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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AUTHORS

Madam Atikah Shaharudin (AS)
Senior Principle Assistant Director
Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division, Ministry of Health Malaysia

Dr. Foo Sze Shir (FSS)
Senior Principle Assistant Director
Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division, Ministry of Health Malaysia

Madam Maharita Ab Rahman (MAR)
Principle Assistant Director
Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division, Ministry of Health Malaysia

Dr. Aidatul Azura Abd Rani (AAAR)
Senior Principle Assistant Director
Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division, Ministry of Health Malaysia

INFORMATION SPECIALIST

Sister Norharlina Che Zakaria
Nursing Officer
Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division, Ministry of Health Malaysia

EXPERT COMMITTEE (alphabetical order)

Dr. Eznal Izwadi Mahidin
Oncologist Consultant
Hospital Kuala Lumpur

Dr. (Ms) Nor Aina Emran
Breast and endocrine Consultant
Hospital Kuala Lumpur

Dr. (Ms) Anita Baghawi
Breast and endocrine Consultant
Hospital Kuala Lumpur

Dr. Izzuna Mudla Mohamed Ghazali
Head of Malaysian Health Technology Assessment Unit (MaHTAS)
MOH, Putrajaya

Dr. Mastura Md Yusof
Clinical Oncology Consultant
Institut Kanser Pantai
Hospital Pantai

Dr. Noranizah Wagino
Patology Consultant
Hospital Pakar Sultanah Fatimah, Johor

Dr. Roza Sarimin
Head of Health Technology Assessment Unit
MOH, Putrajaya
Malaysian Health Technology Assessment Unit (MaHTAS)

Dr Shantini Arasatnam
Radiology Consultant
Hospital Kuala Lumpur

Dr. Vaishanavi Jeyasingam
Clinical Oncology Consultant
Hospital Kuala Lumpur

Dr Zahurin Ismail
Pakar Radiologi
Jabatan Radiologi
Institut Kanser Negara

Pn. Haarathi Chandriah
Formulary & Pharmacoeconomic
Pharmaceutical Service Programme
Pharmacy Practice & Development Division

Profesor Dato' Dr. Fuad Ismail
Clinical Oncology Consultant
Pusat Perubatan Universiti Kebangsaan Malaysia

Professor Madya Dr. Zafar Ahmed
Senior Lecturer
Medicine and Health Science Faculty
UniMAS, Sarawak

EXTERNAL REVIEWERS (alphabetical order)

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- Health Technology Assessment and Clinical Practice Guidelines Council
- Technical Advisory Committee for Health Technology Assessment

EXECUTIVE SUMMARY

Background

Breast cancer is the most prevalent type of malignancy in females, a heterogeneous disease which can be divided into several subtypes. 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). 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. Current Malaysian practices 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 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). Both drugs (pertuzumab and lapatinib) were registered under National Pharmaceutical Regulatory Agency (NPRA) but not included in the FUKKM. 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. 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**.** 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).

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 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 United States Food and drug Administration (US 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 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. 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)

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. 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.

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 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 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.

Methods

Part A: Systematic Review of Literature

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.

Appendix 3 shows the detailed search strategies.

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	○ 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 (monotherapy or combination with chemotherapy: taxane-based, anthracyclines, cyclosphosphamide, carboplatin) ○ chemotherapy + dual targeted therapy ○ chemotherapy + single targeted therapy
c	Comparator	○ chemotherapy + single targeted therapy ○ chemotherapy only
d	Outcomes	Primary Outcomes: ○ 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 Secondary outcomes: ○ Conserving surgery rates/Conservative breast surgery (for early breast cancer) Safety ○ Adverse events (any grade 3-4 adverse event) Economic impacts ○ Cost effectiveness analysis ○ Cost utility analysis ○ Cost benefit analysis ○ Cost analysis ○ Any other measure of economic outcomes Organisational issues ○ Length of hospital stay (LOS) ○ Hospital Admission ○ Day care Social implication ○ Preferences ○ Tolerability ○ Satisfaction
e	Study design	HTA reports, systematic review with network meta-analysis, systematic review with meta-analysis, randomised controlled trial (RCT), cohort and economic evaluation studies.
f	English full text articles	

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 three reviewers. Disagreement will be resolved by discussion.

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, Cochrane assessing of bias tools (RoB 2) for

Randomised Controlled Trials and Critical Appraisal Skill Programme (CASP) checklist for cohort and economic studies.

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: pathological complete response (pCR) rate and safety data. The data was pooled when heterogeneity, I^2 was less than 80%. 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 and Conclusion

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, 86 relevant abstracts were retrieved in full text. After applying inclusion and exclusion criteria, 67 articles were excluded with reasons. There were 19 studies included in this review: two systematic review (SR) and network meta-analysis (NMA), nine randomized controlled trials (RCTs), three cohort studies, one cross-sectional study and four economic analyses.

Based on retrievable evidence, targeted therapy had shown to improve the pathologic complete response rates in HER2-positive early and locally advanced breast cancer population particularly with the treatment of dual-targeted therapy. Combination of pertuzumab plus trastuzumab plus chemotherapy (with or without anthracyclines) was significantly 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 significantly better than mono chemotherapy. From indirect meta-analysis, they found that there was no difference in pCR between the two groups with and without anthracyclines. However, according to the SUCRA rank, the group without anthracyclines took the highest percentage of pCR for both additions of pertuzumab or lapatinib. The used of trastuzumab biosimilar plus chemotherapy (with or without anthracyclines) was also ranked higher than 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-arms (neutropenia), lapatinib-arms (diarrhea and skin disorders) and chemotherapy with commonly reported side effects of diarrhea 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, mono chemotherapy (pertuzumab plus trastuzumab plus taxol) was more effective with the highest health benefits (10.73 QALYs) and less costly (US $ 415 833) cost 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 found that SC trastuzumab treatment resulted in cost savings to the MOH of RM7561 per patient compared to IV trastuzumab treatment while it generated a cost savings of RM7820 per patient to the society.

Part B: Local Economic Evaluation

DECISION ANALYTIC AND ECONOMIC MODELLING

OBJECTIVE

The general objective of this economic evaluation was to assess the cost-effectiveness of addition of 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) with standard neoadjuvant chemotherapy for early HER2-positive breast cancer patients with high risk of recurrence.

METHODS

A literature-based 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.[18,20,22,44] Taking the current practice and availability of drugs available in FUKKM, the single targeted therapy assessed was the trastuzumab biosimilar (Herzuma) 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 (Herzuma)
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[33-34,47] 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 local economic evaluation was designed from the Ministry of Health (MOH) perspective.

The simulated clinical pathways are 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,
    a. Chemotherapy only,
    b. Single targeted therapy [(IV Trastuzumab 8mg/kg loading dose (LD) then 6mg/kg maintenance dose (MD)) + (3 EC, 3 Doxetaxel)], or
    c. 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 (Herzuma) 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.

Results

From the decision analytic modelling that has been conducted, addition of six cycles of neoadjuvant trastuzumab biosimilar (Herzuma) or neoadjuvant Pertuzumab/

Trastuzumab on top of standard neoadjuvant chemotherapy considered as a cost-effective strategy for high-risk early breast cancer with HER2 positive, yielding an ICER of RM 16,471.59 and RM 96,013.20 per QALY gained, which is within the suggested value of cost-effectiveness threshold by WHO (1-3 times GDP per capita). 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 ~ RM 43,884.75. Definition of one Malaysian GDP per capita per QALY gained is USD10,500 ~ RM 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.

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.

TABLE OF CONTENTS

ABBREVIATION (example)	
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

1.0 BACKGROUND

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 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 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, 2019), 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 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 practices 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 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).[8] Both drugs (pertuzumab and lapatinib) were registered under National Pharmaceutical Regulatory Agency (NPRA) but not included in the FUKKM.[8-9] 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.[9] 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.**[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 Clinical Oncologist, 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]

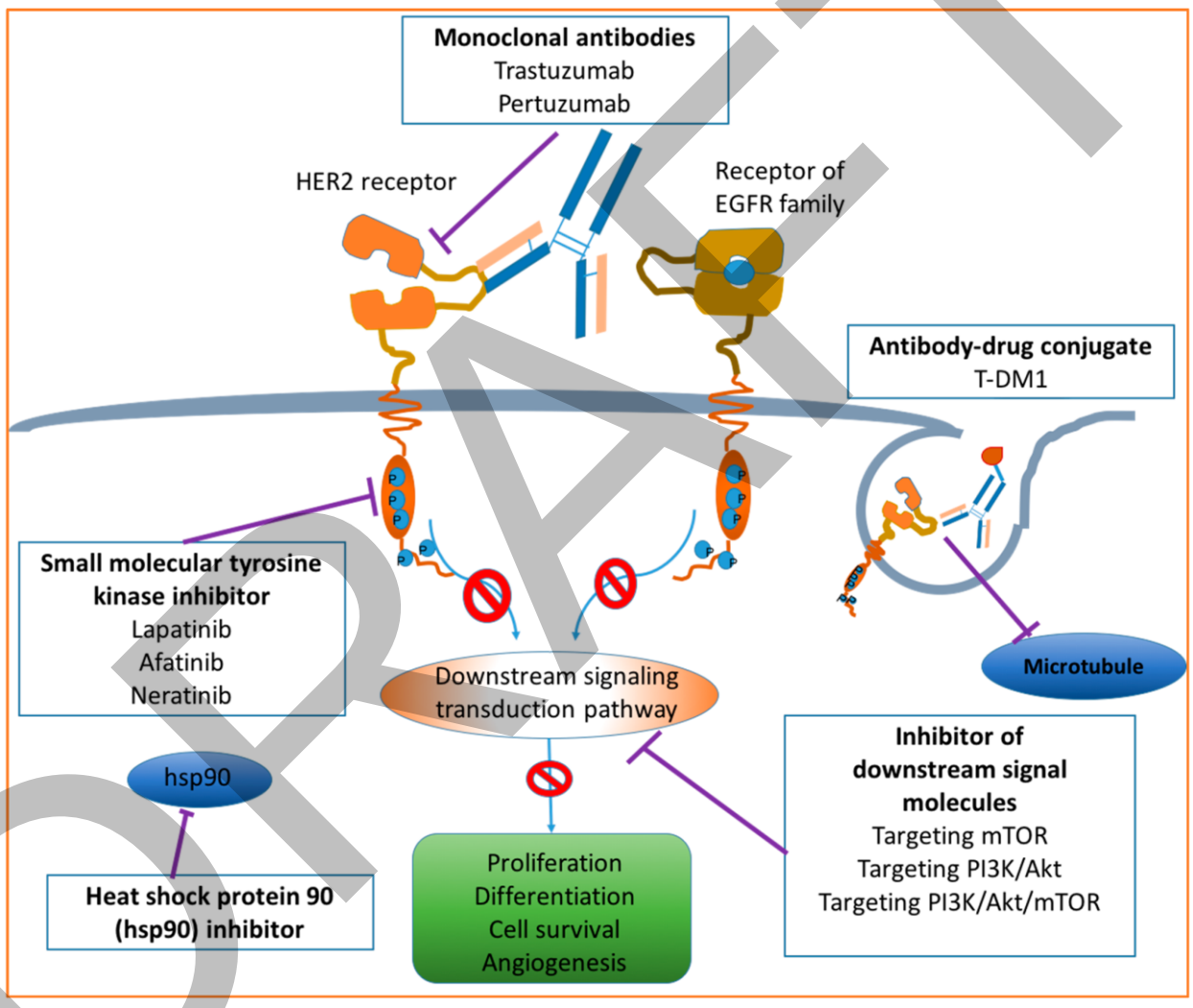


Figure 1. Mechanism of Action for Targeted Therapies on breast cancer cells (Sources from: International Journal of Molecular Sciences. 2016; 17(12):2095)[10]

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 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.[13-14]

d) 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]

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 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.

5.0 PART A- SYSTEMATIC REVIEW OF LITERATURE

5.1 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.

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	○ 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 (monotherapy or combination with chemotherapy: taxane-based, anthracyclines, cyclosphosphamide, carboplatin) ○ chemotherapy + dual targeted therapy ○ chemotherapy + single targeted therapy

c	Comparator	○ chemotherapy + single targeted therapy ○ chemotherapy only
d	Outcomes	Primary Outcomes: ○ 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 Secondary outcomes: ○ Conserving surgery rates/Conservative breast surgery (for early breast cancer) Safety ○ Adverse events (any grade 3-4 adverse event) Economic impacts ○ Cost effectiveness analysis ○ Cost utility analysis ○ Cost benefit analysis ○ Cost analysis ○ Any other measure of economic outcomes Organisational issues ○ Length of hospital stay (LOS) ○ Hospital Admission ○ Day care Social implication ○ Preferences ○ Tolerability ○ Satisfaction
e	Study design	HTA reports, systematic review with network meta-analysis, systematic review with meta-analysis, randomised controlled trial (RCT), cohort and economic evaluation studies.
f	English full text articles	

Exclusion criteria

c. Study design: Non-randomised controlled trials, animal study, laboratory study, narrative review, editorials, and letter to the editors.

d. 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, Cochrane assessing of bias tools (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: pathological complete response (pCR) rate and safety data. The data was pooled when heterogeneity, I^2 was less than 80%.[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, 86 relevant abstracts were retrieved in full text. After applying inclusion and exclusion criteria, 67 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.

