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DOI: https://doi.org/10.2165/11535560-000000000-00000

Cost-Effectiveness of Cytotoxic and Targeted Therapy for Metastatic Breast Cancer: A Critical and Systematic Review

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Running title: Cost Effectiveness of Metastatic Breast Cancer Therapies

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Abstract

Breast cancer is the leading cancer type diagnosed among females in Western countries. Despite great advantages in cancer therapies, many of these patients develop a non-curable metastases. The objective of cancer treatment is mainly to control symptoms and to prolong survival. The selection of the optimal chemotherapeutic regimen is affected by performance status, tumor biology, site and extent of the disease and the exposure to prior therapies. Recent developments in new kind of cancer drugs contributed not only to an immense progress in clinical outcomes, but also raised treatment related health costs dramatically. Cost-effectiveness analysis is a type of economic evaluation that refers to both costs and health outcomes of alternative intervention strategies in a systematic way. In this review, a systematic literature search was performed and the evidence on the cost-effectiveness of conventional chemotherapy and targeted therapy for metastatic breast cancer was explored.

Cost-effectiveness/-utility analysis of treatment regimens for metastatic breast cancer patients were identified using literature and reference searches (MEDLINE). Published reports on conventional and targeted cancer therapies were scrutinized and incremental cost-effectiveness ratios (ICERs) were abstracted. Furthermore, the quality of reporting, as well as methodological and modeling issues were extensively discussed.

From full-text article reviews, six cost-effectiveness analyses on conventional and seven studies on targeted therapies were included. Eight analyses were conducted in European countries, three in the United States and two in Canada. Primarily, the economic models were based in clinical trial data (69%). Results from sensitivity analyses and perspectives were reported by all studies. Discount rates was mentioned in five articles (39%). The methods of reporting costs and effects varied considerably. Considerable differences in trial designs across conventional chemotherapies raise difficulties to compare those analyses.

The results from the pharmaco-economic studies came to different conclusions. The actual clinical evidence does not suggest one conventional chemotherapy regimen as superior. Studies on cytotoxic agents showed mainly favorable cost-effectiveness ratios. Targeted therapies indicated both favorable and non-favorable ratios. Currently, trastuzumab is the only anti-body based targeted therapy which is established in the clinic for the metastatic setting.

Introduction

Breast Cancer is the most common cancer diagnosed in women in Western countries. About 25-40% patients develop a metastasis in the course of their illness [1, 2]. Since metastatic breast cancer is not curable, one of the main goals of treating these patients with metastatic or recurrent breast cancer is to provide palliation of symptoms and the maintenance or improvement of quality of life. The prolongation of life expectancy is a secondary goal. The armamentarium for palliative treatment contains potent endocrine treatments for the hormone receptor positive breast cancers, bisphosphonates for the subset of patients with bone disease, targeted therapy for, so far, mainly the subgroup of HER2 positive patents and finally conventional cytotoxic chemotherapy.

Conventional chemotherapeutics do not act on the diverse signaling pathways which help the tumor progressing but rather target dividing cells in general and are therefore associated with a wide range of side effects. For breast cancer in particular conventional chemotherapy for metastatic disease is usually administered after the failure of endocrine treatment. The fact that nowadays a high percentage of patients with early breast cancer receive adjuvant combination chemotherapy affects the decision of the regimen administered for recurrent or metastatic disease. Patients recurring after anthracyclines in the adjuvant setting usually receive a taxane-containing regimen, whereas patients after adjuvant taxanes usually receive an anthracycline-based regimen.

