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TRASTUZUMAB AS AN ADJUVANT THERAPY FOR EARLY BREAST CANCER AND ECONOMIC EVALUATION

HEALTH TECHNOLOGY ASSESSMENT SECTION
MEDICAL DEVELOPMENT DIVISION
MINISTRY OF HEALTH MALAYSIA

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DISCLOSURE

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EXECUTIVE SUMMARY

Background

In Malaysia, breast cancer is the most common cancer in females and also the first most common cancer among population regardless of gender. According to the National Cancer Registry Report 2007, the age pattern showed a peak age-standardised rate (ASR) at the 50-59 age groups.

The percentage of breast cancer detected at stage I and II was 61%, another 27% with Locally Advanced Cancer and 11% with late stage metastatic cancer. From the total, 65% were found to have Estrogen Receptor (ER) Positive, 57% Progesterone Receptor (PR) Positive, 28% Human Epidermal Growth Factor Receptor 2 (HER2) positive and 12% triple negative. For patients with HER2 positive, access to targeted therapy (trastuzumab) was very limited; only 19% of eligible patients could be treated.

Human epidermal growth factor receptor 2 (HER2) is a member of the human epidermal growth factor receptor (HER/EGFR/ERBB) family. Amplification or over-expression of this oncogene has been shown to play an important role in the development and progression of certain aggressive types of breast cancer. Trastuzumab is use for the treatment of early-stage breast cancer that is HER2 positive, has or has not spread into the lymph nodes. Although this treatment has been routinely used, there are still controversial on the timing of the addition of trastuzumab to the chemotherapy regimen (simultaneously or sequentially).

In Malaysia, trastuzumab 440mg injection has been approved by Ministry of Health Formulary to be used only in adjuvant setting for patients with HER2 over-expressed breast cancer, which is HER2 3+ by immunohistochemistry and over-expressed by Fluorescence in situ hybridization (FISH) and high risk group. Oncologist suggested that Echocardiogram (ECHO) should be performed prior to first dose and every three months during treatment.

This review was requested by clinical oncologist from Hospital Kuala Lumpur to review the safety, efficacy/effectiveness and cost-effectiveness of trastuzumab as an adjunct in early breast cancer patients either concurrently or sequentially to chemotherapy.

Objective/aim

i.) To assess the safety, efficacy/effectiveness and cost-effectiveness of trastuzumab as an adjunct in early breast cancer patients either concurrently or sequentially to chemotherapy through a systematic review of literatures. The optimal duration for the usage of trastuzumab will also be reviewed.

ii.) To calculate the incremental cost-effectiveness ratio (ICER) between chemotherapy + trastuzumab and chemotherapy alone as adjuvant treatment for early breast cancer.

Results and conclusions

A total of 901 titles were identified from the OVID interface. One Cochrane systematic reviews, one systematic review and meta-analysis, two recent randomised controlled trials and four economic evaluations were included in this review.

Safety

There was high level of evidence to suggest that the risk of CHF was significantly higher in patients treated with trastuzumab compared to non-trastuzumab control group (RR 5.11; 90% CI:3.00, 8.72, p<0.00001) in one Cochrane review, (RR 3.19; 95% CI:2.03, 5.02, p<0.00001) in one systematic review and meta-analysis. Evidence also suggest that the risk was significantly higher with longer duration of treatment (> 6 months) RR 5.39; 90% CI: 3.56, 8.17, P<0.00001 and also with higher loading dose of treatment (8mg/kg) RR 6.79; 95% CI: 2.03, 22.73, p<0.00001.

Effectiveness

Overall Survival (OS)

The OS significantly favoured trastuzumab containing regimen over non-trastuzumab control group, (HR 0.66; 95% CI: 0.55, 0.77, p<0.00001). In terms of duration, subgroup analysis reported that the OS significantly favoured trastuzumab containing regimen over non-trastuzumab control group trials where trastuzumab was given longer (> 6 months), HR 0.67; 95% CI: 0.57,0.80, P<0.00001. In the trials that gave trastuzumab and chemotherapy concurrently, HR significantly favoured trastuzumab-containing regimens (HR 0.64; 95% CI: 0.57, 0.80, P<0.00001).

Disease Free Survival (DFS)

The evidence from Cochrane systematic review suggests that DFS favoured trastuzumab containing regimen over non-trastuzumab control group (HR 0.60; 95% CI: 0.50, 0.71, P<0.00001). In terms of duration of treatment, there was no significant difference in DFS when trastuzumab was used for less than six months, or more than six months. The DFS significantly favoured trastuzumab containing regimen over non-trastuzumab control group when used either concurrently or sequentially. Limited evidence to suggest that two years duration of adjuvant trastuzumab was not more effective that one year of treatment. However, six months treatment with trastuzumab failed to show that it was non-inferior to twelve months of trastuzumab. Despite the higher rates of cardiac events, twelve months of adjuvant trastuzumab should remain the standard of care.

Cost/Cost-effectiveness

Systematic review of cost-effectiveness evaluation reported a wide range of ICER/QALY ranging from USD 7,676 to USD 71,491.

Local economic evaluation

From the decision analytic modelling that has been conducted, addition of 1-year treatment with trastuzumab on top of standard adjuvant chemotherapy is considered as a cost-effective strategy for early breast cancer with HER2 positive, yielding an ICER of RM 83,544.59 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 $\leqslant$1 GDP per capita, this treatment may not be a cost-effective strategy.

Based on one-way sensitivity analysis performed, these components have shown to be a sensitive parameter for ICER determination: discount rate, disease-free state utility values, route of trastuzumab administration and cost of trastuzumab.

Methods for systematic review

Electronic databases were searched through the Ovid interface: Ovid MEDLINE® In-process and other Non-indexed citations and Ovid MEDLINE® 1948 to present, EBM Reviews – Cochrane Central Register of Controlled Trials – July 2016, EBM Reviews – Cochrane Database of Systematic Reviews – 2009 to Jun 2016, EBM Reviews – Health Technology Assessment – 2nd Quarter 2016, EBM Reviews – Database of Abstracts of Reviews of Effects – 2nd Quarter 2016, EBM Reviews – NHS Economic Evaluation Database 2nd Quarter 2016, Embase – 1988 to 2016 week 33. Searched were also run in PubMed. Google was used to search for additional web-based materials and information.

A critical appraisal of the retrieved papers was performed and the evidence level was graded according to the US/Canadian Preventive Services Task Force.

Methods for local economic evaluation

A state transition model (Markov cohort simulation) was developed using Microsoft Excel Workbook 2007 to estimate the cost-utility of adjuvant trastuzumab compared with chemotherapy alone for treatment of early breast cancer with HER2 positive status. A hypothetical cohort of women with HER2 positive early breast cancer was simulated in two treatment strategies: chemotherapy + trastuzumab as adjuvant treatment and chemotherapy alone as adjuvant treatment. This Markov model included six health states which were projected to lifetime horizon and the cycle length was one year. All costs and outcomes were discounted at 3% and the cost-effectiveness result was expressed in ICER.

TRASTUZUMAB AS AN ADJUVANT THERAPY FOR EARLY BREAST CANCER AND ECONOMIC EVALUATION

1. BACKGROUND

In Malaysia, breast cancer is the most common cancer in females and also the first most common cancer among population regardless of gender. According to the National Cancer Registry Report 2007, the age pattern showed a peak age-standardised rate (ASR) at the 50-59 age groups.[1]

The percentage of breast cancer detected at stage I and II was 61%, another 27% with Locally Advanced Cancer and 11% with late stage metastatic cancer. From the total, 65% were found to have Estrogen Receptor (ER) Positive, 57% Progesterone Receptor (PR) Positive, 28% Human Epidermal Growth Factor Receptor 2 (HER2) positive and 12% triple negative. For patients with HER2 positive, access to targeted therapy (trastuzumab) was very limited; only 19% of eligible patients could be treated.[2]

Human epidermal growth factor receptor 2 (HER2) is a member of the human epidermal growth factor receptor (HER/EGFR/ERBB) family. Amplification or over-expression of this oncogene has been shown to play an important role in the development and progression of certain aggressive types of breast cancer. Trastuzumab is use for the treatment of early-stage breast cancer that is HER2 positive, has or has not spread into the lymph nodes. Although this treatment has been routinely used, there are still controversial on the timing of the addition of trastuzumab to the chemotherapy regimen (simultaneously or sequentially).[3]

In Malaysia, trastuzumab 440mg injection has been approved by Ministry of Health Formulary to be used only in adjuvant setting for patients with HER2 over-expressed breast cancer, which is HER2 3+ by immunohistochemistry and over-expressed by Fluorescence in situ hybridization (FISH) and high risk group.[4] Oncologist suggested that Echocardiogram (ECHO) should be performed prior to first dose and every three months during treatment.

