined as the interval between randomization and death from any cause. DFS and PFS endpoints used disease status assessment by mammogram, physical examination, other radiology.</p> <p>Statistical analysis: statistical analysis using SAS software version 9.1.3 or later.</p>						<p>Conclusion CT-P6 showed equivalent efficacy to reference trastuzumab and adverse events were similar. CT-P6 was well tolerated, with comparable safety and immunogenicity to trastuzumab. Availability of trastuzumab biosimilars could increase access to this targeted therapy for HER2-positive early-stage cancer.</p>	



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14. Jackisch C, Hegg R, Sirovakovský D, Ahn JS, Melichar B, Chen SC, Kim SB, Lichtner M, Staroslawska E, Kunz G, Falcon S, Chen ST, Crepelle-Flechaix A, Heinzmann D, Shing M, Pivot X. HamaH phase III randomised study: Association of total pathological complete response with event-free survival in HER2-positive early breast cancer treated with neoadjuvant-adjuvant trastuzumab after 2 years of treatment-free follow-up. Eur J Cancer. 2016 Jul;62:62-75. doi: 10.1016/j.ejca.2016.03.087. Epub 2016 May 20. PMID: 27208905.	Phase III, open-label, RCT HamaH study Aim To report associations between tpCR and event-free survival (EFS) from HamaH (the largest population from a single study of patients presenting with newly diagnosed HER2-positive breast cancer treated with neoadjuvant adjuvant trastuzumab to date) plus long-term efficacy and safety. Methods HamaH is an open-label, multicentre, international, randomised phase III study, the design of which has been described. Study selection: Patients were randomised to receive eight cycles of neoadjuvant chemotherapy, administered concurrently.	II-1	From 19 October 2009 to 1 December 2010. 596 Her2-positive early BC	297 Docetaxel (75mg/m ²) + Fluorouracil (500mg), Epirubicin (75mg), Cyclophosphamide (500mg) (4 + 4 cycles) + SC Trastuzumab (600mg/kg) 3-weekly Post-surgery: 10 cycles of Trastuzumab	299 Docetaxel (75mg/m ²) + Fluorouracil (500mg), Epirubicin (75mg), Cyclophosphamide (500mg) (4 + 4 cycles) + IV Trastuzumab (8mg/kg, 6mg/kg) 3-weekly Post-surgery: 10 cycles of Trastuzumab	At clinical cut-off (17th January 2014), median follow-up was 40.3 months with SC trastuzumab and 40.6 months with IV trastuzumab	Event-free survival (EFS)-3 Years EFS rates were 76% in the SC arm and 73% in the IV arm (HR was 0.95, (95% CI 0.69-1.30). HRs were similar in both body weight, age, the HR for SC vs IV trastuzumab being: 0.94 (95% CI 0.67e1.31) in patients aged <65 years 1.03 (95% CI 0.39e2.72) in patients aged ≥65 years. EFS results were also similar: -oestrogen receptor-positive disease (HR 0.86 [95% CI 0.54-1.38]) -oestrogen receptor-negative (HR 1.04 95% CI 0.68-1.59) In addition, 3-year EFS rates were higher in oestrogen receptor-positive disease versus oestrogen receptor-negative disease/unknown oestrogen receptor status for both subcutaneous and intravenous trastuzumab: 79% and 73% in the subcutaneous arm and 76% and 71% in the intravenous arm. Patients who achieved tpCR had a >60% reduction in the risk of an EFS event compared with those who did not: HR 0.38 (95% CI 0.22e0.65) in the SC arm and 0.32 (95% CI 0.18-0.60) in the IV arm. Overall survival (6-Year) OS rate was 92% for SC trastuzumab and 90% for IV trastuzumab (HR 0.76, 95% CI 0.44-1.32) Adverse Effects More patients reported serious adverse events in the SC arm but no pattern in the types of events was identified that would account for different rates between the arms.	