Targeted drugs however exploit specific molecular characteristics of the tumor and do usually not affect cells without that specific target. Several classes of antibody-based targeted therapies have raised hope in the treatment of breast cancer[3]. Trastuzumab (Herceptin®, Roche Pharma, Switzerland), a monoclonal antibody targeted to the human epidermal growth factor receptor 2 (HER-2) is currently routinely used in both the adjuvant and metastatic settings for patients with HER-2-positive tumors[4]. The efficacy and safety of trastuzumab as first-line treatment in metastatic breast cancer patients has been demonstrated in several randomized controlled trials [5-8]. However, trastuzumab is limited to 15-25% of breast cancer patients overexpressing the protein or amplifying the HER-2 oncogene [9-11]. Lapatinib is a oral available dual tyrosine kinase inhibitor of the HER-2 kinase and has been approved in some countries for metastatic HER-2 patients progressing under trastuzumab treatment or as first line oral treatment in combination with endocrine therapy [12]. Pertuzumab, a further monoclonal antibody binding a different epitope on HER-2 than trastuzumab is under clinical assessment. This agent has been developed for breast cancer patients whether overexpressing HER-2 or not [13, 14]. Bevacizumab (Avastin®, Roche Pharma, Switzerland) is a monoclonal antibody directed against vascular endothelial growth factor-A. Given its antiangiogenic properties, it is being evaluated in the metastatic setting, and is showing promising results [15]. Bevacizumab has been approved in a combination therapy for metastatic breast cancer with a negative HER-2 status [16].

The complex economics of new oncology drug developments are an important area of research [17]. However, the progress in the development of new cancer treatments are connected to costs, namely

treatment-related expenses and effects on quality of life. Especially expensive drugs have to demonstrate relevant improvements in regard to length of life, quality of life or if there is no other alternative available to be regarded as justified [18, 19]. In response to the growing concern about the costs of pharmaceutical products, pharmacoeconomic studies investigate the impact of new drugs or interventions on the patient's quality of life and the health care outcome through, e.g. cost-effectiveness studies. Economic analyses ideally cover clinical and economic outcomes achieved in randomized controlled trials. Such models play an important role in the decisions of policy makers in terms of coverage and reimbursement of the product.

According to the International Society for Pharmacoeconomics and Outcome Research (ISPOR)[20], economic studies would require a wide-ranging sensitivity analysis, the inclusion of the adequate time horizon and discount rate, the statement of the related perspective and the inclusion of a systematic and extensive literature review. However, the present review aimed at assessing the cost effectiveness of cytotoxic and targeted chemotherapeutic regimens for metastatic breast cancer in the published literature. Besides the extensive discussion of all studies, we placed particular emphasis on the key drivers of cost effectiveness of the various treatment agents.

Objective

The aim of this review was to identify published, original cost-effectiveness analyses of chemotherapy and targeted non-chemotherapy regimens for metastatic breast cancer presented as cost per life year gained (LYG) or quality adjusted life year (QALY) and to compare and summarize findings. The quality of reporting was critically assessed.

Methods

Data source and selection

MEDLINE and PubMed were searched systematically for all original cost-effectiveness analysis published between 2000 and 2009. Given that the field of targeted therapies is new, we included studies published only from the year 2000 onwards to ensure a comparable study population in both conventional and targeted therapeutic setting. The search was conducted with the text keywords cost, effectiveness, utility, breast, cancer metastatic, advanced. A total of 671 articles were recognized in the initial literature search. Title and abstracts were screened by two independent reviewers to determine whether the reports were an original health economic study. Studies considered important after the first screening cycle were evaluated at full-text. For literature saturation, reference lists were explored for relevant reports. Studies were included if they were reports on cost-effectiveness or cost-utility reports of metastatic breast cancer therapies. Descriptive cost studies, posters, editorials, publications not showing primary data or reports written in other languages than English were excluded. Cost-effectiveness analyses describing primary the health economic impact of hormonal

therapies or predictive testing in targeted non-chemotherapy settings were not taken into account. Figure 1 outlines how the final sample size was reached.