This review was requested by clinical oncologist from Hospital Kuala Lumpur to review the safety, efficacy/effectiveness and cost-effectiveness of trastuzumab as an adjunct in early breast cancer patients either concurrently or sequentially to chemotherapy.

2. OBJECTIVE/AIM

i.) To assess the safety, efficacy/effectiveness and cost-effectiveness of trastuzumab as an adjunct in early breast cancer patients either concurrently or sequentially to chemotherapy through a systematic

review of literatures. The optimal duration for the usage of trastuzumab will also be reviewed.

ii.) To calculate the incremental cost-effectiveness ratio (ICER) between chemotherapy + trastuzumab and chemotherapy alone as adjuvant treatment for early breast cancer.

3. TECHNICAL FEATURES

Trastuzumab is a humanised monoclonal antibody against the extracellular domain of the HER2 receptor. It is the treatment for patients with early HER2 positive breast cancer when given concomitantly or in sequence to adjuvant chemotherapy.

The following is the regime for single agent trastuzumab

	Cycle length[d]= 21		Anti-emetic[e]= 1	
Drugs[a]	Dose[b] (mg/kg)	Route[c]	Infusion time[f]	Days[g]
Trastuzumab	8 (loading dose)	IV	90 mins	First infusion
Followed by				
Trastuzumab	6 (maintenance dose)	IV	60 mins (30min)	3 weekly for 1 year

Key

a.	Drugs used in regimen
b.	Dose in milligram per squae meter • The figure refers to the individual dose, even if it is a bid or tds dosing • The figure refers to dose per day. Total dose per cycle will be multiplied by the number of days of the infusion • In certain cases, absolute doses are given; e.g. Bleomycin 30mg
c.	Method of administration i.e. oral, intravenous, intra-muscular
d.	Cycle length indicates duration of a chemotherapy cycle 21 day cycle means Day 1of Cycle 2 is on Day 22 of Cycle 1
e.	Recommended anti-emetic as per guidelines
f.	Time for infusion • Bolus is generally given over 5-10 minutes • Continuous infusion means infusion over at least 24 hours • Some chemotherapy drugs are infusion time sensitive. Altering infusion time would alter drug exposure and toxicity without obvious increase in efficacy
g.	Which day(s) drug(s) should be given within the cycle duration

4. METHODS

4.1. Searching

Electronic databases searched through the Ovid interface: Ovid MEDLINE® In-process and other Non-Indexed Citations and Ovid MEDLINE® 1948 to present, EBM Reviews - Cochrane Central Register of Controlled Trials-2nd Quarter 2016, EBM Reviews – Database of Abstracts of Review of Effects (2nd Quarter 2016), EBM Reviews - Cochrane database of systematic reviews - 2005 to Jun 2016, EBM Reviews - Health Technology Assessment – 2nd Quarter 2016

Google was used to search for additional web-based materials and information. No other limits were applied. Additional articles such as from reviewing the bibliographies of retrieved articles. Appendix 1 showed the detailed search strategies.

4.2. Selection

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the selected full-text articles for final article selection.

The inclusion and exclusion criteria were:

Inclusion criteria

Population	HER2 positive early breast cancer patients
Interventions	Trastuzumab (Herceptin)
Comparators	chemotherapy without trastuzumab as adjuvant
Outcomes	• safety - adverse events/complications - cardiac events - Left ventricular ejection fraction (LVEF) • efficacy/effectiveness - Disease free state (DFS) - Overall survival (OS) - Quality of life • economic evaluation - cost - cost analysis - cost-effectiveness
Study design	Health Technology Assessment (HTA), Systematic Review, Randomised controlled trial (RCT), cohort studies
	English full text articles

Exclusion criteria

Study design	Case series, case reports, surveys, anecdotal, narrative reviews
	Non English full text articles

Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) and evidence graded according to the US / Canadian Preventive Services Task Force (Appendix 2).

5. RESULTS AND DISCUSSION

A total of 901 titles were identified from the OVID interface. One Cochrane systematic reviews, one systematic review and meta-analysis, two recent randomised controlled trials and four economic evaluations were included in this review.

5.1 SAFETY

From the review, cardiotoxicity [(principally congestive heart failure (CHF))], was the most important adverse effect of trastuzumab. Trastuzumab was not associated with the adverse events that typically occur with chemotherapy, such as alopecia, myelosuppression, and severe nausea and vomiting.[5]

5.1.1 Cardiac events

Moja L et al. (2012) in the Cochrane systematic review included eight RCTs in the review namely B31, BCIRG006, Budzar, FinHer, HERA, N9831, NOAH and PACS-04. Five RCTs were multicentric (B31; FinHer; HERA; N9831; NOAH) while two RCTs (BCIRG006; PACS-04) were stated to be multicentric but the number and names of the centres and the number of patients enrolled in each centre were not clearly reported. The Buzdar trial was monocentric. This Cochrane systematic review stated that out of total 10,281 patients in eight RCTs, there were 135 cases of CHF out of 5471 patients (2.5%) in the trastuzumab group and 20 cases out of 4810 (0.4%) in the control group. The overall result indicated a higher risk of CHF with trastuzumab [Relative Risk (RR) 5.11; 90% Confidence Interval (CI):3.00, 8.72, p<0.00001)]. Comparison was done for the duration for trastuzumab usage of more than six months and less than six months. There was a significantly higher risk of CHF in regimens which trastuzumab was given for more than six months than in regimens without trastuzumab (RR 5.39; 90% CI: 3.56, 8.17, P<0.00001). A shorter treatment period did not appear to be associated with an increase in the risk of CHF (RR 0.50; 90% CI: 0.07, 3.74, P=0.57).[6 Level I]

Long HD et al. (2016) in a systematic review and meta-analysis that included six RCTs where 18,111 patients were identified stated that overall incidence of high-grade CHF in patients treated with trastuzumab

versus placebo was 1.44% (95% CI: 0.79%, 2.64%) and the RR was 3.19 (95% CI: 2.03, 5.02; p<0.00001). Comparison between loading dose of 4mg/kg and 8mg/kg of traztuzumab reported incidence rates of CHF as 0.95% (95% CI: 0.68%, 1.33%) and 1.64% (95% CI: 0.74%, 3.57%) for high and low doses, respectively, with no statistically significant difference (p=0.23). Nevertheless, the overall RRs of CHF for high and low doses were 6.79 (95% CI: 2.03, 22.73) and 2.64 (95% CI: 1.62, 4.33), respectively, for which a significant difference was found (p<0.00001). Comparison of duration of trastuzumab given for one year, two years and nine weeks indicated CHF incidence of 1.45% (95% CI: 0.78%, 2.66%), 1.09% (95% CI: 0.67%, 1.78%), and 0.94% (95% CI: 0.19%, 4.51%), respectively. The respective RRs were 3.29 (95% CI: 2.07, 5.25), 9.54 (95% CI: 2.19, 41.43), and 0.50 (95% CI: 0.05, 5.49). The difference in incidence was not statistically significant (p=0.75) but the RR was (p<0.00001). The authors concluded that although no different in incidence rate was found between high and low doses of trastuzumab, but the risk of CHF was higher in patients receiving higher dose of trastuzumab. [7 Level I]

5.2. EFFICACY/ EFFECTIVENESS

When considering the outcomes of trastuzumab as an adjuvant in early breast cancer patients, most of the literatures reported the effectiveness in term of overall survival (OS) and disease free survival (DFS).