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	<p>Safety overview (study population).</p> <table border="1"> <thead> <tr> <th rowspan="2">Overall</th> <th colspan="2">Treatment:pre follow-up</th> </tr> <tr> <th>Subcutaneous trastuzumab (n = 29)</th> <th>Intravenous trastuzumab (n = 29)</th> </tr> </thead> <tbody> <tr> <td>Patients with ≥1 adverse event (any grade)</td> <td>29 (100%)</td> <td>29 (100%)</td> </tr> <tr> <td>Patients with ≥1 grade 3-5 adverse event</td> <td>18 (62%)</td> <td>18 (62%)</td> </tr> <tr> <td>Patients with ≥1 serious adverse event</td> <td>6 (21%)</td> <td>6 (21%)</td> </tr> <tr> <td>Patients with ≥1 related serious adverse event</td> <td>3 (10%)</td> <td>3 (10%)</td> </tr> <tr> <td>Patients with adverse events leading to death</td> <td>4 (14%)</td> <td>4 (14%)</td> </tr> </tbody> </table> <p>Data are number (%).</p> <p>Statistical analysis: EFS rates and unstratified hazard ratios (HRs)/confidence intervals (CIs) were estimated using the Kaplan Meier method and Cox regression, respectively. IpCR/pCR/EFS associations were analysed using multivariable Cox modelling. Analyses were performed with SAS, v9.2 (SAS Institute Inc., Cary, NC, USA).</p>	Overall	Treatment:pre follow-up		Subcutaneous trastuzumab (n = 29)	Intravenous trastuzumab (n = 29)	Patients with ≥1 adverse event (any grade)	29 (100%)	29 (100%)	Patients with ≥1 grade 3-5 adverse event	18 (62%)	18 (62%)	Patients with ≥1 serious adverse event	6 (21%)	6 (21%)	Patients with ≥1 related serious adverse event	3 (10%)	3 (10%)	Patients with adverse events leading to death	4 (14%)	4 (14%)					<p>Conclusion Long-term efficacy supports the established non-inferiority of subcutaneous trastuzumab, and its safety profile remains consistent with the known intravenous profile. In each of Hannah's treatment arms, IpCR was associated with improved EFS, adding to evidence that IpCR is associated with clinical benefit in HER2-positive early breast cancer.</p>	
Overall	Treatment:pre follow-up																										
	Subcutaneous trastuzumab (n = 29)	Intravenous trastuzumab (n = 29)																									
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Evidence Table : Social/Ethical/Organisational
Question : What are the social/ethical/organisational issues regarding to use of BTAs?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
15. Pivot X, Gligorov J, Müller V, Curigliano G, Knoop A, Verma S, Jenkins V, Scotto N, Osborne S, Fallowfield L; PreHer Study Group. Patients' preferences for subcutaneous trastuzumab versus conventional intravenous infusion for the adjuvant treatment of HER2-positive early breast cancer: final analysis of 488 patients in the international, randomized, two-cohort PreHer study. <i>Ann Oncol</i> . 2014 Oct;25(10):1979-1987. doi: 10.1093/annonc/mdl364. Epub 2014 Jul 28. PMID: 25070545	<p>A randomisation process</p> <p>Aim To report patient preference, healthcare professional satisfaction, and safety data pooled from Cohort 1 and also Cohort 2, where s.c. trastuzumab was delivered via hand-held syringe.</p> <p>Methods Patients were randomized to receive four adjuvant cycles of 600 mg fixed-dose s.c. trastuzumab followed by four cycles of standard i.v. trastuzumab, or vice versa. The primary endpoint was overall preference proportions for s.c. or i.v., assessed by patient interviews in the evaluable ITT population.</p> <p>Statistical analysis Preference for s.c. was compared in a nonprotocol-specified analysis with a two-sided test against a null hypothesis value of 65%. Each cohort was powered independently. Factors potentially influencing preference were assessed in terms of their effect on the primary endpoint using logistic regression (forward selection by stepwise regression with α 0.05) in an exploratory manner. Differences in adverse event (AE) rates were assessed using a 2 x 2 χ^2 test. Statistical analyses were carried out with SAS (version 9.1.3).</p>	-	<p>Patients, n=488</p> <p>A total of 245 patients were randomized to receive s.c. followed by i.v. and 243 received i.v. followed by s.c. (evaluable ITT populations: 235 and 232 patients, respectively).