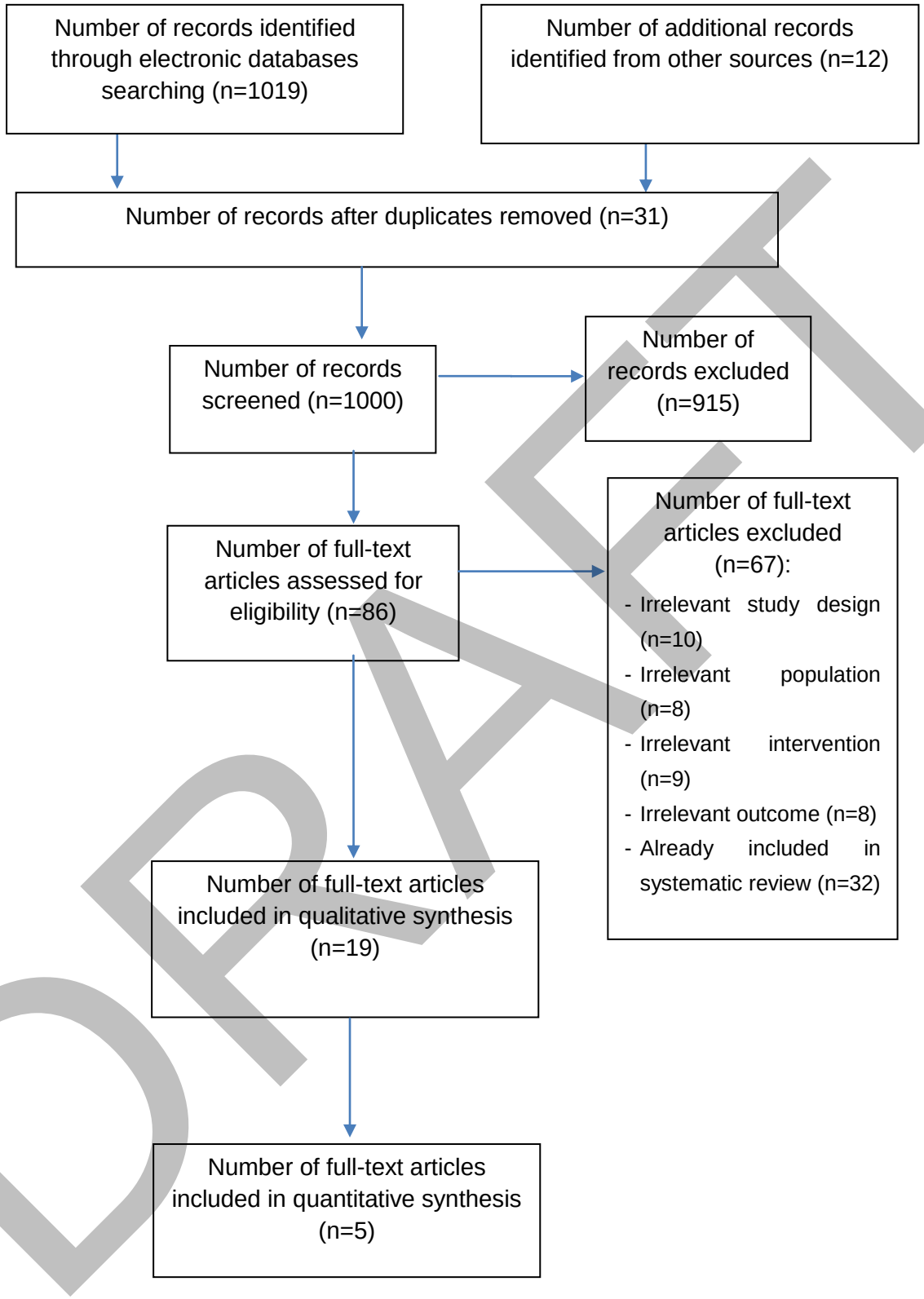


Figure 2: Flow chart of study selection

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 (NCT02161)	n=549	CT-P6 (Biosimilar) vs Trstuzumab	• Pathological complete response rate • Adverse events: neutropenia, diarrhea, febrile neutropenia, hepatotoxicity
	Baselga, 2012 (NeoALTTO) Carey, 2016 (CALGB 40601) Bonnefoi, 2015 (EORTC) Guarneri, 2012 (CHER-LOB) Holmes, 2013 (LPT 109096) Robidoux, 2013 (NSABP B-41) Hurvitz, 2020 (TRIO-USB07)	n=455 n=305 n=128 n=121 n=100 n=529 n=128	Trastuzumab + Lapatinib + Chemotherapy vs Lapatinib + Chemotherapy vs Trstuzumab + Chemotherapy	• Pathological complete response rate • Adverse events: neutropenia, diarrhea, febrile neutropenia, hepatotoxicity
	Untch, 2012 (GeparQuinto) Alba, 2014 (GEICAM)	n=615 n=102	Lapatinib + Chemotherapy vs Trstuzumab + Chemotherapy	• Pathological complete response rate • Adverse events: neutropenia, diarrhea, febrile neutropenia, hepatotoxicity
Nakashoji et al. (2018)	Buzdar, 2013 (ACOSOG Z1041) Gianni, 2010 (NOAH) Pierga, 2010 (REMAGUS) Steger, 2013 (ABCSG-24)	n=282 n=235 n=120 n=93	Trastuzumab Chemotherapy vs Chemotherapy (FEC+ Pacli+cyclo+doce)	• Pathological complete response rate • Adverse events: neutropenia, diarrhea, febrile neutropenia, hepatotoxicity
Randomised Controlled Trials (RCTs)				
Gianni et al. (2012)	Locally advanced breast cancer	n=417	Pertuzumab+Trastuzumab +Docetaxel vs Trastuzumab + Docetaxel	• Pathological complete response rate • Safety
Gianni et al. (2016)	Locally advanced breast cancer	n=417	Pertuzumab+Trastuzumab +Docetaxel vs Trastuzumab + Docetaxel	• 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	• 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	• Relapse-free survival • Death/Overall survival
Huober et al. (2019)	NeoALTTO study (BIG 1-06), early breast cancer, patients with operable, unilateral, non-inflammatory	n=455	Lapatinib Trastuzumab, Paclitaxel	• 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	• 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 ≥ 2.0), tumour lesions size of ≥ 2cm	n=620	EC+ Lapatinib vs EC + Trastuzumab	• Disease-free survival/Event-free survival • Adverse event(s)
Stebbing et al. (2021)	NCT 02162667 stage I–IIIa operable HER2-positive breast cancer	n=549	CT-P6 Biosimilar vs Trastuzumab	• Pathological complete response rate • Disease-free survival • Overall survival • Adverse event(s)
Jackisch et al.	HannaH study, early breast cancer	n=596	SC Trastuzumab vs IV Trastuzumab	• 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	• 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	• Pathological complete response rate • Breast conservation • Toxicity
Murthy et al. (2018)	Locally advanced breast cancer	n=977 n=45	Pertuzumab + Trastuzumab +Paclitaxel/Docetaxel+ FEC/ (Doxorobucin+ Carboplatin	• Pathological complete response rate • Breast conservation • Toxicity
Hussain et al. (2018)	Locally advanced breast cancer		Pertuzumab+ Trastuzumab + Docetaxel + Carboplatin vs Trastuzumab + Docetaxel + Carboplatin	• 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	• Cost-effectiveness analysis (CEA)
Kunst et al. (2020)	Locally advanced breast cancer	NA	S1 & S2: DDAC-THP, S3: THP, S4: HP, S5: TCHP	• 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	• Single Technology Appraisal by NICE
Lee et al. (2016)	HER2+ Early Breast Cancer	NA	1) SC trastuzumab 2) IV trastuzumab	• 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	• 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 relevant articles using these checklist or risk of bias tools 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 were used.[15-17] Review authors' judgements involved answering pre-specified questions and discrepancies were resolved by consensus. For the economic studies (Squires et al.), the appraisal was done by the Evidence Review Group Perspective of a NICE Single Technology Appraisal hence we did not include it in economic appraisal.

Assessment for Systematic Review (SR) using ROBIS[15]

Two SR were included in this assessment and the risk of bias is shown in Table 3. The data collection and included study appraisal domain for article by Nakashoji et al. was attached in supplemental data which cannot be downloaded, thus was judged to have some concern of bias for the third domain.

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

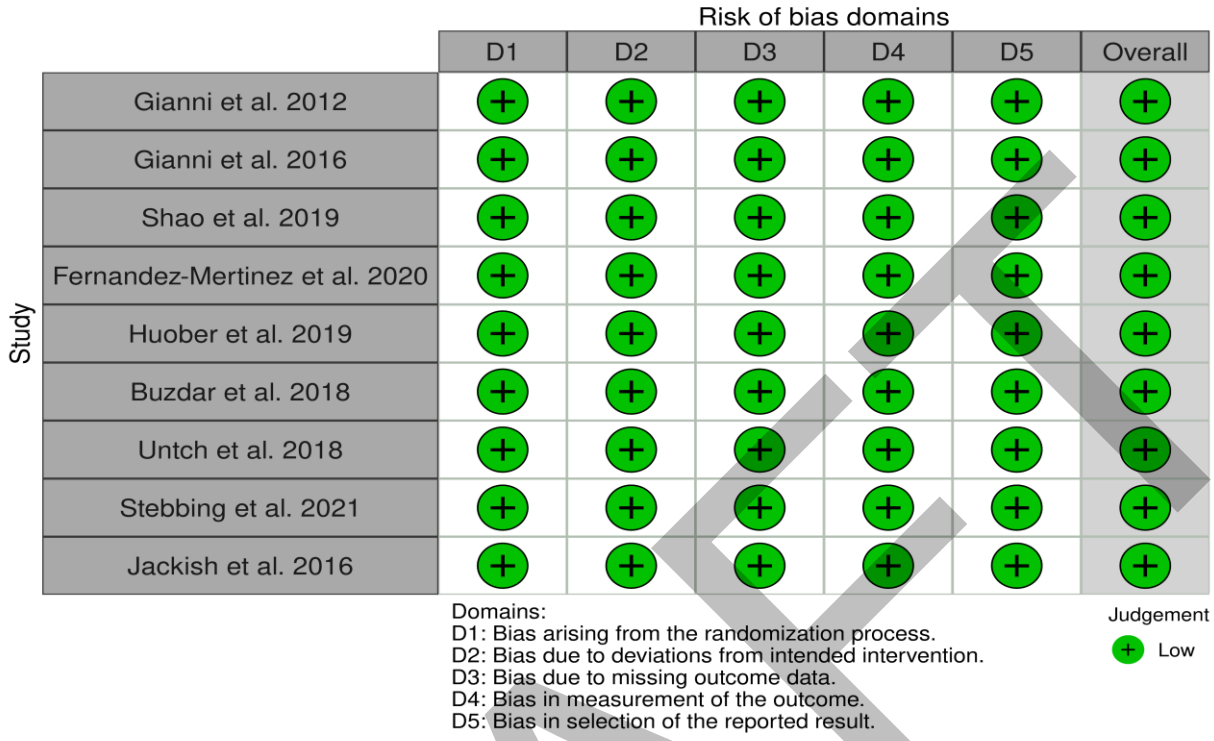
Review	Phase 2				Phase 3
	1. STUDY ELIGIBILITY CRITERIA	2. IDENTIFICATION AND SELECTION OF STUDIES	3. DATA COLLECTION AND STUDY APPRAISAL	4. SYNTHESIS AND FINDINGS	RISK OF BIAS IN THE REVIEW
Zhang et al. 2021	+	+	+	+	+
Nakashoji et al. 2018	+	+	-	+	+

X High risk - Unclear + low risk of bias

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 is shown in figure 4. All of them were judged as overall low risk of bias for all domains.

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) Checklist[17]

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 there is common side effect such as neutropenia had not been measured.

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

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

Assessment for Economic Evaluation Studies using Critical Appraisal Skills Programme (CASP) Checklist[17]

Three cost-effectiveness analyses were included in this assessment and was 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.

Table 6: Summary qual. ity assessment for economic studies using CASP checklist

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

6.3 EFFICACY/ EFFECTIVENESS

There were fourteen included studies on the effectiveness of targeted therapies in combination with neoadjuvant chemotherapy for HER2-positive breast cancer of which two were SR with NMA, nine RCTs and three were cohort studies. The results were reported based on outcomes as follow; pathologic complete response (pCR), progression free survival (PFS), number of patients 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 will be divided into five types of comparison; combination of Pertuzumab with Trastuzumab, combination of Lapatinib with Trastuzumab, comparison between Trastuzumab and chemotherapy alone, comparison between Trastuzumab and Lapatinib and comparison between Trastuzumab biosimilar and Trastuzumab only.

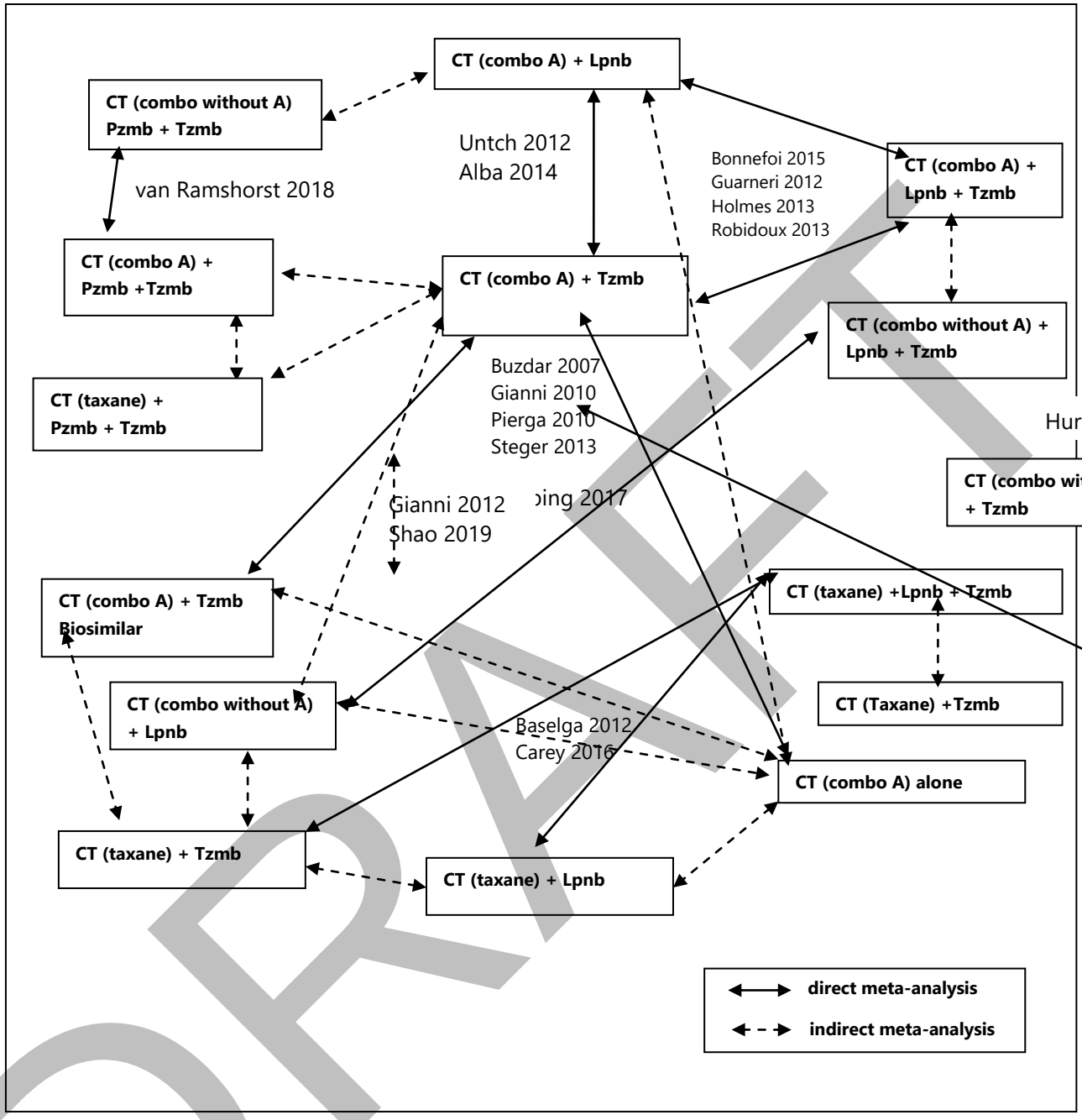


Figure 1. Network Meta-analysis for outcome pCR studies in Zhang et al. 2021 that will be used in the extraction data (list of articles)

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).