5.2.1 Overall Survival (OS)

Moja L et al. (2012) in the Cochrane systematic review that included eight trials and a total of 9935 patients and 655 events in the analysis stated that hazard ratio (HR) for overall survival (OS) significantly favoured trastuzumab-containing regimens over non-trastuzumab control groups (HR 0.66; 95% CI: 0.57, 0.77, P<0.00001). In the six trials where trastuzumab was given for more than six months, involved 9962 patients and 622 events, the hazard ratio significantly favoured the trastuzumab-containing regimens (HR 0.67; 95% CI: 0.57, 0.80, P<0.00001), while in the subgroup of two trials that used trastuzumab for less than six months, involved 273 patients and 33 events, the efficacy failed to reach statistical significant (HR 0.55; 95% CI: 0.27, 1.11, P=0.1). In the six trials that gave trastuzumab and chemotherapy concurrently, accounting for 6006 patients and 466 events, the HR significantly favoured the trastuzumab-containing regimens (HR 0.64; 95% CI: 0.53, 0.76, P<0.00001), while the other two trials, where trastuzumab was administered sequentially, accounting for 3929 patients and 189 events, failed to reach statistical significance (HR 0.85; 95% CI: 0.43, 1.67, p=0.64). The test for differences between subgroups was not significant (p=0.406). [6 Level I]

5.2.2 Disease Free Survival (DFS)

Moja L et al. (2012) in the Cochrane systematic review that included eight trials and a total of 9935 patients and 1604 events in the analysis stated that hazard ratio for disease free survival significantly favoured trastuzumab-containing regimens over non-trastuzumab control groups (HR 0.60; 95% CI: 0.50, 0.71, P<0.00001). For the six trials that used trastuzumab for more than six months, accounting for 9662 patients and 1562 events, the hazard ratio for disease free survival significantly favoured trastuzumab (HR 0.62; 95% CI: 0.52, 0.72, P<0.00001). For the two trials that used trastuzumab for less than six months, accounting for 273 patients and 42 events, the hazard ratio for disease free survival significantly favoured trastuzumab (HR 0.31; 95% CI: 0.10, 0.96, P=0.04). [6] Level I

In comparison, trials that used trastuzumab concurrently or sequentially, Moja L et al. stated five trials that used trastuzumab concurrently with chemotherapy, accounting for 6006 patients and 965 events, the hazard ratio for DFS significantly favoured trastuzumab-containing regimens (HR 0.54; 95% CI: 0.44, 0.67, P<0.00001). For two trials that used trastuzumab sequentially, accounting for 3929 patients and 639 events, the hazard ratio for DFS significantly favoured trastuzumab-containing regimens (HR 0.71; 95% CI 0.53, 0.95, P=0.02). [6] Level I

Goldhirsch A et al. (2013) in HERA trial, which is an international, multicentre, randomised, open-label, phase three trial comparing treatment with trastuzumab for one and two years with observation after standard neoadjuvant chemotherapy, adjuvant chemotherapy, or both in 5102 patients with HER2-positive early breast cancer stated that the study recorded 367 events of DFS in 1552 patients in the one year group and 367 events in 1553 patients in the two years group. A comparison of DFS in this two groups showed no significant difference between groups (HR 0.99, 95% CI: 0.85, 1.14, p=0.86). This study concluded that two years duration of adjuvant trastuzumab was not more effective than one year of treatment for patients with HER2 positive early breast cancer. [8] Level I

Pivot et al. (2013) stated that since 2005, twelve months of adjuvant trastuzumab has been the standard treatment for patients with HER2-positive early breast cancer. However, the optimum duration of treatment has been debated. Therefore, a non-inferiority trial of a shorter exposure of six months versus the standard twelve months of trastuzumab for patients with early breast cancer was done. This study is an open-label, randomised, phase three trial in 156 centres in France. The primary endpoint was DFS, with a prespecified non-inferiority margin of 1.15. A total of 1691 patients were randomly assigned to receive 12 months of trastuzumab and 1693 to receive six months of trastuzumab; 1690 patients in each group were included in the intention-to-treat analyses.

After a median follow-up of 42.5 months (IQR 30.1-51.6), 175 (10.4%) DFS events were reported in the 12-months group and 219 (13.0%) events were reported in the 6-months group. The 2-years DFS was 93.8% (95% CI: 92.6, 94.9) in the 12-months group and 91.1% (95% CI: 89.7, 92.4) in the 6-months group. The estimated hazard ratio was 1.28 (95% CI 1.05-1.56; p=0.29). The authors concluded that after 3.5 years follow-up, it is failed to show that six months of treatment with trastuzumab was non-inferior to twelve months of trastuzumab. Despite the higher rates of cardiac events, twelve months of adjuvant trastuzumab should remain the standard of care.[9] Level I

5.3 COST/COST-EFFECTIVENESS

Aboutorabi A et al. performed a Markov model to estimate outcomes and costs over a 20-year time period using a cohort of women with HER2 positive early breast cancer, treated with or without twelve months trastuzumab adjuvant. The model included four health states (disease free state, loco-regional recurrence, metastases recurrence and death). On the basis of BCIRG006 trial, the model showed that adjuvant trastuzumab treatment in early breast cancer yield 0.87 quality-adjusted life years (QALY) compared with non-trastuzumab regimen. Adjuvant trastuzumab treatment yielded an incremental cost-effectiveness ratio (ICER) of USD 51,302 per QALY. The authors reported that by using threshold of 3 times GDP per capita, as per World Health Organization (WHO) recommendation, twelve months trastuzumab adjuvant chemotherapy is not a cost-effective therapy for patients with HER2-positive breast cancer in Iran.[10]

Buendia JA et al. assesses the cost-effectiveness of adjuvant trastuzumab treatment in Colombia. A Markov health-state transition model was built to estimate clinical and economic outcomes in HER2 positive breast cancer with or without twelve months trastuzumab adjuvant over a lifetime perspective with annual transition cycles. The model incorporated five health states (disease-free, local recurrence, distant recurrence, cardiac failure, and death). Baseline event rates and 3-year hazard ratio (HR=0.51, 95% CI: 0.44,0.59; p<0.0001) were derived from 4-year follow up of the N9831 and NSABP B-31 trial. Costs and utility weights were obtained from the literature and were discounted by 5% annually. The model showed that the utilization of adjuvant trastuzumab treatment in early breast cancer can prolong 0.80 quality-adjusted life-years (QALY), compared with standard chemotherapy, an ICER of USD 71,491 per QALY gained. The authors concluded that 1-year trastuzumab adjuvant is not cost-effective in Colombia, using the definition of WHO cost-effectiveness threshold of 3 times GDP per capita.[11]

Chen et al. constructed a Markov health-state transition model to simulate the natural development of breast cancer, estimate costs and disease progression over a lifetime perspective with annual transition cycles, and evaluated the cost-effectiveness of 1-year trastuzumab adjuvant treatment group compared with the non-trastuzumab standard chemotherapy group in three province in China, namely Beijing, Shanghai and GuangZhou. On the basis of HERA data, the model results showed that the utilization of trastuzumab adjuvant treatment in early breast cancer can prolong 2.87 life years, compared with the non-trastuzumab standard chemotherapy group. The incremental cost for an additional life-year gained (LYG) was USD7,564, USD7,933 and USD7,929 in Beijing, Shanghai and Guangzhou respectively. The ICER was USD7,676 per QALY, USD8,049 per QALY, and USD8,046 per QALY respectively. The authors concluded that 1-year adjuvant trastuzumab treatment is cost-effective. Both clinical and economic benefits were superior for the 1-year adjuvant trastuzumab treatment group compared with the standard adjuvant chemotherapy group. [12]

Kurian AW et al. conducted a Markov health-state transition model to simulate three therapy options for a cohort of 49-year old women with HER2 positive early stage breast cancer. The three options are: i.) conventional chemotherapy without trastuzumab (NT) ii.) Anthracycline-based regimens with trastuzumab adjuvant (AAT) and iii.) non-anthacycline-based regimens with trastuzumab (NAT). Treatment with NT yields 9.35 QALYs at a cost of USD133,429, AAT yields 10.77 QALYs at a cost of USD190,092, and NAT yields 10.61 QALYs at a cost of USD206,561. Compared with NT regimen, the AAT regimens arm has an ICER of USD39,982 per QALY gained.[13]