</p>	245 patients received SC	243 patients received IV	27 October 2011 to 3 December 2012	<p>Preferences SC was preferred by 415/467 (88.9%); 95% confidence interval (CI) 85.7-91.6; $P < 0.0001$; two-sided test against null hypothesis of 65% SC; preference 45/467 preferred IV (9.6%; 95% CI 7-13); 7/467 indicated no preference (1.5%; 95% CI 1-3).</p> <p>Results were consistent in both study arms: SC \rightarrow IV arm, 89.8% of patients (211/235, 95% CI 85.2-93.3) preferred SC, 8.9% (21/235, 95% CI 5.6-13.3) preferred IV, and 1.3% (3/235, 95% CI 0.3-3.7) had no preference; IV \rightarrow SC arm, 87.9% of patients (204/232, 95% CI 83.0-91.8) preferred SC, 10.3% (24/232, 95% CI 6.7-15.0) preferred IV, and 1.7% (4/232, 95% CI 0.5-4.4) had no preference.</p> <p>Reasons for patients' preferences The two main reasons that patients gave for preferring SC when asked in an open-ended question were that it saved time and that it resulted in less pain/discomfort/ side effects. When specifically asked about pain and bother from bruising or irritation to the injection site, patients reported that SC was the least painful [60.6% (283/467 patients) versus 17.3% for IV (81/467); 22.1% (103/467) reported no difference], and caused less bother from bruising [41.1% (192/467) versus 16.1% (75/467); 42.8% (200/467) reported no difference], or irritation to the injection site [33.0% (154/467) versus 14.6% (68/467); 52.5% (245/467) reported no difference]</p> <p>Adverse event Clinician-reported adverse events occurred in 292/479 (61.0%) and 245/478 (51.3%) patients during the pooled SC and IV periods, respectively ($P < 0.05$; 2 x 2 χ^2 (2)); 16 patients (3.3%) in each period experienced grade 3 events; none were grade 4/5.</p>	

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
							<p>Author's conclusion PrefHer revealed compelling and consistent patient preferences for s.c. over i.v. trastuzumab, regardless of SID or hand-held syringe delivery. s.c. was well tolerated and safety was consistent with previous reports, including the Hannah study (NCT00950300). No new safety signals were identified compared with the known i.v. profile in EBC. PrefHer and Hannah confirm that s.c. trastuzumab is a validated and preferred option over i.v. for improving patients' care in HER2-positive breast cancer.</p>	



Evidence Table : Economic evaluation
Question : Is targeted therapies in combination with neoadjuvant chemotherapy is cost-effective for HER2-positive breast cancer?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
1. Hassett MJ, Li H, Burstein HJ, Punglia RS. Neoadjuvant treatment strategies for HER2-positive breast cancer: cost-effectiveness and quality of life outcomes. <i>Breast Cancer Res Treat</i> . 2020 May;181(1):43-51. doi: 10.1007/s10549-020-05887-5. Epub 2020 Mar 17. PMID: 32185586.	<p>Cost-effectiveness analysis (CEA)</p> <p>Aim To determine the optimal chemotherapy/anti-HER2 treatment strategy.</p> <p>Methods We created a decision-analytic model for patients with stage II-III HER2-positive breast cancer that incorporated utilities based on toxicity and recurrence. We separately modeled hormone receptor-negative (HR-) and positive (HR+) disease and calculated quality-adjusted life years (QALYs) and costs through 5 years. Simulated patients received one of the following neoadjuvant treatments: three 'intensive' regimens (TCHP: docetaxel, carboplatin, trastuzumab, pertuzumab; THP + AC: taxol, trastuzumab, pertuzumab then doxorubicin and cyclophosphamide; THP: taxol, trastuzumab, pertuzumab)</p> <p>Analysis We report the incremental cost-effectiveness ratios (ICER) based on total accrued costs for each treatment strategy and utilities at 5-years. Since our model assumed that the recurrence rate varied only by pCR status, we conducted two sensitivity analyses for these patients. First, we doubled the recurrence rates. Second, among patients treated with TH who did not experience a pCR, we modelled the cost-effectiveness of adding TCHP in addition to TDM-1 during the post-operative treatment period, including its corresponding utility decrements and costs. We assumed that the addition of this therapy would decrease the recurrence risk by 15% on a relative basis (HR0.85).