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

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)+ traztuzumab +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

- **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 chemotherapy, pertuzumab plus trastuzumab versus combination of chemotherapy plus trastuzumab and 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 this outcome for this intervention, mono chemotherapy by 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 plus docetaxel/paclitaxel with trastuzumab plus docetaxel/paclitaxel in early and locally advanced HER2 positive breast cancer patients. Pooled data from our RCTs showed that combination of pertuzumab, trastuzumab plus docetaxel/paclitaxel significantly increased pathological complete response (pCR) rate with OR 2.33 (95% CI 1.57 to

3.47) compared with trastuzumab plus docetaxel, when we include observational study the rate was better in combination of pertuzumab, trastuzumab plus docetaxel with OR 2.99 (95% CI 2.17 to 4.13) compared with trastuzumab plus docetaxel only (Figure 3).

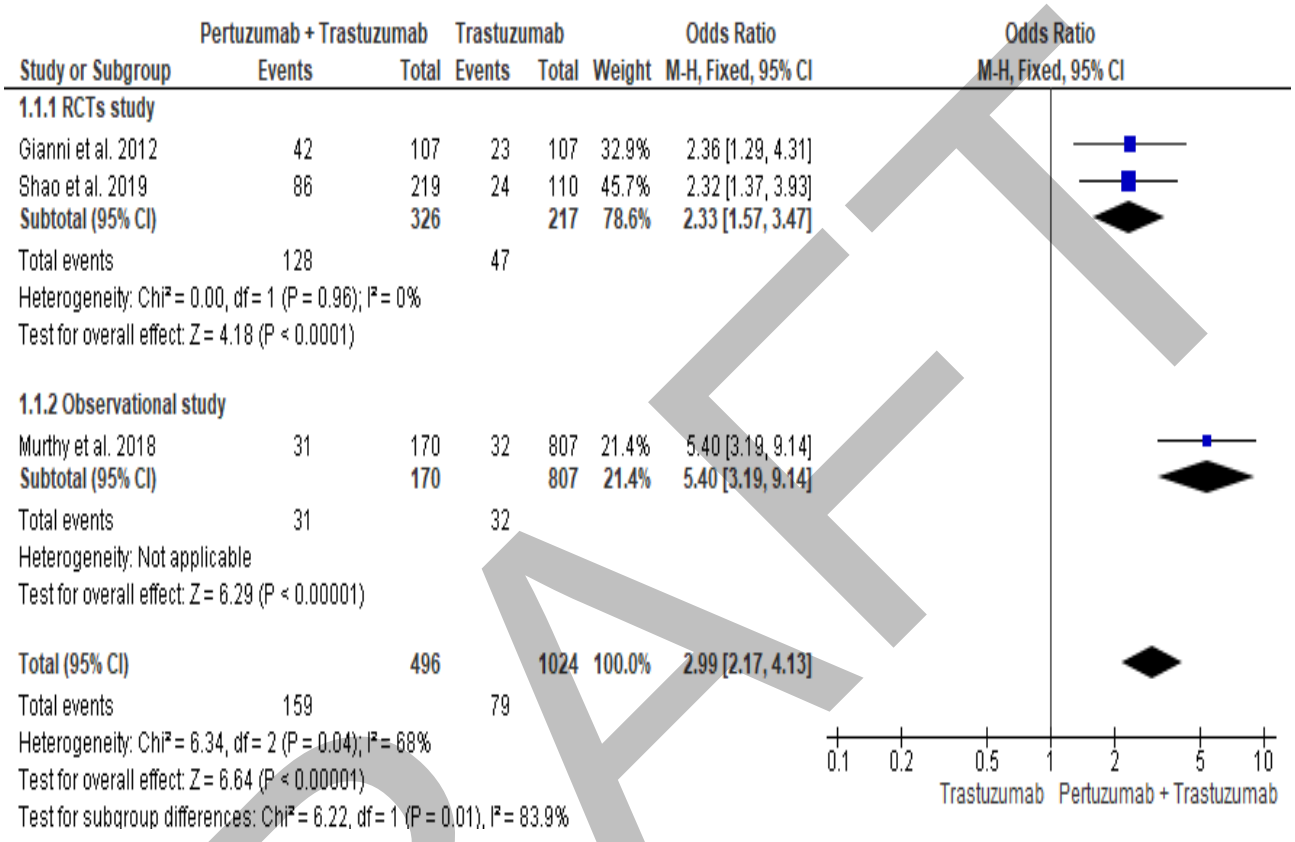


Figure 2. Pertuzumab, Trstuzumab plus Docetaxel versus Trastuzumab plus Docetaxel; Outcome: Total pathological complete response rate

When 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 plus trastuzumab plus docetaxel than the treatment of trastuzumab plus docetaxel (Figure 4).

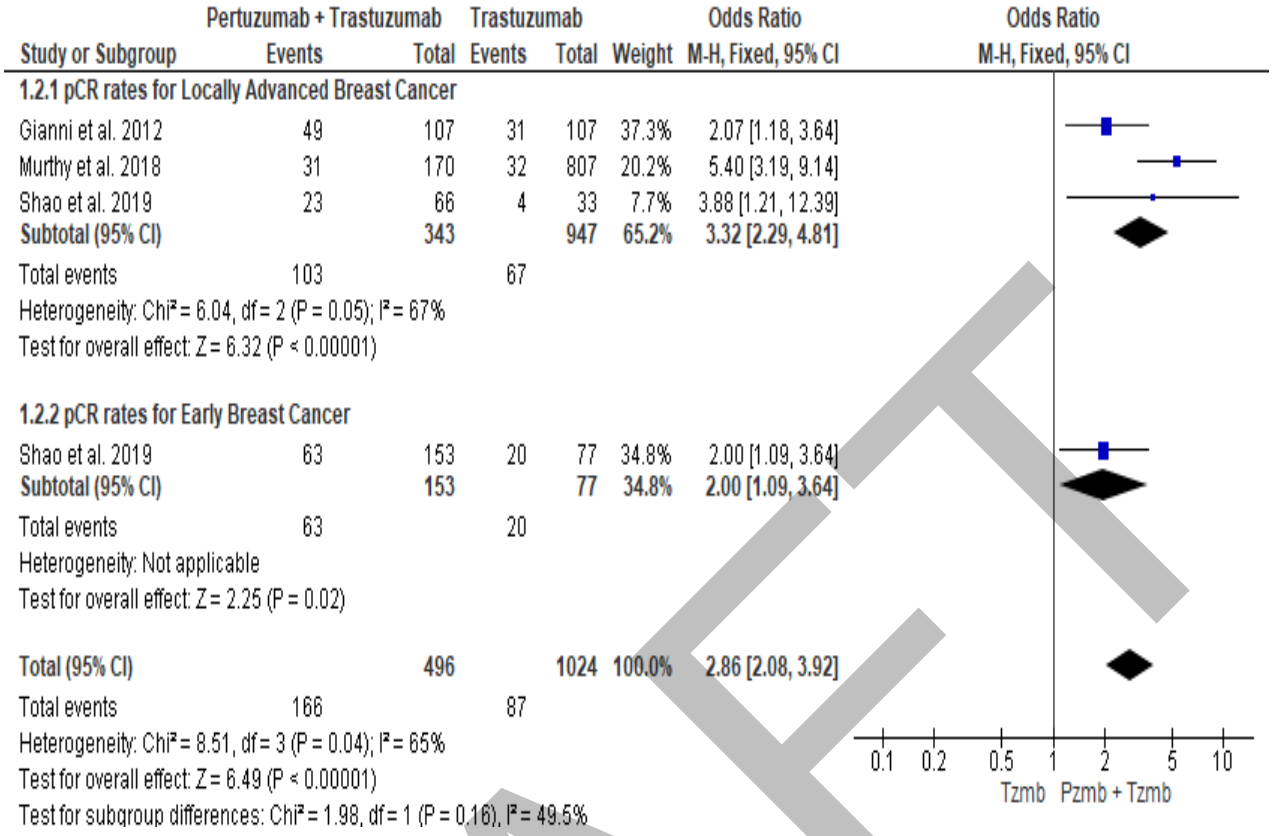


Figure 3. Pertuzumab, Trstuzumab plus Docetaxel versus Trastuzumab plus Docetaxel; Outcome: Total pathological complete response rate; Subgroup: Locally Advanced and early BC

- **Combination of Lapatinib, Trastuzumab plus Chemotherapy versus Lapatinib plus Chemotherapy / Trastuzumab plus 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 plus chemotherapy versus combination of lapatinib plus 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 plus 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 plus trastuzumab resulted in not significant pCR rate when compared with combination of chemotherapy plus 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 plus trastuzumab significantly increased the pCR rate, OR 3.33 (95% CI 1.94 to 5.37)] compared with mono chemotherapy plus

lapatinib only.[18, level I] Combination of mono chemotherapy, lapatinib plus trastuzumab was significantly increased pCR rate when compared with mono chemotherapy plus trastuzumab only [OR 1.83 (95% CI 1.12 to 2.82)].

- **Combination of Trastuzumab plus 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] Thirteen studies that enrolled 3184 patients were included. For this intervention, five studies with a total of 537 patients were involved. Combination of trastuzumab with 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 cohort study in 2019 to compare the pCR in 131 patients with locally advanced breast cancer between trastuzumab plus taxane-based chemotherapy with 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% which was double in comparison. This difference was statistically significant with a p-value of 0.002 (<0.05).[22, level I]

- **Trastuzumab plus Chemotherapy versus Lapatinib plus Chemotherapy**

a) Combination chemotherapy (with or without anthracyclines)
In SR and NMA conducted by Zhang et al, in direct meta-analysis comparison between trastuzumab plus chemotherapy with lapatinib plus chemotherapy, the pooled analysis showed that trastuzumab plus chemotherapy (with anthracyclines) significantly increase pCR compared to lapatinib plus 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 plus chemotherapy (without anthracyclines) and trastuzumab plus chemotherapy (without anthracyclines) OR 0.43 (95% CI 0.12 to 1.12).[18, level I]

- **Trastuzumab Biosimilar plus Chemotherapy versus Trastuzumab plus 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 plus chemotherapy (with anthracyclines) versus trastuzumab plus 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 plus Trastuzumab/ Pertuzumab plus 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 randomized to treatment group pertuzumab plus trastuzumab plus chemotherapy (docetaxel) (n=107), group trastuzumab plus docetaxel (n=107), group pertuzumab plus trastuzumab (n=107) and pertuzumab plus docetaxel (n=96). The five-year progression-free survival rates were higher in group pertuzumab plus trastuzumab plus docetaxel, 86% (95% CI 77 to 91) than in group trastuzumab plus docetaxel, 81% (95% CI 71 to 87) with hazard ratio (HR) 0.69 (95% CI 0.34 to 1.40). However, the PFS rate was lower in group pertuzumab plus trastuzumab when compared with group pertuzumab plus trastuzumab plus docetaxel which was 73% (95% CI 64 to 81) with HR 1.25 (95% CI 0.68 to 2.30) and also lower in group pertuzumab and docetaxel [73% (95% CI 63 to 81)] compared with group pertuzumab plus trastuzumab plus docetaxel with HR 2.05 (95% CI 1.07 to 3.93). [24, level II-1]

- **Trastuzumab Biosimilar plus Chemotherapy versus Trastuzumab plus Chemotherapy**

a) Combination chemotherapy (with or without anthracyclines)

Stebbing et al. (2021) conducted 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] Estimated hazard ratio (HR) were similar between group CT-P6 (trastuzumab biosimilar) plus chemotherapy (with anthracyclines) and group trastuzumab reference plus chemotherapy (with anthracyclines) 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)] with HR 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 intervention.

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

a) Mono chemotherapy

In 2016, RCT (NeoSphere) conducted by Gianni et al. analysed disease-free survival in patients who had surgery that include intervention of pertuzumab and trastuzumab. [24, level II-1] They found that disease-free survival results were consistent

with progression-free survival that was highest in the group of pertuzumab plus trastuzumab plus chemotherapy (docetaxel) [84% (95% CI 72 to 91)], followed by combination of trastuzumab plus docetaxel [81% (95% CI: 72, 88)], combination pertuzumab plus trastuzumab [80% (95% CI 70 to 86)] and combination of pertuzumab plus docetaxel [75% (95% CI 64 to 83)].[24, level II-1]

- **Combination of Lapatinib, Trastuzumab plus Chemotherapy versus Lapatinib plus Chemotherapy / Trastuzumab plus 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: lapatinib plus trastuzumab plus chemotherapy (paclitaxel) (n=118), trastuzumab plus paclitaxel (n=120) and lapatinib plus paclitaxel (n=67). They found at more than seven years of follow-up, for outcome RFS, events were highest in dual-targeted group which was 93% (95% CI 88 to 98) for lapatinib plus trastuzumab plus paclitaxel, followed by 79% (95% CI 71 to 87) for trastuzumab plus paclitaxel and 69% (95% CI 58 to 82) for lapatinib plus paclitaxel.[26, level II-1]

- **Combination of Trastuzumab plus Chemotherapy versus Chemotherapy only**

a) Combination chemotherapy (with or without anthracyclines)

Buzdar et al. (2019) in their ACOSOG trial compared the combination of trastuzumab plus 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 randomized 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 plus Chemotherapy versus Lapatinib plus Chemotherapy**

a) Combination chemotherapy (with or without anthracyclines)

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

- **Trastuzumab Biosimilar plus Chemotherapy versus Trastuzumab plus 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)

plus chemotherapy (docetaxel with anthracyclines) versus trastuzumab reference plus 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, number of patients had progressed or died were 16% in group pertuzumab plus trastuzumab plus docetaxel (n=17), 18% in group trastuzumab plus docetaxel (n=19), 25% in group pertuzumab plus trastuzumab (n=24) and 25% in group pertuzumab plus docetaxel (n=27). [24, level II-1].