5.4 ECONOMIC EVALUATION USING DECISION ANALYTIC MODEL

5.4.1 METHODOLOGY

A state transition model (Markov cohort simulation) was developed using Microsoft Excel Workbook 2007 to estimate the cost-utility of adjuvant trastuzumab compared with chemotherapy alone for treatment of early breast cancer with HER2 positive status. This type of model was chosen for its ability to extrapolate efficacy data from short-term clinical trials in early breast cancer to longer term cost-effectiveness results, which has been conducted by other published economic evaluations.[10-15] A hypothetical cohort of women with HER2 positive early breast cancer were simulated in two treatment strategies:-

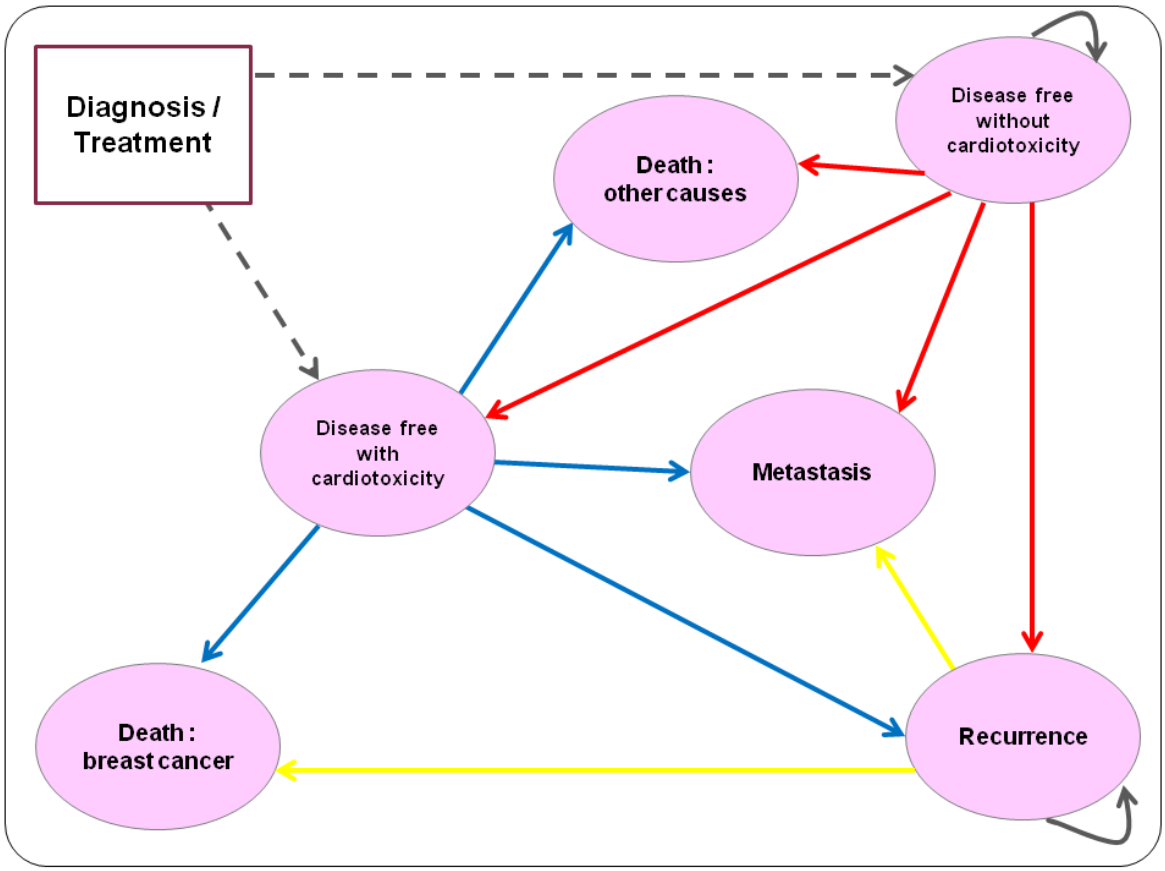
i) chemotherapy + trastuzumab as adjuvant treatment (ChemoTx+Tras)
ii) chemotherapy alone as adjuvant treatment (ChemoTx)

In view of no head-to-head comparison on concurrent versus sequential strategies of trastuzumab treatment and no significant difference between effectiveness of these two strategies when compared with chemotherapy alone, this model focuses on trastuzumab as concurrent treatment for early breast cancer.

The underlying clinical pathways were obtained from Clinical Practice Guidelines (CPG) on Management of Breast Cancer 2010 and Systemic Therapy Protocol for Oncology 2016 by Ministry of Health Malaysia.[16, 17] The structure of the model was developed by consultation with clinical oncologist from Hospital Kuala Lumpur. This Markov model included six health states: disease free with and without cardiotoxicity, recurrence (local, regional and contralateral), metastasis, death due to breast cancer and death due to other causes (**Figure 1).** The simulated clinical pathways are as follow:

1) Patients entered the model in the post-diagnosis post-surgery state after knowing the HER2 status, and started on trastuzumab concurrently with adjuvant chemotherapy of any regimes (trastuzumab arm). IV trastuzumab was given for 17 cycles in 52 weeks, 8mg/kg loading followed by 6mg/kg maintenance.[17] Chemotherapy was given for 6 to 8 cycles, both in trastuzumab arm and chemotherapy alone arm.[16, 17]
2) Patients remained in a state of disease-free state until they either died with background mortality or they experienced recurrence or metastasis.
3) Patients who were in recurrence state can move to metastasis state or die due to breast cancer.
4) Cardiotoxicity, the main side-effect of trastuzumab was incorporated in the model. All patients receiving trastuzumab will have echocardiogram performed every 3 months during trastuzumab treatment.[17]
5) All patients followed-up in the surgical/oncology clinics 3-monthly for the first year, then 6-monthly for five years, then annually.

Figure 1 : Markov model structure



The clinical parameters were extracted from published systematic reviews and clinical trials as shown in **Table 1**. Disease-free survival (DFS) was the primary endpoint in most trials and 5-year overall survival (OS) obtained from a meta-analysis by Moja L et al.[6] Annual rate of recurrence for the first year was calculated based on FinHER trial [18] and the rates for subsequent years were obtained from Early Breast Cancer Trialists' Collaborative Group (EBCTCG).[19] Other data such as prevalence of HER2 positive disease, breast cancer mortality and all-cause mortality for Malaysian population were derived from local studies and National Cancer Registry.[1, 2, 20-22]

The costs used in this analysis were based on the published literature using local data, unit cost for breast cancer treatment from University Malaya Medical Centre and also from Ministry of Health Malaysia.[23, 24] Direct medical costs included were cost of drugs, cost of procedures such as IV administration of drugs in daycare setting, cost of investigations such as echocardiogram and cost of specialist clinic follow-ups. All costs are expressed in Malaysian Ringgit (RM) and adjusted to costs of the year 2016. The parameters for costs input are presented in **Table 2**.

Analyses were projected to lifetime horizon and the cycle length was one year. The outcome was measured as quality-adjusted life-year (QALY). However, in absence of local data for early breast cancer, published literatures were used to obtain health states utilities and presented as **Table 3**.[11, 25] Costs and QALYs were both discounted at 3% rate.

Deterministic sensitivity analysis was performed as one-way sensitivity analysis to determine the parameter uncertainty. All results were presented as incremental cost-effectiveness ratio (ICER).