</p>	-	<p>55-year old women, stage II-III HER2-positive cancer that incorporated utilities based on toxicity and recurrence.</p> <p>The model compared five different neoadjuvant treatment strategies. The choice of post-operative chemotherapy depended on the neoadjuvant treatment regimen and response to therapy at surgery. All patients received one year of HER2-directed therapy.</p>	<p>Two 'de-escalated' regimens TH: taxol, trastuzumab; TDM-1+ Pzmb</p>	<p>TCHP: docetaxel, carboplatin, trastuzumab, pertuzumab</p> <p>THP+AC: taxol, trastuzumab, pertuzumab then doxorubicin and cyclophosphamide;</p> <p>THP: taxol, trastuzumab, pertuzumab)</p>	5-year progression-free survival	<p>Overview of included studies</p> <p>Types of cost analysis Cost-effectiveness analysis (CEA)</p> <p>Sources of information</p> <p>Perspective of the analyses We estimated direct treatment and health state costs using a payer (Medicare) perspective, with data for an average 55-year-old woman living in the USA (weight 80 kg, height 162.1 cm).</p> <p>Time Horizon Not mentioned</p> <p>Discounting Not mentioned</p> <p>Key findings Among 'intensive' neoadjuvant strategies, treatment with THP was more effective and less costly than TCHP or THP + AC. When 'de-escalated' strategies were included, TH became the most cost-effective. For HR-negative cancer, TH had 0.003 fewer quality-adjusted life years (QALYs) than THP but was less costly by \$55,831, resulting in an incremental cost-effectiveness ratio of over \$18M/QALY for THP, well above any threshold. For HR-positive cancer, neoadjuvant TH dominated the THP strategy.</p> <p>Conclusion (Mono chemotherapy with Trastuzumab + Pertuzumab strategy was more cost-effective compared with combination chemo with Carboplatin or Anthracyclines) An adaptive-treatment strategy beginning with neoadjuvant THP or TH followed by tailoring post-operative therapy reduces treatment costs, and spares toxicity compared to more intensive chemotherapy regimens for women with HER2-positive breast cancer.</p>	

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
	<p>The model was created and analyzed with TreeAge Pro 2019 (TreeAge Software, Williamstown, MA) and simulated 5-year outcomes using 1 week cycles. Model validation was performed using an adapted AdViSHE construct.</p> <p>Definition of outcomes PCR was defined as no residual cancer in either the breast or the lymph nodes to reflect the KATHERINE study</p>							



Evidence Table : Economic evaluation
Question : Is targeted therapies in combination with neoadjuvant chemotherapy is cost-effective for HER2-positive breast cancer?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
2. Kunst N, Wang S, Hood A, et al. Cost-Effectiveness of Neoadjuvant-Adjuvant Treatment Strategies for Women With ERBB2 (HER2)-Positive Breast Cancer. JAMA Netw Open. 2020;3(11):e2027074. doi:10.1001/jamanetworkopen.2020.27074	<p>Cost-effectiveness analysis (CEA)</p> <p>Aim To examine the costs and disease outcomes associated with selection of various neoadjuvant followed by adjuvant treatment strategies for patients with ERBB2-positive breast cancer.</p> <p>Methods a decision-analytic model was developed to evaluate various neoadjuvant followed by adjuvant treatment strategies for women with ERBB2-positive breast cancer. The model was informed by the KATHERINE trial, other clinical trials with different regimens from the KATHERINE trial, the Flatiron Health Database, McKesson Corporation data, and other evidence in the published literature. Starting trial median age for KATHERINE patients was 49 years (range, 24-79 years in TDM1 arm and 23-80 years in trastuzumab arm). The model simulated patients receiving 5 different neoadjuvant followed by adjuvant treatment strategies.