6.3.5 Event-free survival

Two RCTs reported on this outcome that involved lapatinib and trastuzumab

- **Combination of Lapatinib, Trastuzumab plus Chemotherapy versus Lapatinib plus Chemotherapy / Trastuzumab plus Chemotherapy**

a) Mono chemotherapy

Huober et al (2019) reported the updated outcome results of the 455 patients enrolled in the NeoALTTO trial from 2008 to 2010 regarding the secondary end-points of event-free survival (EFS).[29, level II-1] The six-year EFS rates were highest in dual-targeted group, lapatinib plus trastuzumab plus chemotherapy (paclitaxel) (74%) followed by lapatinib plus paclitaxel (67%) and trastuzumab plus paclitaxel (67%). The estimated hazard ratio for group lapatinib plus paclitaxel versus trastuzumab plus paclitaxel was higher [0.98% (95% CI 0.64 to 1.51, p=0.56)] than for group lapatinib plus trastuzumab plus paclitaxel versus trastuzumab plus paclitaxel [0.81% (95% CI 0.52 to 1.26, p=0.35)].[29, level II-1]

- **Combination of Trastuzumab plus 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 randomized to receive intravenous (IV) or subcutaneous (SC) trastuzumab plus 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 different of 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 plus Chemotherapy versus Lapatinib plus Chemotherapy / Trastuzumab plus 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 group lapatinib plus trastuzumab plus chemotherapy (paclitaxel) had a significant improvement in overall survival compared with trastuzumab plus 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 plus trastuzumab plus paclitaxel (96%) followed by trastuzumab plus paclitaxel (88%) and lapatinib plus paclitaxel (84%) with corresponding four death (3.4%) occured in lapatinib plus trastuzumab plus paclitaxel, nine death (13.4%) occured in lapatinib plus paclitaxel and 14 deaths (11.7%) occured 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 lapatinib plus trastuzumab plus chemotherapy (paclitaxel) followed by group lapatinib plus paclitaxel (82%) and group trastuzumab plus paclitaxel (79%).[29, level II-1] However the differences were not statistically significant in lapatinib plus trastuzumab plus paclitaxel group as compared with trastuzumab plus paclitaxel group [HR 0.72% (95% CI 0.41 to 1.27), p=0.26] and when lapatinib plus paclitaxel compared with trastuzumab plus paclitaxel group [HR 0.85% (95% CI 0.49 to 1.46) p=0.56].[29, level II-1]

- **Combination of Trastuzumab plus 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 plus chemotherapy (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]

- **Trastuzumab Biosimilar plus Chemotherapy versus Trastuzumab plus Chemotherapy**

a) Combination chemotherapy (with or without anthracyclines)

The estimated three-year overall survival rate in RCT by Stebbing et al. (2021) was similar between trastuzumab biosimilar (CT-P6) with HR 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 trastuzumab plus 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 between hormone receptor-positive and hormone receptor-negative in their NeoSphere trial.[19, level II-1] Pathological complete response (pCR) were noted higher in 36 of 57 (63·2%) in patients with hormone receptor-negative tumours than 13/50 (26%) in patients with hormone receptor-positive who received pertuzumab plus trastuzumab plus chemotherapy. In group who received pertuzumab plus trastuzumab only, 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 (Table 8).[19, level II-1]

Table 8. Pathological complete responses according to subtype hormone analysis[19]

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)

Murthy et al. (2018) in their observational study, when they did a univariate analysis within the pertuzumab plus 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 than 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 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 (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).[29, level II-1]

In analysis did by Untch et al. (2018), patients who achieved pCR had statistically significant 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 patents. However, there was a statistically significant for outcome OS in patients treated with lapatinib plus

trastuzumab 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 that the results for EFS were similar 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

6.4.1 United State Food and Drug Administration (US FDA)

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) is currently 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 until to treat HER2-overexpressed breast cancer. All biosimilars of trastuzumab have demonstrated efficacies and safety outcomes similar to those of the standard trastuzumab

6.4.2 Side Effects/ Adverse events

The side effects 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 neutropenia 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]

Table 9. Most frequent WHO grade 3-5 side effects in each experimental arm in SR with NMA by Zhang et al.[18]

Interventions	neutropenia	diarrhoea	hepatotoxicity	febrile neutropenia
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

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, neutropenia 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 incidences of diarrhea and skin disorders compared with trastuzumab plus chemotherapy. However, combination of trastuzumab plus pertuzumab had significantly lower incidences of neutropenia compared with the chemotherapy-containing arms. The incidences 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]

Table 10. Rank according to the types of adverse events for all interventions[22]

Diarrhea	Neutropenia	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	-	-

- ***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 plus trastuzumab plus chemotherapy (docetaxel) showed a significant higher incidence of diarrhea in patients treated with pertuzumab plus trastuzumab plus docetaxel compared to patients treated with trastuzumab and docetaxel with OR 2.90 (95% CI 1.73 to 4.88). However, there were no difference for total number of serious adverse events with OR 1.31 (95% CI 0.80 to 2.13), neutropenia OR 0.93 (0.65, 1.33), febrile neutropenia OR 1.23 (95% CI 0.51 to 2.97), and leucopenia OR 0.43 (0.16, 1.18) (Figure 5).[20,24,32]

In details of PEONY trial by Shao et al. that reported there a higher incidence of diarrhea in the pertuzumab plus trastuzumab plus chemotherapy group than in the trastuzumab plus chemotherapy plus placebo group.[20, level I] Most of the incidence was grade 1 [58 of 218 (26.6%) versus 13 of 110 (11.8%) in the placebo group] or grade 2 [24 of 218 (11.0%) versus 5 of 110 (4.5%)], while two of 218 patients in the pertuzumab group (0.9%) had grade 3 events. Of the most common grade 3 or higher adverse events, there was a higher incidence of neutropenia in the pertuzumab group [83 of 218 (38.1%) versus 36 of 110 (32.7%) in the placebo group]. Serious adverse events (febrile and neutropenia) 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.[20, level I]

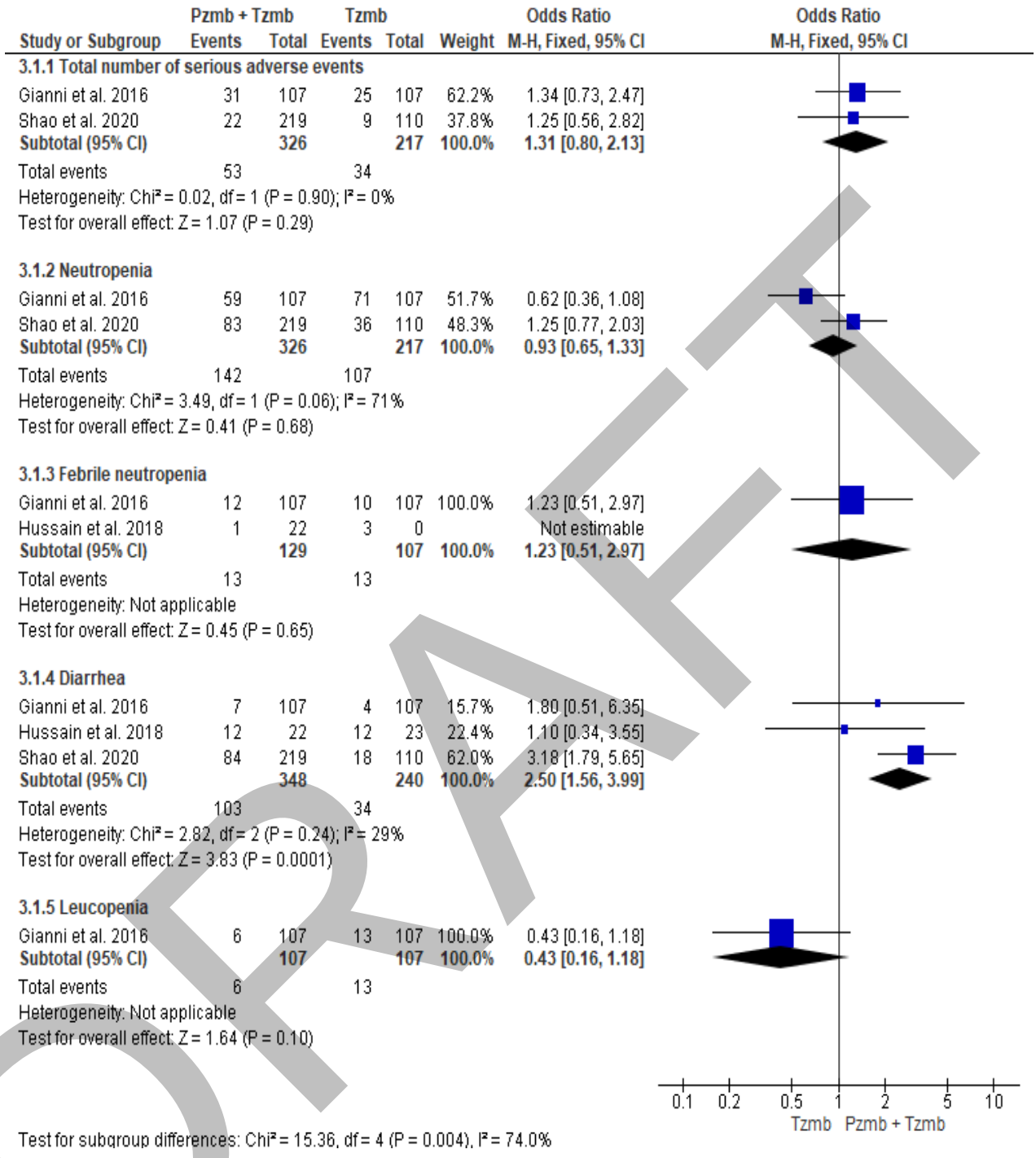


Figure 4. Combination of Pertuzumab plus Trastuzumab plus Chemotherapy versus Trastuzumab plus Chemotherapy; Outcome: Adverse events

- **Combination of Lapatinib, Trastuzumab plus Chemotherapy versus Lapatinib plus Chemotherapy / Trastuzumab plus Chemotherapy**

In details reviewed by Nakashoji et al. when they did the direct comparisons to all treatments arms for adverse events, they found that combination lapatinib plus trastuzumab plus chemotherapy had significantly higher incidences of diarrhea [OR 14.36 (95% CI 7.84 to 26.32)] and skin disorders [OR 4.11 (95% CI 1.78 to 9.51)] compared with combination of trastuzumab plus chemotherapy.[22, level I] In terms of incidences of neutropenia and cardiac events, no statistical significance differences were observed between lapatinib plus trastuzumab plus chemotherapy group and trastuzumab plus chemotherapy group [neutropenia; 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]

When they did comparison between lapatinib plus chemotherapy group versus lapatinib plus trastuzumab plus chemotherapy group, they found no significant difference between these two groups in the occurrence of diarrhea OR 1.23 (95% CI 0.85 to 1.78), neutropenia: 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).

- **Combination of Trastuzumab plus Chemotherapy versus Chemotherapy only**

SR with NMA conducted by Nakashoji et al. 2018 that included more studies (five studies) when evaluating comparison between trastuzumab plus chemotherapy versus chemotherapy found that there were no significant difference in all main adverse events that include diarrhea (OR 0.24 95% CI 0.03 to 2.17), neutropenia (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 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 which 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]

- **Trastuzumab plus Chemotherapy versus Lapatinib plus Chemotherapy**

When Nakashoji et al. did meta-analysis to compare between lapatinib plus chemotherapy versus trastuzumab plus chemotherapy they found there was a significant increase in the occurrence of diarrhea (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 neutropenia (OR1.59 95% CI 0.87 to 2.91) and cardiac events, OR 0.78 (95% CI 0.52 to 1.15).[22, level I]

- **Trastuzumab Biosimilar plus Chemotherapy versus Trastuzumab plus Chemotherapy**

In SR with NMA conducted by Zhang et al., they include one biosimilar study that compares trastuzumab biosimilar (CT-P6) plus chemotherapy (with anthracyclines) with trastuzumab plus chemotherapy (with anthracyclines) (Stebbing et al).[18, level I] According to the WHO grade 3-5 side effects, the occurrence of neutropenia in biosimilar group was 4.4% (Table 9). In details 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 neutropenia [four (1%) versus one (<1%)] and neutropenia [one (<1%) versuss 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 neutropenia in ten (4%) versus 14 (5%). 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) for a payer 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.[33]

Table 11. Strategies for patients with different neoadjuvant-adjuvant treatment[33]

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 followed by strategy 5 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, 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).[33]

Squires et al. conducted a Review Group Perspective of a NICE Single Technology Appraisal in 2018 on the clinical data submitted by company that were mainly taken from a phase II, randomised, open-label, active controlled study (NeoSphere trial).[34] 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.[34]

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).[35]

The analysis was performed from two perspectives (MOH and societal). Analysis for MOH 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 RM7561 per patient compared to IV trastuzumab treatment. 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. The used of SC trastuzumab generated a cost savings to society of RM7820 per patient.[35]

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.

- **American Society of Clinical Oncology Guideline (ASCO)**

The ASCO in 2021 developed recommendations concerning optimal neoadjuvant therapy for invasive breast cancer including chemotherapy and targeted therapies.[36]
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.[36]

- **National Comprehensive Cancer Network (NCCN)**

A clinical guideline on breast cancer was developed by NCCN in 2020.[37] 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. 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.[37]

- **European Society for Medical Oncology (ESMO)**

International consensus guideline on metastatic breast cancer was developed by ESMO in 2020.[39] 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 was currently unknown. Combination of chemotherapy plus trastuzumab is superior to combination of chemotherapy plus 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 chemotherapy plus trastuzumab in terms of OS for this population.[39]

- **Ministry of Health Malaysia**

Latest guideline 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

One cross-sectional, PrefHer study by Pivot et al. conducted in France 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 randomized 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.[39, level II-3]

The analysis was done using two-sided test against null hypothesis of 65% SC preference and it 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).[39, 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.[39, 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. 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].[39, level II-3]

No evidence retrieved on ethical and legal issues.