Table 1 : Clinical Parameters

Parameter	Base case estimate	Range	Reference
Prevalence of HER2 +ve	28%	-	Lim GCC et al (2014) [2]
Probability of death due to breast cancer	0.143	-	Yip CH et al (2014) [20] Abdullah NA et al (2013) [21]
Annual rate of all-cause mortality for Malaysian	Age specific	-	Abridged Life Tables Malaysia 2012-2015 [22]
ChemoTx+Tras treatment effects			
Hazard ratio for DFS	0.6	0.50, 0.71	Moja L et al (2012) [6]
Duration of treatment effect	5 years	-	Slamon D et al (2011) [26]
Hazard ratio for OS	0.66	0.57, 0.77	Moja L et al (2012) [6]
Probability of recurrence (year 1)	0.054	-	FinHER (2009) [18]
Annual rate of recurrence (year 5-9)	0.049	-	EBCTCG (2005) [19]
Annual rate of recurrence (year 10-14)	0.035	-	EBCTCG (2005) [19]
Annual rate of recurrence (≥ year 15)	0.027	-	EBCTCG (2005) [19]
Risk of cardiotoxicity (RR)	5.11	3.00, 8.72	Moja L et al (2012) [6]
Incidence of cardiotoxicity	2%	-	Slamon D et al (2011) [26]
Duration of cardiotoxicity	3 months	-	Hall PS et al (2011) [15]
ChemoTx alone treatment effects			
Hazard ratio for DFS	0.64	-	Slamon D et al (2011) [26]
Probability of recurrence	0.062	-	FinHER (2009) [18]
Incidence of cardiotoxicity	0.7%	-	Slamon D et al (2011) [26]

Table 2 : Cost Parameters

Cost description	Reference
Trastuzumab 440mg (per vial)	Personal communication with pharmacist from National Cancer Institute
IV administration in daycare oncology (per procedure)	UMMC breast cancer treatment unit cost 2016
IV reconstitution (pharmacy) cost	Lee WC et al (2016) [23]
SC drug administration cost (per procedure)	Lee WC et al (2016) [23]
Chemotherapy (any combination regime, per cycle)	UMMC breast cancer treatment unit cost 2016
Echocardiogram	UMMC breast cancer treatment unit cost 2016
Surgical/Oncology clinic follow-up (per visit)	UMMC breast cancer treatment unit cost 2016
Best supportive care (per month)	Dranitsaris G et al (2011) [24]

**IV = intravenous, SC = subcutaneous*

Table 3 : Health States Utility Values

Health states	Base case estimate	Reference
Disease free	0.847	Buendia JA et al (2013) [11]
Cardiac events	0.700	Buendia JA et al (2013) [11]
Recurrence	0.779	Lidgren M et al (2007) [25]
Metastasis	0.484	Buendia JA et al (2013) [11]

5.4.2 ASSUMPTIONS

It is a common approach to use assumptions based on available published literature or expert consultations in economic modeling due to limited available data. The following key assumptions were used in this model:

1. All health states are mutually exclusive, the patient will not be in other health states while in one particular health states
2. Breast cancer recurrence include local, regional and contralateral recurrences, and combined as episode of recurrence
3. All patients with recurrence are given second line chemotherapy and subsequently best supportive care
4. There were no breast cancer recurrences beyond year 20 of the model [10,11]
5. Patients in metastasis state will receive best supportive care
6. The clinical benefit of trastuzumab was assumed to last for 5 years [10,11]
7. Adjuvant trastuzumab patients experience cardiotoxicity within the first year of treatment, and this drug adverse effect is reversible [10,11]
8. Since cardiotoxicity adverse effect in trastuzumab is reversible, the model assumed that no additional mortality as a result of cardiotoxicity
9. The age-specific death rates due to other causes for disease-free states and recurrence state were assumed to be the same as that of the females population taken from the Malaysian Department of Statistics life table
10. Chemotherapy, radiotherapy, endocrine therapy and post-treatment follow-up protocols are assumed to be identical in both groups (except echocardiography in trastuzumab group for the first year)
11. The cost and effectiveness of chemotherapy is assumed to be the same regardless of any combination or regime

5.4.3 RESULTS

The results of this Markov model reflected the incremental cost-effectiveness ratio if trastuzumab is used concurrently with chemotherapy as adjuvant treatment for early breast cancer with HER2 positive status. The base case result considers 100% access to treatment of trastuzumab, whereby all the patients with HER2 positive status receive trastuzumab, as presented in **Table 4**. The mean discounted cost and QALY per patient receiving chemotherapy + trastuzumab was RM 167,788.81 and 4.099 respectively. For chemotherapy alone, the mean discounted cost and QALY was RM 82,129.71 and 3.074 respectively.

Table 4 : Incremental cost-effectiveness ratio (ICER) for base case

	Total discounted cost per patient	***Total discounted QALY per patient***	***Increment. Cost***	***Increment. QALY***	***ICER***
ChemoTx + Tras	RM 167,788.81	4.099*	RM 85,659.10	1.025*	**RM 83,544.59**
ChemoTx alone	RM 82,129.71	3.074*			

** QALY values used in the model were up to 5 decimal points.*

The base case analysis indicated that 1-year adjuvant trastuzumab treatment generates a deterministic ICER of **RM 83,544.59 per QALY gained**. Over the lifetime of the patient cohort, there is a marginal cost increase of RM 85,659.10 and a marginal benefit of 1.025 QALYs per patient when trastuzumab is added to standard chemotherapy compared with no trastuzumab strategy. This result is within the suggested value of cost-effectiveness threshold by WHO, between 1-3 times gross domestic product (GDP) per capita.

The results were based on a model with time horizon of approximately 35 years which may not fully reflect the real-life situation of the patients. It may be used as supportive information for reimbursement policy making processes to widen access of treatment to patients. However, further considerations on provider's affordability must be taken into account in view of financial constraint.

5.4.4 SENSITIVITY ANALYSIS

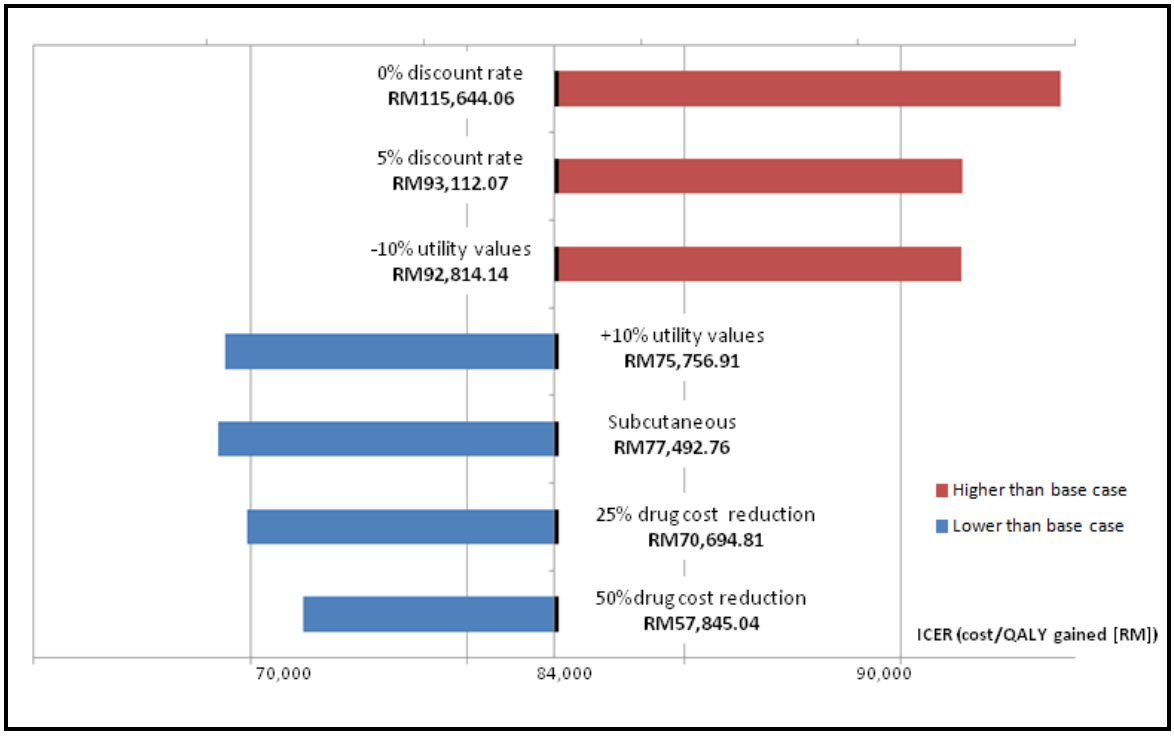
One-way sensitivity analysis was conducted to determine the parameters that may affect the ICER by varying the percentage of patients' access to trastuzumab, discount rate, route of trastuzumab administration, value of the clinical parameters and costs. The findings from the analysis are illustrated in **Table 5** and presented as tornado diagram **(Figure 2)** to demonstrate the ICER obtained from different scenarios in comparison to the deterministic ICER.