Detailed information from the reports was abstracted by a pre-specified list. A standardized extraction form was used to gather the following issues from the studies: characteristics of the study (study design, population, perspective), the type and outcome of the economic analysis, the key aspects (cancer treatment and comparator strategy, clinical outcome, costs and discount rate) and parameters of the sensitivity analysis (if available). For the base-case analysis, incremental cost-effectiveness ratios (ICERs) were reported. Studies were grouped into cost-effectiveness analyses addressing either conventional chemotherapy or targeted regimens. Particular emphasis on the key drivers of cost effectiveness of the various chemotherapy and non-chemotherapy regimens was given. As year of reference, the reported monetary year or the year of publication was used. Costs are shown in US Dollars ($) (1 Euro (€) ≅ $1.47; 1 GBP (£) ≅ $1.74; 1 CAD ≅ $1).

Results

Overview of included papers

The studies included were focused on breast cancer patients in a metastatic disease state. Outcome measures were given in either quality adjusted life year (QALY) (7/13) or in life year gained (LYG) (6/13). Eight analyses were conducted in European countries (France, Greek, Norway, Switzerland United Kingdom), three in the United States and two in Canada. Only one article was published in a pharmaeconomic and outcome research journal, whereas the remaining articles were published in oncology journals. The funding source was mentioned by nine studies (69%).

The methodologies used varied considerably. The studies included were all using model-based analyses for their calculations. Three reports mentioned in their articles that Markov-models have been established, whereas only two clearly described the model. The remaining studies used other economic models. Data included derived primarily from randomized controlled trial data (9/13). Two studies were based on cancer registry and medical record information, respectively. One study was conducted with data from an open controlled prospective study and one article was adapted from published literature. The studies were simulated from a healthcare payer (10/13), a hospital (1/13) or a societal (2/13) perspective. A discount rate of 3% (3/13), 3.5% (1/13) or 5% (1/13) was applied. Sensitivity analyses were conducted mainly for costs and effects. The economic analyses based on conventional chemotherapies were all considered cost-effective by the authors except one study with ixabepilone. In the studies of targeted non-chemotherapeutic agents, authors concluded the monoclonal anti-body treatment as cost-effective (3/7), not cost-effective (3/7) or gave no clear statement (1/7).

The summary of cost-effectiveness results of conventional and targeted therapies is given in table 1 and 2, respectively.

Cost-effectiveness studies of conventional chemotherapies

Maniadakis et al analyzed the cost-effectiveness of three taxane-based regimens which are administered as 1st line chemotherapy in patients with metastatic breast cancer that have already received anthracyclines in the adjuvant setting [21]. This economic analysis, that was conducted from the perspective of the Greek national health system, was based on the randomized phase III trial comparing carboplatin and paclitaxel to paclitaxel weekly and to docetaxel and gemcitabine[22]. The comparator was carboplatin (area under the curve (AUC) of 6) and paclitaxel (175 mg/m2) administered every three weeks for six cycles. Paclitaxel (80 mg/m2) at weekly administration for 12 weeks and docetaxel (75 mg/m2) combined with gemcitabine (1000 mg/m2) were the two other arms. The paclitaxel weekly arm appeared to be the most preferable choice among the three regimens as it prolonged the overall survival more than the other combinations without being associated with higher side effects. The quality of life was similar in all three arms. Gemcitabine with docetaxel incurred the lowest total costs per patients (19,343€; $28434) but proved to be less effective than the two paclitaxel containing regimens and was causing more sever myelotoxicity and mucositis. Paclitaxel with carboplatin every three weeks cost about the same amount per patients as paclitaxel weekly (20,498€ vs. 20,578€; $30,132 vs. $30,250) but was significantly less effective. These results remained fairly constant in sensitivity analyses.