7.0 DISCUSSION

For effectiveness and safety outcomes, our review included two SR with NMA, nine RCTs and three cohort studies. Another one cross-sectional study was on the preference of using either subcutaneous or intravenous trastuzumab among patients. Evidence was grouped into five groups of interventions that covered dual-targeted therapy, single-targeted therapy and trastuzumab biosimilar whereby each of interventions have mono chemotherapy as well as combination chemotherapy (with or without anthracyclines) as follows:

- pertuzumab plus trastuzumab plus chemotherapy
- trastuzumab plus lapatinib plus chemotherapy
- pertuzumab plus trastuzumab without chemotherapy
- trastuzumab plus lapatinib without chemotherapy
- pertuzumab plus chemotherapy
- trastuzumab plus chemotherapy
- lapatinib plus chemotherapy
- chemotherapy alone
- trastuzumab biosimilar plus chemotherapy

We also divided the outcomes into nine that include: 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 improvement outcomes in HER2-positive early and locally advanced breast cancer patients. This finding is in agreement with several SR with MA published in many years (Chen et al. 2019, Clavarezza et al. 2016 and Hicks et al. 2015).[40-42]

7.1 INTERPRETATION OF THE EVIDENCE

Dual-targeted therapy versus Single-targeted therapy

In terms of effectiveness, evidence showed that dual-targeted therapy (pertuzumab plus trastuzumab followed by lapatinib plus 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 in two SR with NMA were consistent where they found that by adding anthracycline to chemotherapy might not improve the pCR outcome and dual-targeted therapy without chemotherapy and chemotherapy alone were both associated with the worst pCR percentages (Table 7).[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 differ between all single-targeted therapy that include trastuzumab, lapatinib, trastuzumab biosimilar and chemotherapy alone.[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 of EFS between SC trastuzumab and IV trastuzumab.[29,30] For outcome OS, the seven-year analysis was higher in dual-targeted therapy (trastuzumab plus lapatinib) compared with single-targeted therapy (trastuzumab, lapatinib).[26,29] However the result of OS did not differ between trastzumab versus chemotherapy alone and trastuzumab biosimilar.[25,27]

For outcomes of adverse events, the evidence showed that addition of pertuzumab is associated with high incidence of neutropenia and occurrence of diarrhea was high with lapatinib treatment.[18,22] These results were consistent in all studies. Our pooled meta-analysis showed the higher incidence of diarrhea with pertuzumab plus trastuzumab than trastuzumab. However there were no differences in number of serious adverse events, neutropenia, febrile neutropenia and leucopenia for between these two groups.[20,24,32] This is in line with the PEONY trial done in 2020.[20] In addition, one SR with NMA found that lapatinib-chemotherapy arms significantly cause diarrhea 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 about potential 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 no significant difference 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.[45]

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.

7.2 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. Because this treatment was established, a lot of trials were available for this population. A lot of systematic review with meta-analysis were also been conducted. The methods were in accordance with those proposed by the Cochrane Collaboration for conducting systematic review of interventions and the PRISMA statement.[16,46]

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. This is due to the short timeline given to complete this report and limited available drugs in Ministry of Health Drug Formulary, Malaysia (FUKKM).

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.

8.0 LOCAL ECONOMIC EVALUATION

8.1 DECISION ANALYTIC AND ECONOMIC MODELLING

8.1.1 OBJECTIVE

The general objective of this economic evaluation was to assess the cost-effectiveness of addition of 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) with standard neoadjuvant chemotherapy for early HER2-positive breast cancer patients with high risk of recurrence.

8.1.2 METHODS

A literature-based 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.[18,20,22,44] Taking the current practice and availability of drugs available in FUKKM, the single targeted therapy assessed was the trastuzumab biosimilar (Herzuma) 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 (Herzuma)
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[33-34,47] 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 local economic evaluation was designed from the Ministry of Health (MOH) perspective.

The simulated clinical pathways are 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,
iii. Chemotherapy only,
iv. Single targeted therapy [(IV Trastuzumab 8mg/kg loading dose (LD) then 6mg/kg maintenance dose (MD)) + (3 EC, 3 Doxetaxel)], or
v. 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.
vi. 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 (Herzuma) 6mg/kg for 6 months.
vii. Patients are in the treated and disease-free state until they experience recurrence, metastasis, or death.
viii. 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]
ix. Patients who had recurrence state can move to metastasis state or die.
x. 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.
xi. 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.

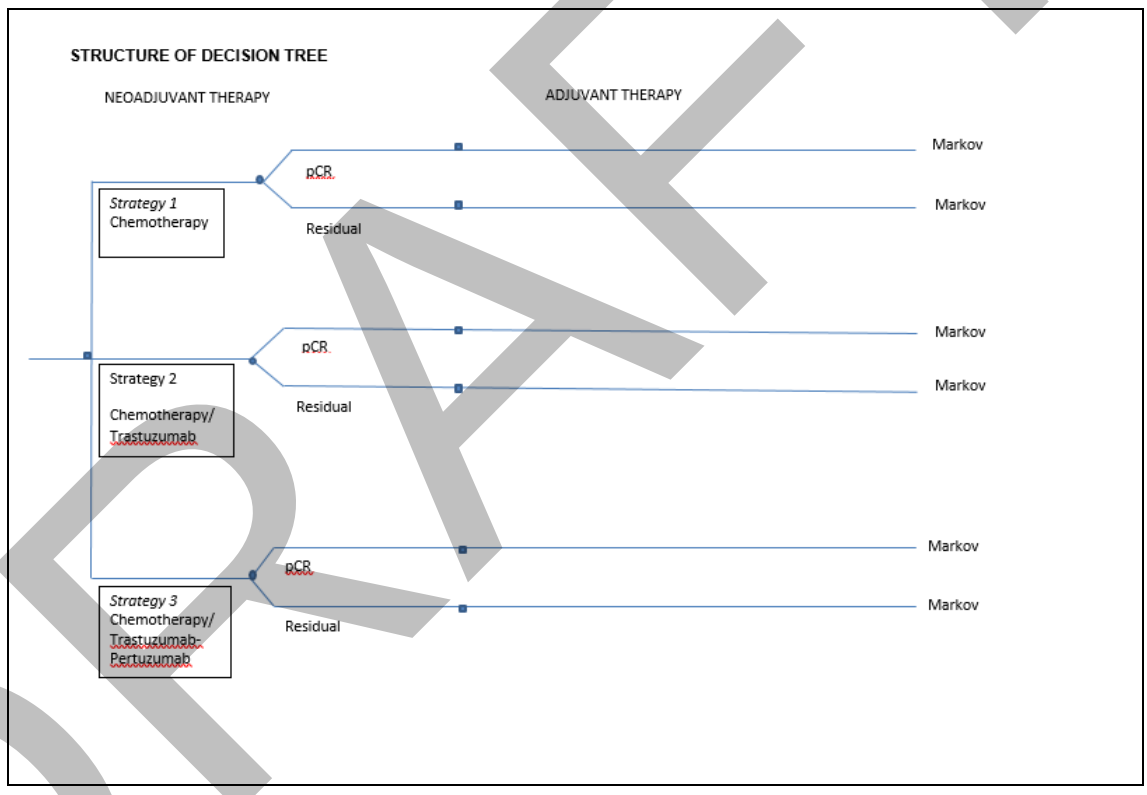


Figure 7. Decision Tree of three strategy arms of neoadjuvant therapy in high risk early HER2 breast cancer patients.

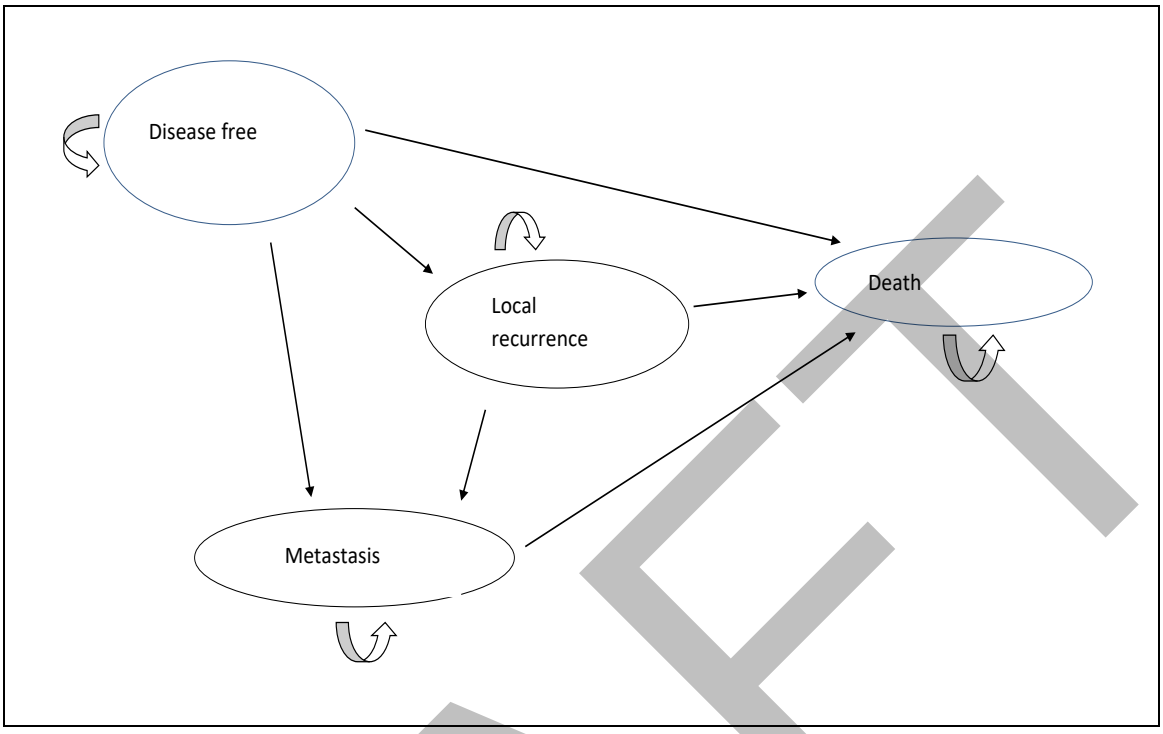


Figure 8. Markov Model of high risk early HER2 breast cancer patients after undergoing initial neoadjuvant systemic therapy, definitive surgery and adjuvant therapy.

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	48,49
Annual rate of all-cause mortality for Malaysian	Age specific	50
Chemotherapy (CT)		
pCR rate (%)	19%	51
5 year EFS (pCR)	54.8%	52
5 year EFS (No pCR)	43.3%	52

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%	52
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)	53
Annual rate of recurrence (Year 5-9)	0.049	55
Annual rate of recurrence (Year 10-14)	0.035	55
Annual rate of recurrence (Year ≥ 15)	0.027	55

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 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.

Table 13. Utility inputs

Health states	Base-case value	95%CI	Reference
Disease free	0.847	0.807 – 0.886	53
Recurrence	0.779	0.745 – 0.811	55
Metastasis	0.484	0.426 – 0.542	53

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 (RM). For the drugs, the most recent costs of drugs in 2021 were used in the model. All the parameters for cost inputs are presented in **Table 14**. All results were presented as incremental cost-effectiveness ratio (ICER).

Table 14. Cost parameters

Cost description	Base case estimate	Reference / Source
Total cost of Neoadjuvant chemotherapy (3x EC/ 3x Docetaxel)	RM 1,054.32	Hospital Kuala Lumpur Oncology Pharmacist
Total cost of IV administration (per cycle)	RM 58	Lee WC et al, 2016[36]
Total cost of IV reconstitution (per cycle)	RM 34	Lee WC et al, 2016[36]
Total cost IV Trastuzumab biosimilar 440mg (per dose)	RM 1,500	Hospital Kuala Lumpur Oncology Pharmacist
Total cost IV Pertuzumab 840mg/ Herceptin 440mg (per dose)	RM 10,500	Hospital Kuala Lumpur Oncology Pharmacist
Average cost of breast surgery per case	RM 830.32	MalaysianDRG
Average cost of clinical oncology/ radiotherapy treatment per case	RM 306.05	MalaysianDRG
Average cost of surgical / oncology outpatient clinic followup	RM 134.40	MalaysianDRG

Notes: EC: Epirubicin, cyclophosphamide; **IV**: intravenous, **MalaysianDRG**: Diagnosis related groups

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)
- Cost of different dual targeted therapy combination (RM 65,715.92)

Assumptions

It is a common approach to use assumptions based on available published literature or expert consultations in economic modelling. 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.

8.1.3 RESULTS AND DISCUSSION

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 15**. The mean total discounted cost and QALY per patient receiving 3-weekly trastuzumab biosimilar with neoadjuvant chemotherapy was RM 36,006.33 and 6.43 respectively, while for 3-weekly Pertuzumab/Trastuzumab added to neoadjuvant chemotherapy was RM 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 RM 27,298.41 and 5.90 respectively.

Table 15. Incremental cost-effectiveness ratios (ICERs) for base-case

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

The base case analysis indicated that the deterministic ICER for addition of 3-weekly trastuzumab to neoadjuvant chemotherapy was **RM 16,471.59 per QALY gained**. Over the lifetime of the patient cohort (20 years), there was a marginal cost increase of RM 8,707.92 and a marginal benefit of 0.53 QALYs per patient when 3-weekly trastuzumab biosimilar (Herzuma) 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 RM 72,815.97 with slightly higher incremental QALY gained of 0.76 compared with neoadjuvant chemotherapy alone.

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 assumed that the biosimilar drug and the originator drug is of the same effectiveness, and now the 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 16**. Results of the sensitivity analysis was plotted as tornado diagram (**Figure 16 and Figure 17)** to illustrate the differences in ICERs obtained given the range of parameter estimates were tested.