</p> <p>Analysis Comprised a decision tree and a state-transition Markov model, developed following the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting guideline¹² and using R statistical software version 3.6.2 (R Project for Statistical Computing).</p> <p>Base-case Analysis, Subgroup analysis and Probabilistic sensitivity analysis were performed.</p> <p>Definition of outcomes</p>	-		<p>S1 DDAC- THP: dose-dense anthracycline/ cyclophosphamide (DDAC) plus THP followed by adjuvant H</p> <p>S2: DDAC- THP: dose-dense anthracycline/ cyclophosphamide (DDAC) plus THP followed by adjuvant TDM1</p> <p>S3: THP: paclitaxel (T) plus H plus P, followed by adjuvant DDAC plus TDM1</p> <p>S4: trastuzumab (H) plus pertuzumab (P) followed by adjuvant DDAC/ THP plus TDM1-1</p> <p>S5: TCHP: docetaxel (T) plus carboplatin (C) plus HP, followed by adjuvant TDM1</p>		<p>Data analyses were performed from March 2019 to August 2020.</p>	<p>Overview of included studies</p> <p>Types of cost analysis Cost-effectiveness analysis. Lifetime costs in 2020 US dollars and quality-adjusted life years (QALYs) were estimated for each treatment strategy, and incremental cost-effectiveness ratios were estimated. A strategy was classified as dominated if it was associated with fewer QALYs at higher costs than the alternative.</p> <p>Sources of information</p> <p>Model Structure The Markov model with 4 main health states (ie, recurrence free, local recurrence, distant recurrence, and death) simulated lifetime costs and quality-adjusted life-years (QALYs) associated with neoadjuvant-adjuvant regimen combinations.</p> <p>Perspective of the analyses from a health care payer perspective in the United States</p> <p>Time Horizon</p> <p>Discounting applying a 3% discounting rate</p> <p>Sensitivity analysis Probabilistic analysis confirmed that this strategy had the highest probability of cost-effectiveness (>70% at willingness-to-pay thresholds of \$0-200,000/QALY) and was associated with the highest net benefit.</p> <p>Key findings In the base-case analysis, costs ranged from \$415 833 (strategy 3) to \$518 859 (strategy 4), and QALYs ranged from 9.67 (strategy 1) to 10.73 (strategy 3). Strategy 3 was associated with the highest health benefits (10.73 QALYs) and lowest costs (\$415 833) and dominated all other strategies.</p> <p>Strategy 5 was associated with the next highest health benefits, of 10.66 QALYs, and strategy 4 was associated with the third highest health benefits, of 10.31 QALYs. However, these treatment strategies were associated with increased costs (strategy 5: \$489 449 and strategy 4: \$518 859) compared with strategy 3. Strategy 1 (ie, KATHERINE trial control arm) was associated with the least health benefits (9.67 QALYs) and the third lowest costs (\$479 226). Strategy 2 (ie, KATHERINE experimental arm) was associated with the second lowest health benefits (10.22 QALYs) and the second lowest costs (\$452 034).</p>	

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
							<p>Conclusion These results suggest that neoadjuvant THP followed by adjuvant H for patients with pCR or followed by adjuvant DDAC plus T-DM1 for patients with residual disease was associated with the highest health benefits and lowest costs for women with ERBB2-positive breast cancer compared with other treatment strategies considered.</p>	



Evidence Table : Economic evaluation
 Question : Is targeted therapies in combination with neoadjuvant chemotherapy is cost-effective for HER2-positive breast cancer?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