Vu et al compared the cost-effectiveness of docetaxel (100 mg/m2) to paclitaxel (175 mg/m2) both administered every three weeks [23]. The analysis was conducted from the perspective of the Canadian health care system. The clinical data, in contrast to many other cost-effectiveness studies, was not based on a clinical trial but was derived from a provincial cancer registry. The overall survival in the docetaxel-treated group was significantly higher than among patients treated with paclitaxel (10.9 vs. 8.3 months). This benefit was comparable to the results of a randomized trial comparing both agents [24]. The costs per patient were substantially higher in the docetaxel group (9,441 CAD vs 2,944 CAD; $9,441 vs. $2,944) that was attributed to the higher acquisition costs of docetaxel. The cost effectiveness ratio was 30,337 CAD ($30,337) per life year (LYG) gained for docetaxel versus paclitaxel.

Benedict et al compared the same regimens for the UK health care system but used clinical data from a randomized controlled trial [25]. In contrast to the Vu et al study, Benedict et al included quality of life data retrieved from the literature. Furthermore, the authors indirectly included two additional regimens (Pac weekly and nabPac every 3 weeks) by including data from other randomized controlled trial to the above mentioned one. However, for paclitaxel weekly, not the best available evidence was included[26] but instead two abstracts from meeting proceedings. In the model, the hazard ratios of docetaxel, paclitaxel weekly and Nab-paclitaxel every 3 weeks compared to paclitaxel every 3 weeks were applied to the baseline hazard with paclitaxel very 3 weeks to model the progression-free and overall-survival curves. Out of them the proportion of patients in each of the three health states (no progression, progression, death) was calculated at each time point for each treatment.

The relative difference between the mean costs per patient in the docetaxel group vs. the paclitaxel group was smaller than in the population based analysis of Vu for Canada. Furthermore, the clinical benefit derived from a randomized clinical trial was higher than in the Canadian study, proving that data from randomized controlled trials usually are not always one to one reproducible in clinical practice. The cost-effectiveness ratio was found to be 4500£ to 14500 £ ($7,800 to $25,230) per QALY, what is regarded as acceptable for the health care system of the United Kingdom.

Verma et al compared the costs of adding capecitabine to docetaxel from the perspective of the Canadian health care system by combining data from a randomized controlled trial [27] with a population based model[28]. The comparator was docetaxel (100 mg/m2) every three weeks. The study arm was docetaxel (75 mg/m2) combined with daily oral capecitabine (2,500 mg/m2). The randomized clinical trial,showed survival benefit of three months (14.5 *v* 11.5 months) for the combination treatment. This benefit, however, was accompanied with increased toxicity (grade 3 events: 71% *vs* 49%), whereas grade 4 events were slightly higher in the monotherapy arm (31% *v* 25%). Verma et al conducted a analysis The incremental costs for the combination treatment were resulted in a cost-effectiveness ratio of 3,691 CAD ($3,691). Unfortunately, this analysis did not account for quality of life.

Recently, a new nanoparticle albumin-bound formulation of paclitaxel (nab-paclitaxel) was developed to improve efficacy and overcome the toxicity associated with the taxanes[29]. The efficacy and safety of nab-paclitaxel in the first- and second-line treatment of metastatic breast cancer (MBC) were demonstrated in a large randomized trial with paclitaxel serving as the control arm. In that study, nab-paclitaxel was statistically superior to paclitaxel in terms of objective tumor (33 vs. 19%; P = 0.001) and progression free survival (23 vs. 16.9 weeks; P = 0.006)[30]. There was also a trend in favour of nab-paclitaxel in overall survival (OS), but it did not reach statistical significance (median = 65.0 vs. 55.7 weeks; P = 0.37). Patients randomized to the nab-paclitaxel arm had a lower incidence of neutropenia but higher grade of sensory neuropathy. In another trial, different dosages of nab-paclitaxel were compared to the other taxane, docetaxel. The trial compared two weekly (100 and 150 mg/m2) and an every 3 week (300 mg/m2 q3w) schedule of nab-paclitaxel to docetaxel [30]. Nab-paclitaxel 150 mg/m^2 weekly demonstrated significantly longer progression-free survival (PFS) than docetaxel by both independent radiologist assessment (12.9 *v* 7.5 months, respectively; *P* = .0065) and investigator assessment (14.6 *v* 7.8 months, respectively; *P* = .012). Based on these data, that included only progression free survival data and no overall survival data, Dranitsaris et al conducted an economic evaluation from the perspective of the United Kingdom health care system[31]. Nab-paclitaxel 150 mg/m^2 weekly was associated with the highest cost per patient (£27,222; $47,366) due to the acquisition cost and due to costs for supportive care (growth factors, blood transfusions, antibiotics and antiemetics). The docetaxel arm was the less expensive treatment arm with £12,923 ($22,486) mean cost per patient. The incremental 5.4 progression free months gained by nab-paclitaxel 150 mg/m^2 compared to docetaxel resulted in a ratio of £31,800 ($55,332) per progression free year gained. Quality of life was not considered in this cost-effectiveness analysis. The authors concluded that nab-paclitaxel can be considered a reasonable alternative to docetaxel as first-line