Table 16. Scenario analysis of key model parameters

a) Addition of Single targeted therapy

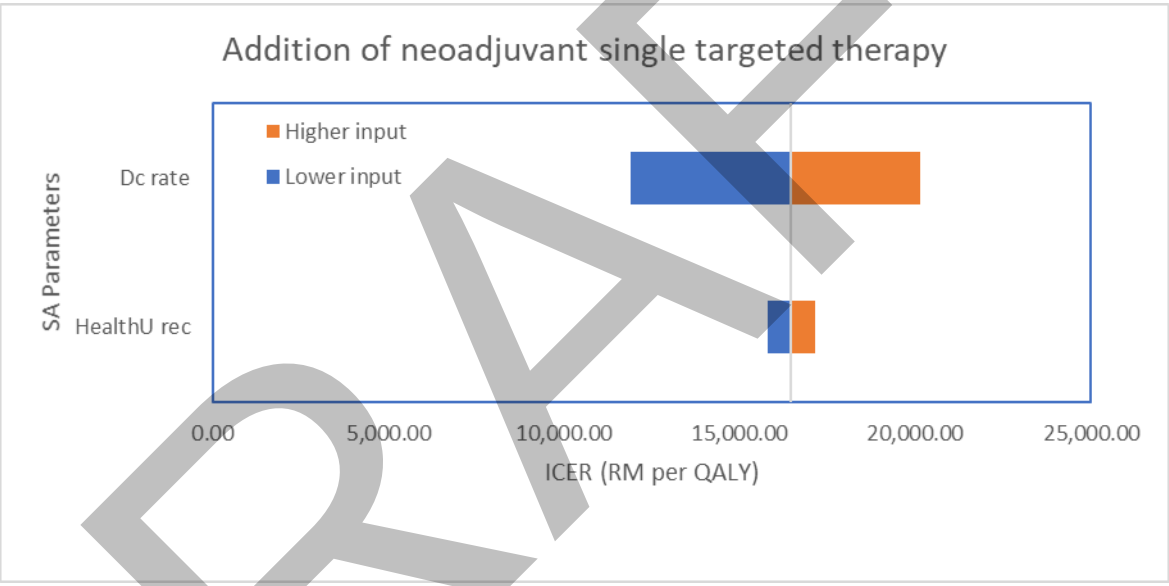
Parameters	Range	ICER of single targeted therapy
BASE CASE ICER		**RM 16,471.00**
Number of neoadjuvant therapy cycles	4	RM 10,796.90
	5	RM 13,634.24

b) Addition of Dual targeted therapy

Parameters	Range	ICER of dual targeted therapy
BASE CASE ICER		**RM 96,013.20**
Number of neoadjuvant therapy cycles	4	RM 76,893.89
	5	RM 82,168.18
Cost reduction of Pertuzumab-Trastuzumab (Herceptin) combo	25%	RM 60,302.38
	50%	RM 47,555.63
	75%	RM 23,326.84
Cost of Pertuzumab with Trastuzumab biosimilar (Herzuma)	RM 65,715.92	RM 82,539.49

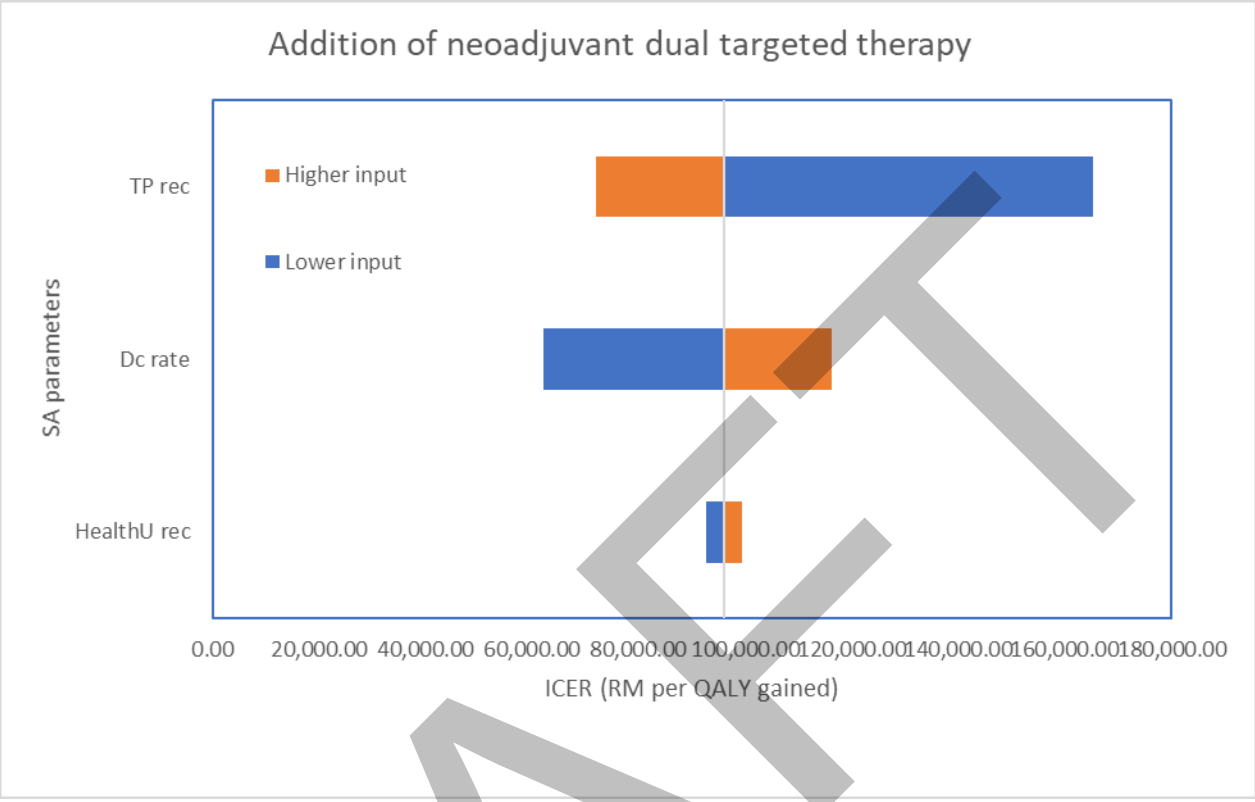
By varying the input parameters, the estimated ICERs ranged from a lower bound of RM 10,796.90 per QALY gained to an upper bound of RM 20,144.54 when comparing addition of single targeted therapy to standard neoadjuvant therapy; and a lower bound of of RM 23,326.84 per QALY gained to an upper bound of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

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.



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

Figure 16. 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 17. Tornado diagram of addition of neoadjuvant Pertuzumab/Trastuzumab to chemotherapy (one-way sensitivity analysis)

LIMITATIONS

One of the main limitations of these analyses was the use of trial-based clinical parameters (pCR rates, transition probability, long term survival, utility values) obtained from the literature review due to lack of real-world 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.

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 in MOH hospitals. Therefore, evaluation of the other targeted therapies such as lapatinib, neratinib, trastuzumab emtansine, were not included in the objective of this local economic evaluation.

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 had shown to improve the pathologic complete response rates in HER2-positive early and locally advanced breast cancer population particularly with the treatment of dual-targeted therapy. Combination of pertuzumab plus 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-arms (neutropenia), lapatinib-arms (diarrhea and skin disorders) and chemotherapy with commonly reported side effects of diarrhea 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 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 RM7561 per patient compared to IV trastuzumab treatment while it generated a cost savings of RM7820 per patient to the society.

From the decision analytic modelling that has been conducted, addition of six cycles of neoadjuvant trastuzumab biosimilar (Herzuma) was the most cost-effective strategy for high-risk early breast cancer with HER2 positive, yielding an ICER of RM 16,471.59 per QALY gained. Addition of neoadjuvant Pertuzumab/ Trastuzumab on top of standard neoadjuvant chemotherapy yielded an ICER of RM 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. Definition of one Malaysian GDP per capita per QALY gained is RM 43,475.

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.

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-I	**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)

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]

e) 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

b. Population: Adult patients with HER2-positive breast cancer, early breast cancer and locally advanced breast cancer

c. Intervention: Targeted therapies: Monoclonal antibodies such as trastuzumab, trastuzumab biosimilar and pertuzumab

Kinase inhibitors: lapatinib
(Combination with chemotherapy: docetaxel, doxorobucin, paclitaxel)

d. 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.

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

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

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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. Ther Adv Med Oncol. 2021 doi: 10.1177/17588359211006948.	**Systematic review (SR) of RCTs and Network Meta-analysis (NMA)** (36/39 included for NMA) **Aim** To compare odds ratios (ORs) for pathologic complete response (PCR) and safety endpoints. **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. **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	I	39 articles from 36 trials including 10,379 patients 1 study chemo alone **8 studies single therapy** **8 studies dual therapy** 2 studies TDM1 2 studies trastu bio-similar **Three steps:** **First steps:** All treatment were divided into several arms	targeted therapy **Dual-target therapy compared with single-target therapy.** Five T-DM1 in neoadjuvant therapy **Five focused on trastuzumab biosimilars.** 24/36 studies in NMA **11 studies direct comparison single vs dual** 4 studies comb chemo vs single chemo	Single therapy, chemotherapy	NA (Evidence was searched up to November 2020.	Combination chemotherapies combined with dual-target therapy were ranked as the top two by SUCRA analysis: **Ranked by NMA of the PCRs in experimental arms** 1. Com +trastuzumab +pertuzumab= 89.8% 2. Com (A) + trastu+ pertu = 84.9% ~~3. T-DM1 (com) = 81.9% posterior probability.~~ ~~4. Com (A) +neratinib + trastu= 79.6%~~ 5. Com + traztu +lapatinib=72.8% 6. Com+ biosimilar=71.7% 7. Comb (A) + trastu + lapatinib= 68.6% ~~8. Comb + trastu= 67.7% (1 arm)~~ 9. Comb (A) + Bio=62.1% ~~10. Com (A) + neratinib=62%~~ ~~11. Com (A) + trastu= 50.8% (1 arm)~~ 12. Mono +trastu +pertu= 47.7% ~~13. T-DM1 (mono) =43.7%~~	Included studies which related: **Tzmb Biosimilar** Stebbing (NCT 02162667) **Tzmb + Lpnb** Baselga (NeoALLTTO) Carey (CALGB) Bonnefoi (EORTC) Guarneri (CHER-LOB) Holmes (LPT109096) Robidoux (NSABP B-42) Hurvitz (Trio-US B07)

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
	administered to at least one arm. If multiple publications were derived from the same clinical study, only the latest result was included. **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. **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		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.** **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	4 studies anthra vs without anthra			14. Mono+ trastu +lapatinib= 37% ~~15. Comb (A) + lapatinib=35% (1 arm)~~ ~~16. Com + lapatinib= 28.8% (1 arm)~~ 17.~~ Chemo =23.6% (1 arm)~~ ~~18. Mono + trastu=18.9% (1 arm)~~ ~~19. Mono+ pertu=13.5% (1 arm)~~ ~~20. Mono + lapatinib=6.1% (1 arm)~~ 21. Trastu + pertu=3.6% -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** **Based on the rank order:** • trastuzumab+pertuzumab • trastuzumab+TKI (lapatinib or neratinib) • as an irreversible TKI, neratinib > lapatinib • T-DM1 better > trastuzumab plus paclitaxel • trastuzumab biosimilars = trastuzumab -dual-target therapy was significantly better than single-target therapy; -combination chemotherapy was significantly better than single-agent chemotherapy;	

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
	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) **Risk of Bias** 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.		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.** **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 chemotherapy, and anthracycline-containing and				-no significant difference was found between anthracycline-containing and non-anthracycline regimens. **PCRs of direct comparison** 11 studies compare dual-target vs single-target ○ **Com (Doce+Carbo)+tzmb + lpnb vs Com + lpnb=** **OR 3.88 (1.22-9.63)** ○ Com (Doce+Carbo)+tzmb + lpnb vs Com + tzmb= OR 1.06 (0.55-1.86) ○ Com (A) + Tzmb + Lnpb vs Com (A) + tzmb= OR 1.39 (0.93-2.02) ○ **Com (A) + Tzmb + Lnpb vs Com (A) + lpnb=** **OR 2.15 (1.42-3.13)** ○ **Mono (Pacli) + tzmb + lpnb vs Mono + tzmb=** **OR: 1.83 (1.12-2.82)** ○ **Mono (Pacli) + tzmb + lpnb vs Mono + lpnb=** **OR: 3.33 (1.94-5.37)** ○ **Com (A) + lpnb vs com (A) tzmb=** **OR 1.56 (1.13-2.11)** Trastuzumab significantly increase pcr compared to lapatinib ○ Com (A) +Biosimilar vs Com (A) +Tzmb=OR 1.21 (0.91-1.56) **Safety** Anthracycline, usually considered a hyperemetic drug that is associated with a high incidence of vomiting or nausea, slightly increased the incidence of cardiac	

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
			non-anthracycline therapy.				disorders. Both lapatinib and neratinib lead to a high incidence of diarrhoea, especially neratinib, which caused diarrhoea in more than 30% of patients. Com + Tzmb + Lpnb: ○ neutropenia 13.79%, diarrhea 27.59% Com (A) + tzmb+ lpnb: ○ neutropenia 23.01%, diarrhea 26.1%, hepatotoxicity 4.41% Com + tzmb + pzmb ○ neutropenia 44.10%, diarrhea 15.28% Com (A)+ tzmb + pzmb ○ neutropenia 53.68%, diarrhea 8.99%, febrile neutropenia 11.72% Mono + tzmb + pzmb ○ neutropenia 40.49%, febrile neutropenia 8.41%, diarrhea 5.61% Mono + Tzmb + Lpnb: ○ neutropenia 8.55%, diarrhea 21.05%, hepatotoxicity 10.53% Tzmb+pzmb ○ neutropenia 0.93%, cardiac disorder, LVEF decreased ≥10%: 0.93% Com (A) + Bio: ○ neutropenia 4.40% **Conclusion** In summary, trastuzumab plus pertuzumab-based dual-target therapy with combination chemotherapy regimens	

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
							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	

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. Cancer Treat Rev. 2018 Jan;62:9-17. doi: 10.1016/j.ctrv.2017.10.009. Epub 2017 Oct 31. PMID: 29127857.	**Systematic review (SR) of RCTs and Meta-analysis (MA) also Network Meta-analysis (NMA)** (13 studies) **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. **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	I	13 studies including 3184 patients **5 Studies** Trastu vs Chemo alone (n=537) **5 Studies** Trastu + Lapatinib vs Trastu vs Lapatinib (n=1513) **2 Studies** Trastu vs Lapatinib (n=717) **1 Study** Trastu + Pertu vs Trastu vs Pertu (n=417)	**5 Studies** CT + Trastu **5 Studies** CT+ Trastu + Lapatinib **2 Studies** CT + Trastu **1 Study** CT+ Trastu + Pertu	vs CT alone vs Trastu vs Lapatinib vs Lapatinib vs Trastu vs Pertu	Up to November 2016	**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 + lpnb **significantly achieved less pCR** than CT + tzmb (OR = 0.62, 95% CI = 0.48–0.81, P=0.003). CT + tzmb + lpnb vs CT + tzmb resulted in a **significant difference** (OR = 2.38, 95% CI = 1.54–3.68, P < 0.0001). CT + lpnb vs CT + tzmb + lpnb which had shown a **significant difference** (OR = 2.34, 95% CI = 1.76–3.10, P < 0.00001), **Number of patients who had grade 3 or 4 adverse events** including diarrhea, neutropenia, and skin disorders. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria (NCI-CTC) version 4.0. o Diarrhea was reported in 10 studies (chemo) and all of them reported grade 3 and 4 events based on NCI-CTC. o Neutropenia was reported in 11 studies (chemo) of which 10 reported grade 3 and 4 events. o Cardiac events were reported in 12 studies (Pertuzumab less cardiac event) o Skin disorder was reported in 10 studies (chemo) and all of them reported grade 3 and 4 events.	