3. Squires H, Pandor A, Thokala P, Stevens JW, Kallenthaler E, Clowes M, Coleman R, Wyld L. Pertuzumab for the Neoadjuvant Treatment of Early-Stage HER2-Positive Breast Cancer: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. <i>Pharmacoeconomics</i> . 2018 Jan;36(1):29-38. doi: 10.1007/s40273-017-0556-7. PMID: 28770452.	<p>Single Technology Appraisal by NICE 12 neoadjuvant studies</p> <p>Aim Review Group Perspective of a NICE Single Technology Appraisal. This is one of a series of single technology appraisal summaries being published in <i>Pharmacoeconomics</i>. Full details of all relevant appraisal documents can be found on the NICE website</p>	-	High-risk women included those with locally advanced (including inflammatory) breast cancer and women with high-risk early-stage breast cancer (classified as T2/3 or N1).	107 to group B pertuzumab + trastuzumab + docetaxel	107 to group A, trastuzumab + docetaxel		<p>Overview of included studies</p> <p>Types of cost analysis NICE Single Technology Appraisal</p> <p>Sources of information This article presents the critical review of the company's submission by the Evidence Review Group and the outcome of the National Institute for Health and Care Excellence guidance. The clinical data were mainly taken from a phase II, randomised, open-label, active controlled study (NeoSphere).</p> <p>Model Structure a cohort-level state transition approach based on six health states: event free, locoregional recurrence, remission, metastatic not progressed, metastatic progressed and death</p> <p>Perspective of the analyses NHS and Personal Social Services perspective</p> <p>Time Horizon Lifetime</p> <p>Discounting Costs and health outcomes were discounted at 3.5% per annum</p> <p>Sensitivity analysis</p> <p>Key findings The probabilistic incremental cost-effectiveness ratio was estimated to be £20,104 per quality-adjusted life-year gained for pertuzumab alongside trastuzumab and docetaxel compared with trastuzumab and docetaxel, which was revised to £21,869 per quality-adjusted life-year gained following the clarification process. The Evidence Review Group corrected an error in the digitisation of the survivor functions and modified the clinically inappropriate assumption that recurrence is zero after 7 years. The Evidence Review Group's probabilistic base case was £23,962 per quality-adjusted life-year gained. Similarly, the ERG's deterministic base-case ICER is estimated to be £23,467 per QALY gained.</p> <p>Conclusion These results suggest that neoadjuvant THP followed by adjuvant H for patients with pCR or followed by adjuvant DDAC plus T-DM1 for patients with residual disease was associated with the highest health benefits and lowest costs for women with ERBB2-positive breast cancer compared with other treatment strategies considered. The estimated base-case ICER reported by both the company and the ERG fell below £30,000 per QALY gained compared with trastuzumab and docetaxel. A Patient Access Scheme (PAS) was proposed by the company, which allowed NICE to recommend pertuzumab for this indication as an expected cost-effective use of NHS resources.</p>	

Evidence Table : Economic evaluation
 Question : Is targeted therapies in combination with neoadjuvant chemotherapy is cost-effective for HER2-positive breast cancer?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
4. Lee W, Haron M, Yu K, Chong F, Goh A, Azmi S. Economic Analysis of Intravenous vs. Subcutaneous Trastuzumab for the Treatment of HER2+ Early Breast Cancer in Malaysia. <i>Advances in Breast Cancer Research</i> . 2016;05:1-13.	<p>Cost-minimisation analysis</p> <p>Aim To investigate cost-savings from subcutaneous trastuzumab in a middle-income Asian country.</p> <p>Methods They performed a local adaptation of a mathematical model developed by Roche, Switzerland, the Herceptin cost-minimisation model (version 1.2). The model was adapted with adjustments for differences in practices and costs in the Malaysian MOH. Costs incurred per patient for the full 1 year course of treatment with IV and SC trastuzumab were taken into consideration. This model was previously utilised in two other CMA studies of SC trastuzumab in England and Scotland.</p> <p>Analysis Base-case analysis was performed by calculating the cost of a full course of treatment (17 cycles over 1 year). The study reference year was fixed at year 2014 as prices used in the study were obtained in late 2014. Costs were reported in Malaysian Ringgit (RM) values (USD1 = RM3.495 based on the exchange rate on 31/12/2014). Sensitivity analyses were performed to determine the robustness of the base-case analysis. One-way sensitivity analyses were performed by varying data points of key variables individually.