chemotherapy for MBC and if considering the favorable side-effect profile of nab-paclitaxel the inclusion of quality of life and utility benefits would further improve its economic profile.

Finally, Reed et al analyzed the cost-effectiveness of adding ixabepilone the capecitabine as a third line chemotherapy after progression under anthracyclines and taxanes from the perspective of the US health care system[32]. The results of this study have to be cautiously compared to the other analysis as the underlying patient population has experienced recurrence or progression despite treatments with anthracyclines and taxanes, which is associated with poorer response to any chemotherapy and poorer survival expectation as such. Clinical data was extracted from a randomized controlled trial from which quality of life results were also available and incorporated. The addition of ixabepilone prolonged the overall survival by 32 quality adjusted days. The incremental costs for the combination therapy amounted at around 30,000$ which results in a cost-effectiveness ratio of $359,000 per QALY. The authors concluded that this ratio is higher than for other new treatments in metastatic breast cancer.

Cost-effectiveness studies of targeted therapies

Norum et al described a model-based cost-effectiveness analysis in MBC patients which included data on efficacy of trastuzumab, tolerability, gain in survival, drug charges and production gain or loss from a third payer perspective[33]. Based on data presented at a breast cancer conference and Medline search, they assessed life years gained and according costs in patients treated with standard chemotherapy (docetaxel, anthracycline plus cyclophosphamide or paclitaxel) compared to the therapy with addition of trastuzumab (4mg/kg i.v. initial dose, 2mg/kg i.v. weekly dose). Direct costs contained drug costs, the assessment of HER-2 status, hospitalization and outpatient clinic costs. Costs for the chemotherapeutic agents were assumed to be similar, hence, this factor was not incorporated in the model. No indirect costs were included. The incremental survival time with trastuzumab was between 0.3 and 0.7 years compared to standard therapy. Drug costs (89% of overall costs) and the prolonged treatment in the outpatient clinic (8% of overall costs) were the key factors driving costs in the trastuzumab group. Depending on survival gain and discount rate applied, incremental cost-effectiveness ranged from €69,212 to €162,417 ($101,742 to $238,753) per LYG. The reduction of drug costs and the additional improvement of survival significantly mainly influenced the base case results in sensitivity analyses. The authors came to the conclusion that the costs of administering trastuzumab to metastatic breast cancer patients for the gain of one year of life are considerable high.

The cost-effectiveness study of trastuzumab published by Perez-Ellis et al was based on a retrospective analysis of medical files and according cost data of HER-2 positive patients treated for first metastatic progression[34]. Trastuzumab administration was given as single agent or in combination with chemotherapy (taxanes). The uptake of trastuzumab was limited to one year or until disease progression (standard schedule: 4mg/kg i.v. initial dose, 2mg/kg i.v. weekly dose). Control patients received standard treatment (taxanes and/or anthracycline based chemotherapy). Treatment costs for the trastuzumab and the no-trastuzumab group were based on hospital direct costs (inpatient