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
	searches. **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. **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						Mostly adverse events occurred with chemo and lapatinib o Lpnb-containing treatment arms **showed significantly less treatment completion with more incidences of diarrhea and skin disorders** compared with CT + tzmb. o Tzmb + pzmb had **significantly lower incidences** of neutropenia compared with the CT-containing arms. o The incidences of cardiac events did not show any statistically significant differences between the treatment arms (more in CT+T+P) **Network Meta-analyses** dual anti-HER2 agents with CT resulted in **significantly higher incidences of pCR** than single agent (CT + tzmb + lpnb 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 = 1.1 3–5.03, P = 0.01), whereas CT and CT + lpnb resulted in **significantly lower incidences of pCR** compared with CT + tzmb. **SUCRA rank** **Treatment rank (pCR + toxicity level)** 1. CT +T + P= 0.97 2. CT + T +L=0.85 3. CT + T=0.62 4. CT + P=0.47 5. CT + L=0.32	

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
	data. **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. 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). **Risk of Bias** Using the Cochrane Collaboration risk of bias tool two independent reviewers (AN and TH) assessed all studies for appropriateness of						6. T + P=0.16 7. CT=0.1 **pCR** 1. CT +T + P= 0.85 2. CT + T +L=0.79 3. CT + T=0.70 4. CT + P=0.41 5. CT + L=0.49 6. T + lpnb=0.32 7. CT=0.53 **Adverse event rank** Diarrhea 1. CT + Tzmb +Lpnb=0.93 2. CT + Lpnb=0.8 3. CT=0.71 Neutropenia 1. CT + Lpnb=0.85 2. CT + Tzmb+L=0.73 3. CT + Pzmb=0.58 Cardiac Event 1. CT + Tzmb+ Pzmb=0.84 2. CT + Tzmb=0.66 Skin disorder	

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
	allocation, blinding, management of incomplete outcome data and the completeness of reporting of outcomes.						1. CT + Lpnb=0.96 2. CT + Tzmb + Lpnb=0.81 **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	

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, Srimuninnimit V, Bianchi G, Szado T, Ratnayake 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. Lancet Oncol. 2012 Jan;13(1):25-32. doi: 10.1016/S1470-2045(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-naive women with HER2-positive breast cancer were randomly assigned (1:1:1:1) 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). The primary endpoint, examined in the	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%	**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	**107** to group A, trastuzumab + docetaxel **107** to group C, pertuzumab + trastuzumab **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%, 5.9-18.8) 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	

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	intention-to-treat population, was pathological complete response in the breast. Neither patients nor investigators were masked to treatment. This study is registered with ClinicalTrials.gov, number NCT00545688. **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.** **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)		or more, as measured by echocardiography or multiple gated acquisition (MUGA).	intravenously, epirubicin 90 mg/m^2 IV, and cyclophosphamide 600 mg/m^2 IV every 3 weeks)			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). **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.	

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4. Gianni L, Pienkowski T, Im YH, Tseng LM, Liu MC, Lluch A, Starosławska E, de la Haba-Rodriguez J, Im SA, Pedrini JL, Poirier B, Morandi P, Semiglazov V, Srimuninnimit 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. Lancet Oncol. 2016 Jun;17(6):791-800. doi: 10.1016/S1470-2045(16)00163-7. Epub 2016 May 11. PMID: 27179402.	**Secondary/post-hoc analysis of Randomised open label of NeoSphere trial** **Aim** To report 5-year progression-free survival, disease-free survival, and safety of NeoSphere trial **Methods** multicentre, open-label, phase 2 randomised trial in hospitals and medical clinics, treatment-naive adults with locally advanced, infl ammatory, or early-stage HER2-positive breast cancer 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/m^2 every 3 weeks, increasing to 100 mg/m^2 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/m^2, epirubicin 90 mg/m^2, and cyclo phosphamide 600 mg/m^2) every	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%	**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	**107** to group A, trastuzumab + docetaxel **107** to group C, pertuzumab + trastuzumab **96** to group D pertuzumab + docetaxel	5 years	**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). **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) 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]). **Tolerability** was similar across groups (neoadjuvant and adjuvant treatment periods combined). **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). The most common grade 3 or **worse adverse**	

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	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. **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)		or more, as measured by echocardiography or multiple gated acquisition (MUGA).	intravenously, epirubicin 90 mg/m² IV, and cyclophosphamide 600 mg/m² IV every 3 weeks)			**events:** **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 **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 **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 **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.	

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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	**PEONY phase 3 Randomised Clinical Trial** **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. **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. **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	II-1	**329** patients from March 2016-March 2017, Early and Locally advanced BC: 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.	**219 patients** **EBC: 153** **LABC: 66** 4 cycles of: -IV pertuzumab (840-mg loading dose and 420-mg maintenance doses) + trastuzumab (8-mg/kg loading dose and 6-mg/kg maintenance doses), + docetaxel (75 mg/m2)	**110 patients** **EBC: 77** **LABC: 33** 4 cycles of: IV placebo, trastuzumab, and docetaxel every 3 weeks.	1 year	**Outcomes of included studies** **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). **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 **diarrhea** in pertuzumab gp (84 of 218 (38.5%) vs 18 of 110 (16.4%). **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.	

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	conducted using SAS, version 9.4 (SAS Institute Inc).							

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6. Murthy RK, Raghavendra AS, Hess KR, Fujii T, Lim B, Barcenas CH, Zhang H, Chavez-Mac-Gregor M, Mittendorf EA, Litton JK, Giordano SH, Thompson AM, Valero V, Moulder SL, Tripathy D, Ueno NT. Neoadjuvant Pertuzumab-containing Regimens Improve Pathologic Complete Response Rates in Stage II to III HER-2/neu-positive Breast Cancer: A Retrospective, Single Institution Experience. Clin Breast Cancer. 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)	**Observational study of data in MD Anderson Cancer Center** **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. **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.** **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+	II-11	**977 patients** from Jan 2005-Jan 2016, Locally advanced BC.	**170 patients** **Trastuzumab + Pertuzumab** 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) **(3 regimens with anthracycline): TP+taxane+ either:** (n=73/170) **A. FEC** **5-Fluorouracil** at 500 mg/m2, **Epirubicin** at 100 mg/m2**, Cyclophosphamide** at 500 mg/m2 (FEC) every 3 weeks (4 cycles) **B. FAC** **5-Fluorouracil** at 500 mg/m2, **Doxorobucin** at 50 mg/m2**, Cyclophosphamide**	**807 patients** **Trastuzumab** 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) **(3 regimens with anthracycline): T+ taxane + either** **A. FEC** **5-Fluorouracil** at 500 mg/m2, **Epirubicin** at 100 mg/m2**, Cyclophosphamide** at 500 mg/m2 (FEC) every 3 weeks (4 cycles) **B. FAC** **5-Fluorouracil** at 500 mg/m2, **Doxorobucin** at 50 mg/m2**, Cyclophosphamide** at 500 mg/m2 (FEC) every 3 weeks	11 years	**Outcomes of included studies** **PCR** The pCR rate was higher for the HP group compared to the H group: **59% vs. 46%, 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).** The pCR rates for the HP group by chemotherapy : **Trastuzumab + Pertuzumab group** Taxane alone 74% Anthra-containing 62% C-containing 48% **Trastuzumab group** Taxane alone 48% Anthra-containing 49% C-containing 30% 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). **Subgroup analysis** In multivariate analysis, a significant predictor of pCR in both groups included HR status (HR->HR+). n a univariate analysis within the HP group, pCR rates were lower for HR+ compared to HR- (51% vs. 71%)	

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	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. **Statistical analysis:** Univariate/multivariate logistic 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).			at 500 mg/m2 (FEC) every 3 weeks (4 cycles) **C. AC** **Doxorobucin** at 60 mg/m2**, Cyclophosphamide** at 600 mg/m2 (FEC) every 2/3 weeks (4 cycles) **or (without anthracycline)** **B. Trastu + Pertu+ taxane alone** (n=31/170) **Paclitaxel** (80 mg/m2 every week) or **Docetaxel** (80 mg/m2 every 3 week) **D. Trastu + Pertu + taxane + Carbo** (n=66/170) 6 cycles of **Docetaxel** at 75 mg/m2 and **Carboplatin** every 3 weeks.	(4 cycles) **C. AC** **Doxorobucin** at 60 mg/m2**, Cyclophosphamide** at 600 mg/m2 (FEC) every 2/3 weeks (4 cycles) **or (without anthracycline)** **B. 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 **Paclitaxel** (80 mg/m2 every week) **D. Trastu + taxane + Carbo** 6 cycles of **Docetaxel** at 75 mg/m2 and **Carboplatin** every 3 weeks.		(OR=0.42; 95% CI 0.22-0.81; p=0.0082). 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). **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	

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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
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.	**Observational study in Pakistan** **Aim** To evaluate the safety issues and adverse efects of using TCHP regimen (docetaxel, carboplatin, trastuzumab, and pertuzumab) versus TCP regimen (docetaxel, carboplatin, and trastuzumab) in older postmenopausal women with non-metastatic HER2-positive breast cancer. **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. **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.	II-11	From Dec 2013-Feb 2016, Locally advanced BC:	**22** Pertuzumab+ Trastuzumab + Docetaxel + Carboplatin trastuzumab (Herceptin , 8 mg/kg IV infusion over 90 minutes on the frst 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 docetaxel (75 mg/m2 IV	**23** Trastuzumab + Docetaxel + Carboplatin Patients receiving the TCP regimen (TCP group) received similar dosage and cycles of trastuzumab, carboplatin, and docetaxel but did not receive pertuzumab. Duration of therapy was up to six months. Following surgery (lumpectomy or mastectomy), both patient groups (TCH-P and TCP) continued trastuzumab alone every 3 weeks for a total	3 years	**Outcomes of included studies** **Safety** **mild fatigue** (36%-PTDC versus 34%-TDC) and **diarrhea** (48%-PTDC versus 49%-TDC) were most common toxicities. **Fever**: (12%-PTDC versus 13%-TDC) was common. **Anorexia**: 16%-PTDC and 21%-TDC **Febrile neutropenia** 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.) **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.	

Table 2: Reported side effects and toxicities associated with TCH versus TCHP. The numbers reflect percentages of patients with recorded side effects and toxicities in their electronic medical files. Mild, moderate, and severe side effects are correlated with CTCAE grade 1, grades 2-3, and grade 4 side effects, respectively.

Side effect/toxicity	TCH group (n = 23)				TCHP group (n = 22)			
Severity	Total (%)	Mild (%)	Moderate (%)	Severe (%)	Total (%)	Mild (%)	Moderate (%)	Severe (%)
General side effects								
Fatigue	36	34	2	2	40	36	2	2
Fever	14	12	1	2	16	13	1	2
Anorexia	21	14	4	3	16	11	4	1
Nausea	21	12	8	1	22	14	7	1
Dry eyes	5	2	2	1	8	3	4	1
Gastrointestinal symptoms								
Diarrhea	54	48	4	2	55	49	4	2
Mucositis	8	4	2	2	7	3	2	2
Respiratory system side effects								
Cough	9	5	2	2	8	2	4	2
Dermatological side effects								
Rash	6	3	2	1	4	2	1	1
Musculoskeletal side effects								
Myalgias	12	6	2	4	12	5	3	4
Neurological side effects								
Neuropathy	4	1	2	1	3	1	1	1
Haematological side effects								
Febrile neutropenia	13	2	0	1	4	3	1	0

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				infusion over 60 minutes on day 1).	of 52 weeks of therapy.			

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

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8. Fernandez-Martinez A, Krop IE. Survival, Pathologic Response, and Genomics in CALGB 40601 (Alliance), a Neoadjuvant Phase III Trial of Paclitaxel-Trastuzumab With or Without Lapatinib in HER2-Positive Breast Cancer. 2020;38(35):4184-93.	**Secondary/post-hoc analysis of RCTs (CALGB 40601 Alliance trial)** **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. **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. **Selection criteria:** Participants underwent four pre-treatment 16-gauge core biopsies for research. The CONSORT	II-1	From Dec 2008-Feb 2015, Locally advanced BC: **305** women **untreated stage II and III** HER2-positive breast cancer receive paclitaxel (80 mg/m2 once/week) with the addition of 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.** It was recommended that all patients receive dose-dense doxorubicin and cyclophosphamide and complete 1 year of trastuzumab adjuvantly.	**118** Trastuzumab + lapatinib + paclitaxel (weekly)	**120** Trastuzumab + paclitaxel (weekly) **67** Lapatinib + paclitaxel(weekly)	40 months for PCR (~3years) 90 months for RFS and OS (~7 years)	**Outcomes of included studies** **PCR** trastuzumab + lapatinib + paclitaxel arm: pCR rates in the ITT subpopulation were 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 **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, 58% to 82%; **TL**), **79%** (95% CI, 71% to 87%; **TH)**, and **93%** (95% CI, 88% to 98%; **THL**). -**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). **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).	Lapatinib was not been used in early breast cancer setting This trial is similar to NeoALTTOtrial population but NeoALTTO (84%) vs CALGB (76%) In event-free survival (non-sig)

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	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. **Definition of outcomes:** PCR was defined as no invasive tumor in the breast at surgery **(ypT0/Tis).** 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. **Statistical analysis:** Clinical data collection and statistical analyses were						-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** **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. 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, ALTTO, 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.**	

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	conducted by the Alliance Statistics and Data Center.							

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
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 double-arm observational (cohort) study** **Aim** To compare the pathological complete 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	**64** trastuzumab + chemotherapy (taxane-based Therapy)	**67** chemotherapy	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. **Conclusion**	

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	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)** **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.		2mg/kg weekly with a loading dose of 4mg/kg in the first cycle concomitantly with taxane-based therapy.				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.	

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10. Huober J, Holmes E, Baselga J, de Azambuja E, Untch M, Fumagalli D, et al. Survival outcomes of the NeoALTTO 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.	**Randomised Controlled Trial NeoALTTO study (BIG 1-06)** **Aim** To report the updated outcome results of the 455 patients enrolled in the NeoALTTO trial with regard to the secondary end-points EFS and OS **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 **(ypT0/is;** for current analysis, it is **ypT0/is ypN0),** and the secondary end-points were disease free survival/event-free survival (EFS) and Overall Survival. **Selection of patients:**	II-1	From 2008-2010 **455** patients with patients with operable, unilateral, non-inflammatory, HER2-positive **early breast cancer**	**152** Lapatinib + Trastuzumab + paclitaxel (weekly) 54 of 152 patients received reduced dose.	**149** Trastuzumab + paclitaxel (weekly) **154** Lapatinib + paclitaxel (weekly)	median follow-up of 6.7 years For OS, being in clinical (survival) follow-up at 30 weeks after randomisation was sufficient for inclusion,	**Event-free survival (six-year rates)** Lapatinib+ paclitaxel= 67% Trastuzumab+ paclitaxel=67% Lapatinib,+ Trastuzumab + paclitaxel= 74% 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) **Overall survival (6-Year)** Lapatinib+ paclitaxel= 82% Trastuzumab+ paclitaxel=79% Lapatinib,+ Trastuzumab + paclitaxel= 85% 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) **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) 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]) **subtype analysis** the pCR rates were higher in all three arms of the NeoALTTO 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	

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	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 HER2status was assessed locally (after laboratory accreditation) or centrally (Vall D'Hebron Institute of Oncology, Barcelona). Hormone receptors were locally tested and considered positive as per local guidelines. Left ventricular ejection fraction at baseline had to be ≥50%. **Definition of outcomes:** **-pCR** was defined as the absence of invasive tumour cells in the breast at the time of surgery. -**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. **Statistical analysis:** 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 performed. All 455 patients (i.e. 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 (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). **Conclusion** 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.	