Table 5 : Scenario-based incremental cost-effectiveness ratio (ICER§)

Variables	Incremental cost	Incremental QALY*	ICER§
20% access of patients	RM 17,131.73	0.205	**RM 83,544.59** $^{\beta}$
50% access of patients	RM 42,829.50	0.513	**RM 83,546.32** $^{\beta}$
0% discount rate	RM 154,553.6	1.336	**RM 115,644.06**
5% discount rate	RM 81,538.24	0.876	**RM 93,112.07**
-10% utility values (disease free state)	RM 85,659.10	0.923	**RM 92,814.14**
+10% utility values (disease free state)	RM 85,659.10	1.131	**RM 75,756.91**
Subcutaneous trastuzumab	RM 79,454.10	1.025	**RM 77,492.76**
25% drug cost reduction	RM 72,484.10	1.025	**RM 70,694.81**
50% drug cost reduction	RM 59,309.10	1.025	**RM 57,845.04**

** QALY values used in the model were up to 5 decimal points.*
β = no significant difference from deterministic ICER

Figure 2 : Tornado diagram trastuzumab : one-way sensitivity analysis



Sensitivity analyses of variables in the model showed that the ICER is sensitive to changes in the discount rate, disease-free state utility values, route of trastuzumab administration and cost of trastuzumab. As shown in Table 5, percentage of patients' access to trastuzumab has little impact on the uncertainty of the ICER as the values are almost similar to deterministic ICER using 100% access of patients.

By varying the discount rate of 0% and 5%, both ICERs are higher than the base case ICER. At 0% discount rate, the ICER of RM 115,644.06 exceeds the cost-effectiveness threshold, while at 5% discount rate, the ICER obtained (RM 93,112.07) almost reaches the maximum recommended cost-effectiveness threshold by WHO which was 3 GDP per capita. This is also seen when the disease-free utility values is reduced by 10% from the base case value.

Simulating trastuzumab effect by increasing 10% of the disease-free state utility value yields an ICER of RM 75,756.91 which is lower than the deterministic value. Changing from IV trastuzumab to subcutaneous route also gives a lower ICER, which may provide an achievable alternative to current practice.

Reducing the cost of trastuzumab by 25% from current cost results in an ICER of RM 70,694.81 while further drug cost reduction to 50% produces a much lower ICER (RM 57,845.04). These results may be used as reference in decision making process for wider accessibility based on the healthcare provider’s affordability.

6. LIMITATIONS

Our study has several limitations. This review has been prioritized to include only trastuzumab as adjuvant in chemotherapy despite a variety of other available adjuvant for early breast cancer. Furthermore, there was no study comparing trastuzumab with other adjuvant in this review as this comparison was not the objective of this review.

The selection of the studies and appraisal was done by one reviewer. Although there was no restriction in language during the search, only English full text articles were included in the report.

In terms of the local economic evaluation, although every effort has been made in retrieving local data as model parameters, some of the values were not locally available. Thus, 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.

7. CONCLUSION

Safety

There was high level of evidence to suggest that the risk of CHF was significantly higher in patients treated with trastuzumab compared to non-trastuzumab control group (RR 5.11; 90% CI:3.00, 8.72, p<0.00001) in one Cochrane review, (RR 3.19; 95% CI:2.03, 5.02, p<0.00001) in one systematic review and meta-analysis. Evidence also suggest that the risk was significantly higher with longer duration of treatment (> 6 months) RR 5.39; 90% CI: 3.56, 8.17, P<0.00001 and also with higher loading dose of treatment (8mg/kg) RR 6.79; 95% CI: 2.03, 22.73, p<0.00001.

Effectiveness

Overall Survival (OS)

The OS significantly favoured trastuzumab containing regimen over non-trastuzumab control group, (HR 0.66; 95% CI: 0.55, 0.77, p<0.00001). In terms of duration, subgroup analysis reported that the OS significantly favoured trastuzumab containing regimen over non- trastuzumab control group trials where trastuzumab was given longer (> 6 months), HR 0.67; 95% CI: 0.57,0.80, P<0.00001. In the trials that gave trastuzumab and chemotherapy concurrently, HR significantly favoured trastuzumab-containing regimens (HR 0.64; 95% CI: 0.57, 0.80, P<0.00001).

Disease Free Survival (DFS)

The evidence from Cochrane systematic review suggests that DFS favoured trastuzumab containing regimen over non-trastuzumab control group (HR 0.60; 95% CI: 0.50, 0.71, P<0.00001). In terms of duration of treatment, there was no significant difference in DFS when trastuzumab was used for less than six months, or more than six months. The DFS significantly favoured trastuzumab containing regimen over non-trastuzumab control group when used either concurrently or sequentially. Limited evidence to suggest that two years duration of adjuvant trastuzumab was not more effective that one year of treatment. However, six months treatment with trastuzumab failed to show that it was non-inferior to twelve months of trastuzumab. Despite the higher rates of cardiac events, twelve months of adjuvant trastuzumab should remain the standard of care.

Cost-effectiveness

Systematic review of cost-effectiveness evaluation reported a wide range of ICER/QALY ranging from USD 7,676 to USD 71,491.

Local economic evaluation

From the decision analytic modelling that has been conducted, addition of 1-year treatment with trastuzumab on top of standard adjuvant chemotherapy is considered as a cost-effective strategy for early breast cancer with HER2 positive, yielding an ICER of RM 83,544.59 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, this treatment may not be a cost-effective strategy.

Based on one-way sensitivity analysis performed, these components have shown to be a sensitive parameter for ICER determination: discount rate, disease-free state utility values, route of trastuzumab administration and cost of trastuzumab.

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9. APPENDIX

9.1. Appendix 1: LITERATURE SEARCH STRATEGY

Ovid MEDLINE® In-process & other Non-Indexed citations and OvidMEDLINE® 1948 to present

1 BREAST NEOPLASMS/
2 (breast adj1 (cancer or carcinoma or neoplasm* or tumor*)).tw.
3 cancer of breast.tw.
4 cancer of the breast.tw.
5 (human mammary adj1 (carcinoma* or neoplasm*)).tw.
6 malignant neoplasm of breast.tw.
7 malignant tumor of breast.tw.
8 mammary cancer.tw.
9 mammary carcinoma* human.tw.
10 mammary neoplasm* human.tw.
11 neoplasm* human mammary.tw.
12 RECEPTOR, ERBB-2/
13 erbb-2 receptor.tw.
14 metastatic lymph node gene 19 protein.tw.
15 neu, proto-oncogene protein.tw.
16 neu receptor.tw.
17 oncogene protein her 2.tw.
18 (proto oncogene protein* adj1 (her 2 or neu)).tw.
19 proto oncogene proteins c erbb 2.tw.
20 proto oncogene c erbb 2.tw.
21 protein, p185erbb2.tw.
22 protein neu, proto-oncogene.tw.
23 proto-oncogene protein, her-2.tw.
24 proto-oncogene protein, erbb-2.tw.
25 proto-oncogene protein, neu.tw.
26 proto-oncogene proteins c-erbb-2.tw.
27 proto-oncogene protein neu.tw.
28 c-erbb-2, proto-oncogene.tw.
29 proto-oncogene c-erbb-2.tw.
30 (receptor* adj1 (erbb2 or erbb-2 or neu)).tw.
31 tyrosine kinase type cell surface receptor her2.tw.
32 c erbb 2 protein.tw.
33 erbb 2 proto oncogene protein.tw.
34 erbb 2 receptor protein tyrosine kinase.tw.
35 neu proto oncogene protein.tw.
36 p185erbb2 protein.tw.
37 or/1-36
38 TRASTUZUMAB/

39 Herceptin.tw.
40 Trastuzumab.tw.
41 or/38-40
42 CHEMOTHERAPY, ADJUVANT/
43 (adjuvant adj1 chemotherapy).tw.
44 (drug therap* adj1 adjuvant).tw.
45 or/42-44
46 41 and 45
47 38 and 46

OTHER DATABASES	
EBM Reviews - Cochrane Central Register of Controlled Trials	Same MeSH, keywords, limits used as per MEDLINE search
EBM Reviews - Database of Abstracts of Review of Effects	
EBM Reviews - Cochrane database of systematic reviews	
EBM Reviews - Health Technology Assessment	
PubMed	
NHS economic evaluation database	
INAHTA	
FDA	