hospitalization stay, drug costs, imagery test etc). Costs for predictive testing of HER-2 status were omitted from the analysis. Data on quality of life was not taken into consideration. In terms of overall survival, the T group showed superior results (37 months vs. 19 months in the Non-T group; $p<0.001$). The per-patient costs in the T-group were considerably higher than in the non-trastuzumab group (€39,607 ($58,222) vs. €12,795 ($18,809), respectively). Main cost drivers were the price of trastuzumab (40% of the total costs in trastuzumab group) and the length of hospitalization (60% of total costs in no-trastuzumab group). Of note, hospital room costs and the number of imagery test were substantially increased in the trastuzumab group. The incremental cost effectiveness ratio assessed by the bootstrapping method was considered as cost-effective (€27,492/LYG; $40,413/LYG). Sensitivity analyses were performed under several assumptions in regard to trastuzumab unit costs and hospitalization costs. The according ICER ranged from €8,000 ($11,760) to €20,000 ($29,400) per additional life year saved.

Poncet and colleagues evaluated the economic impact of a 3-weekly dosage schedule of trastuzumab in a open controlled prospective study[35]. Costs and effects of patients receiving a combination therapy of trastuzumab and paclitaxel (trastuzumab+ paclitaxel; 3-weekly schedule of trastuzumab: 4mg/kg initial dose, 2mg/kg i.v.) or control therapy (any chemotherapy without trastuzumab) were evaluated. According to the medical files of those patients, all costs generated from the hospital were included in the analysis (overall care costs, drug costs, immunohistochemical tumor analysis, hospital stay, etc). Effectiveness was assessed in terms of overall and progression free survival. The 1-year overall survival rate showed a significant difference between comparator and control group (0.85 vs. 0.47, respectively; $p=0.007$). The 1-year progression free survival was 60% in the trastuzumab+ paclitaxel arm and 42% in the control arm, without a statistical significance. The mean cost-effectiveness ratio was estimated with the incremental overall survival (+1.43 years) and incremental overall costs (+21,980€; +$32,311) yielding an ICER of 15,370€ ($22594) per additional saved year of life gained in the trastuzumab group compared to the non-trastuzumab group. According to the conclusion of Poncet et al, the strategy of adding trastuzumab to paclitaxel therapy seems to be affordable from the perspective of a French health care system. To obtain an equivalent mean cost-effectiveness ratio in both groups, the threshold analysis evaluated the costs of a trastuzumab flask at 432€ ($635) instead of the 626€ ($920) paid during 2002.

The study by Hornberger et al assessed the cost-effectiveness of first-line trastuzumab treatment of MBC HER-2+ patients (trastuzumab+ paclitaxel vs. paclitaxel)[36]. Patients with progressing cancer were allowed to receive trastuzumab as second-line treatment (75% in paclitaxel group, 47% in trastuzumab+ paclitaxel group). Data on response duration and overall survival derived from a randomized-controlled study (n=469)[6]. The model comprised the costs of chemotherapy, the rate, severity, and costs of adverse events, and quality of life. Clinical benefits were measured in achieved prolonged survival and improved QALYs. The combined therapy arm achieved a survival mean of 25.0 months compared to 15.2 months in the paclitaxel arm. In addition to this, the trastuzumab+ paclitaxel treatment gained higher QALYs than the control group (12.3 QALY months vs. 6.4 QALY months, respectively), but also increased health care costs by £18,330 ($31,894). However, the corresponding ICER was assumed to be cost-effective (£37,500/QALY; $65,250/QALY) and upon the

recommendation of the NICE Appraisal Committee, the treatment with trastuzumab+ paclitaxel of MBC patients was regarded as justified.