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	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 (version 9.3)							

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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. JAMA Oncol. 2019 Jan 1;5(1):45-50. doi: 10.1001/jamaoncol.2018.3691. PMID: 30193295; PMCID: PMC6331049.	**Randomised Controlled Trial of ACOSOG Z1041 (Alliance)** **Aim** To assess DFS and OS for patients treated with sequential vs concurrent anthracycline plus trastuzumab **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. **Selection of patients:** The study enrolled 282 women 18 years or older with invasive HER2-positive breast cancer (either 3+ by immunohistochemistry or amplification by fluorescence in situ hybridization 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. **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	II-1	From September 2007- December 2011 in 36 centers in US and Puerto Rico **282** HER2-positive **operable breast cancer** (invasive bc with 3+ IHC/ amplification by fluorescence in situ hybridization)	**Sequential Arm 1**: **138** received 500 mg/m2of **fluorouracil** 75 mg/m2of **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 initial dose; 2 mg/kg for subsequent doses) on days 1, 8, and 15.	**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.	4 years	**Outcomes of included studies** **PCR** Proportion of patients who had pCR in the breast. Arm 1: 56.5% (95% CI 47.8–64.9) (78 of 138) Arm 2: 54.2% (95% CI 45.7–62.6) (77 of 142) **Disease-free survival/Event-free survival** Did not differ significantly HR: 1.02, 95% CI: 0.56-1.83 **Overall survival (6-Year)** Did not differ significantly HR: 1.17, 95% CI: 0.48-2.88 **Adverse effects** No treatment-related deaths occurred. The most common severe toxic effects were: neutropenia (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. **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,	

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	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 **Statistical analysis:** Kaplan-Meier Curves for diseases survival and overall survival						concurrent administration of trastuzumab with FEC was not found to offer additional clinical benefit and is not warranted.	

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12. Untch M, von Minckwitz G, Gerber B, Schem C, Rezai M, Fasching PA, Tesch H, Eggemann H, Hanusch C, Huober J, Solbach C, Jackisch C, Kunz G, Blohmer JU, Hauschild M, Fehm T, Nekljudova 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.	**RCT on GeparQuinto (G5) Study (CBG 44)** **Aim** To report results on long-term outcomes in patients with HER2-positive tumours from the GeparQuinto trial. **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 N3) as described previously. **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. In the case of inflammatory disease, the clinical extent of inflammation was used as measurable lesion. Patients with	II-1	From November 2007-June 2010, 620 patients were enrolled in the HER2-positive cohort of the GeparQuinto study	**311 ECL-DL** Epirubicin + Cyclophosphamide followed by (day 1, 3 weekly **Lapatinib** 1,250 mg/day, starting on day 1 of the first cycle of EC until day 21 of the fourth cycle of **docetaxel** concomitantly with all chemotherapy cycles. The dose of lapatinib was reduced to 1,000 mg/day to improve tolerability	**309 ECT-DT** Epirubicin 90 mg/m2 + Cyclophosphamide 600 mg/m2 followed by (day 1, 3 weekly) **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).	Median Follow-up of 55 months (0.2-79.9months) Results were at 3-year follow-up	**Outcomes of included studies** **Primary: PCR** **Secondary:** **Disease-free survival (DFS)** **Distant DFS (DDFS)** **Time to loco-regional relapse (TTLRR)** **Time to CNS metastases (TTCNSM)** **Overall survival (OS)** 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 **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).** 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) 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	

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	locally advanced tumors stage cT4 or cT3, hormone receptor–negative tumors (estrogen receptor [ER] and pro gesterone receptor [PgR] , 10%), or hormone receptor–positive tumors (ER and/or PgR < 10%) with clinically positive axillary nodes (cN+ for cT2 or pNSLN+ for cT1) were eligible. **Definition of outcomes:** pCR rate **(ypT0 ypN0)** after treatment with trastuzumab or lapatinib, administered concomitantly with neoadjuvant chemotherapy. 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.						pCR (HR, 0.15; P = .010) **Hormone receptor–negative tumors**, DFS, DDFS, and OS were not different between the two treatment arms. **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). **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. **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. **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) **Conclusion** pCR correlated with long-term outcome. In patients with hormone receptor–positive tumors, prolonged anti-HER2 treatment—neoadjuvant lapatinib for 6	

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	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. **Statistical analysis:** Hazard ratio (HR) of 0.6 for DFS to the two-sided significance level of a =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. 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)						months, followed by adjuvant trastuzumab for 12 months—significantly improved survival compared with anti-HER2 treatment with trastuzumab alone.	

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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
13. Stebbing J, Baranau YV, Baryash V, Manikhas A, Moiseyenko V, Dzagnidze G, Zhavrid E, Boliukh D, Pikiel 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. Breast Cancer Res Treat. 2021 Aug;188(3):631-640. doi: 10.1007/s10549-021-06240-5. Epub 2021 Jun 20. PMID: 34148205; PMCID: PMC8272708.	**RCT phase III trial** **NCT 02162667 (CT-P6 Biosimilar)** **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. **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	II-1	Between Aug 7, 2014 and May 6, 2016 549 patients Patients were recruited from 112 centers in 23 countries.	**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/m^2 on day 1 of cycles 1–4) and **FEC** (fluorouracil [500 mg/m^2], epirubicin [75 mg/m^2], and cyclophosphamide [500 mg/m^2]; day 1 of cycles 5–8) therapy.	**278** [51%] to reference **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/m^2 on day 1 of cycles 1–4) and **FEC** (fluorouracil [500 mg/m^2], epirubicin [75 mg/m^2], and cyclophosphamide [500 mg/m^2]; day 1 of cycles 5–8) therapy	Results were at 3-year follow-up	**Outcomes of included studies** **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) **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** **Adverse effects** Safety findings were comparable between groups for the overall study and follow-up period, 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. **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 neutropenia (four [1%] vs one [<1%]) and neutropenia (one [<1%] vs two [1%]).** Grade 3 or worse treatment-related adverse events	

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
	masked central review of local histopathology reports. The equivalence margin was –0·15 to 0·15 **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 measureable lesion; and known oestrogen and progesterone receptor status. **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. **Statistical analysis:** statistical analysis using SAS software version 9.1.3 or later.						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 **neutropenia in ten (4%) versus 14 (5%).** **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.	

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
14. Jackisch C, Hegg R, Stroyakovskiy D, Ahn JS, Melichar B, Chen SC, Kim SB, Lichinitser M, Starosławska E, Kunz G, Falcon S, Chen ST, Crepelle-Fléchais A, Heinzmann D, Shing M, Pivot X. HannaH 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 HannaH study **Aim** To report associations between tpCR and event-free survival (EFS) from HannaH (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** HannaH 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. **Definition of outcomes:** **EFS** was defined as time from randomisation to the date of disease recurrence or progression (local, regional, distant, or contralateral), or death from any cause. **OS** was defined as time from randomisation to death and a final analysis will be carried out once 5 years of survival data have been collected. **Adverse events** were recorded and graded according to standard criteria.	II-1	From 19 October 2009 to 1 December 2010. **596 Her2-positive early BC**	297 Docetaxel (75mg/m^2) + Flurouracil (500mg), Epirubucin (75mg), Cyclophosphamide (500mg) (4 + 4 cycles) + **SC Trastuzumab** (600mg/kg) 3-weekly Post-surgery: 10 cycles of Trastuzumab	299 Docetaxel (75mg/m2) + Flurouracil (500mg), Epirubucin (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	

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
	Safety for this analysis is focused on the treatment-free follow-up phase. **Statistical analysis:** EFS rates and unstratified hazard ratios (HRs)/confidence intervals (CIs) were estimated using the Kaplan Meier method and Cox regression, respectively. tpCR/pCReEFS associations were ana lysed using multivariable Cox modelling. Analyses were performed with SAS, v9.2 (SAS Institute Inc., Cary, NC, USA).						rates between the arms. Safety overview (safety population). Overall / Treatment-free follow-up Subcutaneous trastuzumab (n = 297) / Intravenous trastuzumab (n = 298) / Subcutaneous trastuzumab (n = 297) / Intravenous trastuzumab (n = 298) Patients with ≥1 adverse event (any grade): 290 (97.6%) / 282 (94.6%) / 7 (2.4%) / 7 (2.3%) Patients with ≥1 grade 3–5 adverse event: 158 (53.2%) / 158 (53.0%) / 2 (0.7%) / 3 (1.0%) Patients with ≥1 serious adverse event: 65 (21.9%) / 43 (14.4%) / 2 (0.7%) / 3 (1.0%) Patients with ≥1 related serious adverse event: 31 (10.4%) / 24 (8.1%) / 1 (0.3%) / 0 Patients with adverse events leading to death: 4 (1.3%) / 3 (1.0%) / 1 (0.3%) / 2 (0.7%) Data are number (%). **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, tpCR was associated with improved EFS, adding to evidence that tpCR is associated with clinical benefit in HER2-positive early breast cancer.	

Evidence Table : Social/Ethical/Organisational
Question : What are the social/ethical/organisational issues regarding to use of BTAs?

No.	Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size	General comment
15.	Pivot X, Gligorov J, Müller V, Curigliano G, Knoop A, Verma S, Jenkins V, Scotto N, Osborne S, Fallowfield L; PrefHer 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 PrefHer study. Ann Oncol. 2014 Oct;25(10):1979-1987. doi: 10.1093/annonc/mdu364. Epub 2014 Jul 28. PMID: 25070545	**A randomisation process** **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. **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. **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 × 2 $\chi 2$ test.	-	Patients, n=488 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).	245 patients received SC	243 patients received IV	27 October 2011 to 3 December 2012	**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). Results were consistent in both study arms: **SC → 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 → 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. **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] **Adverse event** Clinician-reported adverse events occurred in 292/479 (61.0%) and 245/478 (51.3%) patients	

		Statistical analyses were carried out with SAS (version 9.1.3).						during the pooled SC and IV periods, respectively (P < 0.05; 2 × 2 χ (2)); 16 patients (3.3%) in each period experienced grade 3 events; none were grade 4/5. **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.	

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. Breast Cancer Res Treat. 2020 May;181(1):43-51. doi: 10.1007/s10549-	**Cost-effectiveness analysis (CEA)** **Aim** To determine the optimal chemotherapy/anti-HER2 treatment strategy. **Methods** We created a decision-analytic model for patients with stage II-III HER2-	-	55-year old women, stage II-III HER2-positive cancer that incorporated utilities based on toxicity and recurrence. The model	**Two 'de-escalated' regimens** **TH**: taxol, trastuzumab; **TDM-1+ Pzmb**	**TCHP:** docetaxel, carboplatin, trastuzumab, pertuzumab **THP+AC:** taxol, trastuzumab,	5-year progression -free survival	**Overview of included studies** **Types of cost analysis** Cost-effectiveness analysis (CEA) **Sources of information** **Perspective of the analyses** We estimated direct treatment and health state costs	

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020-05587-5. Epub 2020 Mar 17. PMID: 32185586.	positive 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) and two 'de-escalated' regimens (TH: taxol, trastuzumab; TDM-1) followed by adjuvant treatment based on pathologic response. **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		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.		pertuzumab then doxorubicin and cyclophosphamide; **THP:** taxol, trastuzumab, pertuzumab)		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. **Time Horizon** Not mentioned **Discounting** Not mentioned **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. **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.	

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
	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). 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.** **Definition of outcomes** pCR was defined as no residual cancer in either the breast or the lymph nodes to reflect the KATHERINE study							

Evidence Table : Economic evaluation
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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
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	**Cost-effectiveness analysis (CEA)** **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. **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 T-DM1 arm and 23-80 years in trastuzumab arm). The model simulated patients receiving 5 different neoadjuvant followed by adjuvant treatment strategies. **Analysis** Comprised a decision tree and a state-	-		**S1 DDAC-THP:** dose-dense anthracycline/cyclophosphamide (DDAC) plus THP followed by adjuvant H **S2: DDAC-THP:** dose-dense anthracycline/cyclophosphamide (DDAC) plus THP followed by adjuvant TDM1 **S3: THP:** paclitaxel (T) plus H plus P, followed by adjuvant DDAC olus TDM1 **S4: HP:**		Data analyses were performed from March 2019 to August 2020.	**Overview of included studies** **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. **Sources of information** **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. **Perspective of the analyses** from a health care payer perspective in the United States **Time Horizon** **Discounting** applying a 3% discounting rate **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	

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	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). **Base-case Analysis, Subgroup analysis and Probabilistic sensitivity analysis were performed.** **Definition of outcomes**			trastuzumab (H) plus pertuzumab (P) followed by adjuvant DDAC/THP plus TDM-1 **S5: TCHP:** docetaxel (T) plus carboplatin (C) plus HP, followed by adjuvant TDM1			was associated with the highest net benefit. **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. **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). **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.	

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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
3. Squires H, Pandor A, Thokala P, Stevens JW, Kaltenthaler 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. Pharmacoeconomics. 2018 Jan;36(1):29-38. doi: 10.1007/s40273-017-0556-7. PMID: 28770452.	**Single Technology Appraisal by NICE** 12 neoadjuvant studies **Aim** Review Group Perspective of a NICE Single Technology Appraisal. This is one of a series of single technology appraisal summaries being published in Pharmacoeconomics. Full details of all relevant appraisal documents can be found on the NICE website	-	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		**Overview of included studies** **Types of cost analysis** NICE Single Technology Appraisal **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). **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 **Perspective of the analyses** NHS and Personal Social Services perspective **Time Horizon** Lifetime **Discounting** Costs and health outcomes were discounted at 3.5% per annum **Sensitivity analysis** **Key findings**	

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							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.** **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.	

Evidence Table : Economic evaluation
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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. Lee W, Haron M, Yu K, Chong F, Goh A, Azmi S. Economic Analysis of Intravenous vs. Subcutaneously Administered Trastuzumab for the Treatment of HER2+ Early Breast Cancer in Malaysia. Advances in Breast Cancer Research. 2016;05:1-13.	**Cost-minimisation analysis** **Aim** To investigate cost-savings from subcutaneous trastuzumab in a middle-income Asian country. **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. **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	-	-	SC trastuzumab 600mg 17 cycles	IV trastuzumab loading dose (8 mg/kg) and 16 subsequent doses (6 mg/kg) 17 cycles	1 year	**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. **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.** **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	

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
	to determine the robustness of the base-case analysis. One-way sensitivity analyses were performed by varying data points of key variables individually.						(NMRR 14-1470-23387). **Discounting** No discounting of future costs was applied as the treatment duration did not exceed 1 year **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. **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	

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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