9.2. Appendix 2

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

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 S2001)

9.3. Appendix 3. Evidence Tables

Evidence Table : Safety

Question: Is trastuzumab safe to be used in breast cancer patients?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size	General comments
1. Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V, D'Amico R. Trastuzumab containing regimens for early breast cancer. *Cochrane Database of Systematic Reviews* 2012, Issue 4. Art.No.: CD006243. DOI: 10.1002/14651858. CD006243.pub2	Cochrane review included eight trials that involved 11,991 women with HER2-positive who were assigned by chance to receive trastuzumab or not.	I	Eight RCTs were included in this Cochrane review. Total of 11,991 women were randomised to 7,020 women receiving trastuzumab and 4,971 women to a treatment without trastuzumab. All included patients had local (axillary) node-positive breast cancer or high risk node-negative disease on the basis of the size of the primary tumour and were HER2-positive.	Trastuzumab given following or in combination with standard chemotherapy regimen.	The same chemotherapy regimen used in the intervention group without trastuzumab	Articles published from 1996 to 2010	Cardiac toxicity data for the BCRIG006 trial were extracted from the Slamon 2006 reference. There were 135 (2.5%) of CHF out of 5471 patients in the trastuzumab group and 20 cases (0.4%) out of 4810 in the control group. The overall result indicated a higher risk of CHF with trastuzumab (RR 5.11, 90% CI 3.00 to 8.72, P<0.00001). Heterogeneity was minimal (I^2=28%) Breast cancer mortality is reduced by one-third but the risk of heart toxicity is five times more likely for women receiving trastuzumab than women receiving standard therapy alone.	

Evidence Table : Safety

Question: **Is trastuzumab safe to be used in breast cancer patients?**

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size	General comments
2. Long HD, Lin YE, Zhang JJ et al. Risk of congestive heart failure in early breast cancer patients undergoing adjuvant treatment with trastuzumab: a meta-analysis. The Oncologist. 2016; 21:547-	Meta analysis involved six randomized control trials	I	Six randomized control trials were included in the meta analysis including 18,111 patients.	HER2-positive early breast cancer patients with trastuzumab in adjuvant chemotherapy	Conventional chemotherapy	Review on Pubmed citations from January 1966 to July 2015	Incidence of CHF among 8,615 patients receiving trastuzumab from six trials was 1.44% (95% CI 0.79%-2.64%) according to the random effects model (Q=45.19; p<.0001; I^2=89%) Overall RR of high-grade CHF with trastuzumab was 3.04-fold higher (95% CI 1.12 to 7.85 fold; p<.00001) than for patients who did not receive trastuzumab. No significant heterogeneity among the included trials was observed (Q=6.92; p=.23; I^2=28%) The incidence rates of CHF were 0.95% (95%CI, 0.98%-1.33%) and 1.64% (95% CI, 0.74%-3.57%) for the high and low doses, respectively, with no statistically significant difference (p=.23). The overall RRs of CHF for the high and low doses were 6.79(95%CI, 2.03-22.73) and 2.64(95%CI, 1.62-4.33), respectively, for which a significant difference was found (p<.00001). The duration of trastuzumab treatment was 1 year, 2 years, or 9 weeks, with CHF incidence of 1.45% (95% CI 0.78%-2.66%), 1.09% (95% CI, 0.67%-1.78%), and 0.94% (95%CI, 0.19%-4.51%), respectively. The respective RRs were 3.29 (95% CI, 2.07-5.25), 9.54 (95% CI, 2.19-41.43), and 0.50 (95%CI, 0.05-5.49).	

Evidence Table : Effective

Question: Is trastuzumab effective to be used in breast cancer patients?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size	General comments
1. Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V, D'Amico R. Trastuzumab containing regimens for early breast cancer. *Cochrane Database of Systematic Reviews* 2012, Issue 4. Art.No.: CD006243. DOI: 10.1002/14651858. CD006243.pub2	Cochrane review included eight trials that involved 11,991 women with HER2-positive who were assigned by chance to receive trastuzumab or not.	I	Eight RCTs were included in this Cochrane review. Total of 11,991 women were randomised to 7,020 women receiving trastuzumab and 4,971 women to a treatment without trastuzumab. All included patients had local (axillary) node-positive breast cancer or high risk node-negative disease on the basis of the size of the primary tumour and were HER2-positive.	Trastuzumab given following or in combination with standard chemotherapy regimen.	The same chemotherapy regimen used in the intervention group without trastuzumab	Articles published from 1996 to 2010	The measure of association chosen for Overall survival (OS) and Disease Free Survival (DFS) was the hazard ratio (HR). The measure of association chosen for combining toxicities was the risk ratio (RR). <u>Overall survival (OS)</u> Overall survival (OS) was estimated from eight trials (B31, BCIRG006, Buzdar, FinHer, HERA, N9831, NOAH, PACS-04). 9935 women were included in the analysis, with 665 reported deaths (6.6%) The HR significantly favoured the trastuzumab-containing regimens over the non-trastuzumab control groups (HR 0.66; 95% CI 0.57 to 0.77, P<0.00001). <u>Duration of trastuzumab treatment (OS)</u> In trials where trastuzumab was given for a longer period, the HR for OS significantly favoured the trastuzumab containing regimens (HR 0.67; 95% CI 0.57 to 0.80, P<0.00001), while in the subgroup of trials that used trastuzumab for less than six months, efficacy failed to reach statistically significance (HR 0.55; 95% CI 0.27 to 1.11, P=0.1). <u>Concurrent or sequential administration of trastuzumab (OS)</u> HERA and PACS-04 gave trastuzumab sequentially to chemotherapy, involving 3929 patients and 189 deaths. B31, BCIRG006, Buzdar, FinHer, N9831, NOAH involving 6006 patients and 466 deaths. HR significantly favoured the trastuzumab-	

Evidence Table : Effective

Question: Is trastuzumab effective to be used in breast cancer patients?

Bibliographic **citation**	Study Type / Methodology	**LE**	Number of patients and patient **characteristics**	**Intervention**	**Comparison**	**Length of follow up**	Outcome measures/ **Effect size**	**General comments**
							containing-regimens given **concurrently** (HR 0.64; 95% CI 0.53 to 0.76, P<0.00001) Trastuzumab administered after chemotherapy, failed to reach statistically significance (HR 0.85; 95% CI 0.43 to 1.67, P=0.64). <u>Disease Free Survival (DFS)</u> Total of 9935 women and 1604 events (16.1%) were analysed. The overall HR for DFS significantly favoured the trastuzumab –containing regimens (HR 0.60; 95% CI 0.50 to 0.71, P<0.00001). <u>Duration of treatment (DFS)</u> In two trials (Buzdar, FinHer) which trastuzumab was given for less than six months, involving 273 patients and 42 events, the HR significantly favoured the trastuzumab –containing regimens (HR 0.31; 95% CI 0.10 to 0.96, P=0.04). In six trials that gave the drug for a longer time (B31, BCIRG006, HERA, N9831, NOAH, PACS-04), involving 9662 patients and 1562 events, the HR also significantly favoured tratuzumab (HR 0.62; 95% CI 0.52 to 0.72, P<0.00001). <u>Concurrent or sequential administration (DFS)</u> In both subgroups, comparing trastuzumab given sequentially or concurrently with chemotherapy and accounting for 3929 patients and 639 events, and 6006 patients and 965 events respectively, the HR significantly favoured the trastuzumab-containing regimens (HR 0.71; 95% CI 0.53 to 0.95, P=0.02; and HR 0.54; 95% CI 0.44 to 0.67, P<0.00001, respectively). The test for differences between subgroups was not significant (P=0.122).	