</p>	-	-	SC trastuzumab 600mg 17 cycles	IV trastuzumab loading dose (8 mg/kg) and 16 subsequent doses (6 mg/kg) 17 cycles	1 year	<p>Sources of information Data used to populate the CMA model was obtained from various sources including official statistics, price lists and estimates from 22 healthcare personnel at four MOH hospitals. Information on treatment practices, drugs and consumables were obtained from four participating MOH hospitals, namely: Penang General Hospital, Sarawak General Hospital, Likas Hospital and Sultan Ismail Hospital. All four hospitals were the main public sector cancer treatment centres in their respective states with oncology departments and in-house pharmacy units for cytotoxic drug reconstitution (CDR). Face-to-face discussions were conducted with healthcare personnel involved in the management of patients and administration of trastuzumab in order to understand the processes of drug preparation and patient management at each site and to collect site estimates of resource and time utilisation. These included oncologists, medical officers, pharmacists and nurses. Interviews and site visits were conducted in November and December 2014.</p> <p>Perspective of the analyses The analysis was performed from two perspectives, namely the MOH and societal perspectives. Analysis from the MOH perspective included the cost categories of healthcare professional time cost, drug cost and consumables cost. Analysis from the societal perspective included the same costs identified in the MOH perspective, but also included patient time costs which were measured by the human capital approach.</p> <p>Time Horizon The analysis time horizon was one year with the study reference year set as 2014, corresponding to the time of data collection. The study was registered with the Malaysian National Medical Research Register (NMRR 14-1470-23387).</p> <p>Discounting No discounting of future costs was applied as the treatment duration did not exceed 1 year</p> <p>Key findings Treatment using SC trastuzumab would result in cost savings to the MOH of RM7561 per patient compared to IV. From a societal perspective, the cost of IV and SC trastuzumab was RM87627 and RM79806 per patient respectively, with patient time costs making up 0.5% of IV cost and 0.3% of SC cost. Use of SC trastuzumab would generate cost savings to society of RM7820 per patient.</p> <p>Conclusion The use of SC formulation has the potential to improve overall efficiency of oncology units and enable more patients to receive treatment. This could be the basis of a future study once the SC formulation is in use. Given the significant issues around cancer care faced by the nation among other competing priorities, the SC formulation has many favourable aspects</p>	



APPENDIX 5: LIST OF EXCLUDED STUDIES

1. Alba E, Albanell J, de la Haba J et al. Trastuzumab or lapatinib with standard chemotherapy for HER2-positive breast cancer: results from the GEICAM/2006-14 trial. *Br J Cancer*. 2014;110(5):1139-1147.
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7. Bernsdorf M, Ingvar C, Jørgensen L et al. Effect of adding gefitinib to neoadjuvant chemotherapy in estrogen receptor negative early breast cancer in a randomized phase II trial. *Breast Cancer Res Treat*. 2011;126(2):463-70.
8. Bianchini G, Pusztai L, Pienkowski T et al. Immune modulation of pathologic complete response after neoadjuvant HER2-directed therapies in the NeoSphere trial. *Ann Oncol*. 2015;26(12):2429-36
9. Chang HR, Glaspy J, Allison MA et al. Differential response of triple-negative breast cancer to a docetaxel and carboplatin-based neoadjuvant treatment. *Cancer*. 2010;116(18):4227-37.
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11. Cheng H, Bai Y, Sikov W, Sinclair N et al. Quantitative measurements of HER2 and phospho-HER2 expression: correlation with pathologic response to neoadjuvant chemotherapy and trastuzumab. *BMC Cancer*. 2014;14(1):326.
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