Evidence Table : Effective

Question: Is trastuzumab effective to be used in breast cancer patients?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size	General comments
2. Goldhirsch A, Gelber RD, Piccart-Gebhart MJ et al. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. Lancet. 2013; 382:1021-1028	The HERA trial involved internationally, multicentre, randomized, open-label, phase 3 trial comparing treatment with trastuzumab for 1 and 2 years with observation after standard neoadjuvant chemotherapy, adjuvant chemotherapy or both.	I	A total of 5102 patients were randomly allocated to three groups: i.) observation, ii.) trastuzumab for 1 year iii.) trastuzumab for 2 years. All patients included had locally assessed HER2-positive early stage invasive breast cancer confirmed by the central lab.	2 years trastuzumab adjuvant	1 year trastuzumab adjuvant	7 Dec 2001 to 20 June 2005	367 events of disease free survival in 1552 patients in the 1 year group and 367 events in 1553 patients in the 2 years group (hazard ratio 0.99, 95% CI 0.85-1.14, p=0.86). Grade 3-4 adverse events and decreases in left ventricular ejection fraction during treatment were reported more frequently in the 2 years treatment group than in the 1 year group (342 [20.4%] vs 275 [16.3%] grade 3-4 adverse events, and 120 [7.2%] vs 69 [4.1%] decreases in left ventricular ejection fraction, respectively). HRs for a comparison of 1 year of trastuzumab treatment versus observation were 0.76 (95% CI 0.67-0.86, p<0.0001) for disease free survival and 0.76 (0.65-0.88, p=0.0005) for overall survival, despite crossover of 884 (52%) patients from the observation group to trastuzumab therapy. Conclusion: 2 years of adjuvant trastuzumab is not more effective than 1 year treatment for patients with HER2-positive early breast cancer. 1year of treatment provides a significant disease free and overall survival benefit compared with observation and remains the standard of care.	

Evidence Table : Effective

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3.Pivot X, Romieu G, Debled M et al. 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial. Lancet Oncol. 2013;14:741-748.	Open-label, randomized, phase 3 trial in 156 centres in France.	I	Total 3384 patients with 1691 patients randomly assigned to receive 12 months of trastuzumab and 1693 to receive 6 months of trastuzumab; 1690 patients in each group were included in the ITT analyses.	6 months trastuzumab adjuvant	12 months trastuzumab adjuvant	30 May 2006 to 31 July 2010	After a median follow-up of 42.5 months (IQR 30.1-51.6), 175 disease free survival events were noted in the 12 months group and 219 in the 6 months group. 2-year disease free survival was 93.8% (95% CI 92.6, 94.9) in the 12-month group and 91.1% (89.7, 92.4) in the 6-month group (HR 1.28, 95% CI 1.05, 1.56; p=0.29). <u>Conclusion:</u> After 3.5 years follow-up, authors failed to show that 6 months of treatment with trastuzumab was non-inferior to 12 months of trastuzumab. Despite the higher rates of cardiac events, 12 months of adjuvant trastuzumab should remain the standard of care.	

Evidence Table : Cost-Effectiveness

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Bibliographic citation	Study Type / Methodology	L E	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size	General comments
1..Aboutorabi A, Hadian M, Ghaderi H et al. Cost-effectiveness analysis of trastuzumab in the adjuvant treatment for breast cancer. Global Journal of Health Science. 2015; 7(1):98-106.	A Markov model based on breast cancer disease states. A Markov model with four health states was designed to estimate outcomes and costs for a hypothetical cohort of women with positive early breast cancer. First strategy The patients received 100mg/m2 docetaxel, 60mg/m2 doxorubicin, 600mg/m2 cyclophosphamide intravenously (AC-T arm) in each session, six times every 3 weeks that prolonged approximately 4 months. Second strategy The above same regimen plus 52 weeks of trastuzumab (AC-T plus H) The model simulated a hypothetical cohort of women with an average age of 50 year with the same entry criteria as in the BCIRG 006 trial. The incidence of adverse effects associated with the adjuvant therapy was also taken into account.		Four health states namely: i.) Disease Free State (DFS) ii.) Loco-regional recurrence iii.) Metastases recurrence iv.) Death were included in the model. Based on the Markov model pts received their assigned adjuvant therapy and remained in a state of disease-free until they either died with background mortality or they experienced a loco-regional or metastatic relapse. Pts who survive with local recurrence can move to DFS or metastases state. Pts remain in a metastases state until they die from breast cancer or die from other causes.	Trastuzumab	Conventional chemotherapy without trastuzumab	Analyses were projected to 20-year horizons. The cycle length was one year.	The model showed that adjuvant trastuzumab treatment in early breast cancer yield 0.87 quality-adjusted life-years (QALY) compared with AC-T regimen. Adjuvant trastuzumab treatment yielded an incremental cost-effectuveness ratio (ICER) of USD 51,302 per QALY. Conclusion By using threshold of 3 times GDP per capita, as per WHO recommendation, 12 months trastuzumab adjuvant chemotherapy is not a cost-effective therapy for patients with HER2-positive breast cancer in Iran.	

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2.Buendia JA, Vallejos C, Pichon-Riviere A. An economic evaluation of trastuzumab as adjuvant treatment of early HER2-positive breast cancer patients in Colombia. Biomedica. 2013; 33:411-417.	A Markov model based on breast cancer disease states. Cost and QALYs were both discounted in the base case analysis by 5% annually.		Patients were eligible if they had invasive breast cancer resected by lumpectomy or mastectomy and axillary dissection with pathologically involved axillary nodes. Five health states were defined in the progression of breast cancer: i.) Disease-free state (DFS) ii.) local recurrence (local and contralateral), iii.) metastasis, iv.) cardiac event v.) death.	Trastuzumab added to standard anthracycline/taxane-based chemotherapy (doxorubicin plus cyclophosphamide followed by paclitaxel.)	Standard chemotherapy	The cycle length was 1 year.	The model showed that the utilization of adjuvant trastuzumab treatment in early breast cancer can prolong 0.80 QALY, compared with standard chemotherapy, an ICER of USD71,491 per QALY gained. The results suggest that 1-year adjuvant Trastuzumab treatment is not cost-effective in Colombia, using the definition of WHO cost-effectiveness threshold of 3 times GDP per capita.	

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3. Chen W, Jiang ZF, Shao Z et al. An economic evaluation of adjuvant trastuzumab therapy in HER2-positive early breast cancer. Value In Health. 2009;12(3):S82-S84.	A Markov health-state transition model was constructed to access the cost-effectiveness of 1-year adjuvant trastuzumab treatment for women with HER2-positive early breast cancer.based on breast cancer disease states. A discounting rate at 3% was used to discount medical expenditures that happened at different years.		The model was built according to HERA study, it was assumed that there were two groups each having 100 fifty-year-old patients in the DFS after surgery followed by adjuvant therapy. Five health states were defined in the progression of breast cancer: i.) disease-free state (DFS), ii.)local recurrence (local and contralateral), iii.)metastasis, iv.)cardiac event v.) death.	1-year adjuvant trastuzumab treatment after surgical therapy of early breast cancer and standard chemotherapy (combination of docetaxel, doxorubicin, and cyclophospha mide) after surgical therapy.	Standard chemotherapy	The cycle length was 1 year and the maximum cycle number was 45.	The incremental cost for an additional life-year-gained (LYG) was USD7564, USD7933, USD7929 in Beijing, Shanghai, and Guangzhou respectively. If measured by quality-adjusted life-year, the incremental cost-effectiveness ratio (ICER) was USD7676, USD8049, and USD8046 per QALY gained respectively.	

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4. Kurian AW, Thompson RN, Gaw AF et al. A cost-effectiveness analysis of adjuvant trastuzumab regimens in early HER2/neu-positive breast cancer. Journal of Clinical Oncology. 2007; 25 (6):634-641.	A Markov health-state transition model was constructed to simulate 3 adjuvant therapy options for a cohort of 49-year-old women with HER2 positive early stage breast cancer.		49-year-old women with early-stage breast cancer positive for amplification or overexpression of the HER2 oncogene, corresponding to the median age of participants in the published randomized AT trials.	1.)Anthracycline -based (AAT) regimens used in the trials group. 2.)Non-anthracycline (NAT) regimens used in the trials group.	Conventional chemotherapy without trastuzumzb. (NT)	2-year median follow-up	In the base case analysis, treatment with the non-trastuzumab(NT) regimen yields 9.35 QALYs at a cost of USD133,429, the AAT regimen yields 10.77 QALYs at a cost of USD190,092 and the NAT regimen yields 10.61 QALYs at a cost of USD206,561. Compared with the NT regimen, the AAT regimen yields an ICER of USD 39,892 per QALY. The AAT regimen dominates the NAT regimen.	