The majority of pharmacoeconomic studies include the projection of one specific indication. Garrison et al established a dynamic life-cycle model to evaluate the use of trastuzumab in multiple indication (adjuvant and metastatic breast cancer with a HER-2 positive expression pattern) to estimate the overall economic value of the agent[37]. Based on publicly available data, QALYs and direct treatment costs were estimated over the product life-cycle of trastuzumab during 18 years. The authors aimed at forecasting the volume of use of trastuzumab over the product life-cycle as well as estimating its cost-effectiveness across early stage and metastatic breast cancer patients from a payer perspective in the United States. The model included costs for HER-2 testing (IHC or FISH), trastuzumab therapy until disease progression, supervising and treating adverse events. The assumptions of costs of trastuzumab treatment in MBC patients were based on current medication costs. Survival estimates and utility weights derived from published studies. The authors projected the number of patients treated with trastuzumab three times lower in MBC compared to the adjuvant setting. Accordingly, 161,000 women with MBC would be treated during the entire modeling period. The volume of trastuzumab use and according costs resulted in an indication specific incremental cost-effectiveness ratio of $85,676 per QALY gained for MBC. The ICER for the overall life-cycle summed up to $35,590/QALY (ICER for early breast cancer: $26,417/QALY).

One article examined the health economic outcome of lapatinib in HER-2 overexpressing metastatic breast cancer patients [38]. The life-long Markov model compromised information on clinical effectiveness from results of two randomized controlled trials of lapatinib (EGF100151, EGF20002 [39]). Published literature was used to gather information on health state utilities, direct and indirect costs of the therapy, primary adverse events, laboratory tests and costs of disease progression. The model took the perspective of the US societal perspective. Adding lapatinib to capecitabine therapy yielded additional costs of $19,630 and 0.12 QALYs. The corresponding ICER resulted in $166,113/QALY gained. The sensitivity analyses revealed lower probability of 2% to reach an ICER below $150,000/QALY. Hence, the willingness-to-pay threshold is most probably not reachable.

The only cost-effectiveness study available with respect to bevacizumab in the first-line treatment of metastatic breast cancer was published by Dedes et al[40]. The study group analyzed the economic outcomes of bevacizumab plus paclitaxel versus paclitaxel mono-therapy in HER-2 negative MBC patients. Study design, progression and survival data were based on a randomized clinical trial[15]. By the help of a Markov model, cost-effectiveness expressed as costs per QALY was assessed. Costs data covered direct costs of chemotherapy treatment, most important adverse events, laboratory tests and disease progression. No indirect costs were taken into account. Utilities derived from published literature. The combined therapy of paclitaxel + bevacizumab summed up to additional per patient costs of €40,369 in combination with a gain of 0.21 QALYs. Consequentially, the incremental cost-effectiveness ratio resulted in 189,427€/QALY ($278,458/QALY). The subgroup analysis showed an increasing ICER with age. Due to the fact of an improved benefit in efficacy, the ICER of the younger population (27-49 years old, ICER: 152,823€/QALY ($224,650/QALY)), was considerably lower

compared with the older population (65-85 years of age, ICER: 1,226,615€/QALY ($1,803,124/QALY). The impact of statistical uncertainties around the main input variables were assessed by one-way and probabilistic sensitivity analyses. By varying time to progression in the paclitaxel + bevacizumab group, this treatment strategy was dominated. The variation of time to progression and time from progression to death (paclitaxel arm) showed a further considerable influence in sensitivity analysis. In conclusion, the authors believe that MBC treatment with additional bevacizumab to paclitaxel is expensive in comparison with a willingness-to-pay of €60,000 ($88,200) per QALY gained.

Quality assessment of key modeling issues

Several factors may have an influence on the cost-effectiveness ratio including funding source, input parameters, under-reporting and the quality of the data integrated in the model.

Input parameters

It is therefore of paramount importance to include reliable input parameters in a model. Some articles mentioned in their study limitations the problem of including data from a small trial sample size. Some few articles were based on data from abstracts, which is probably not the best way to include reliable information. Several trials have been powered to show significant results in regard to clinical response or progression free survival, but not in terms of overall survival. Hence, those trials may identify significant improvements in primary endpoints, but the gain in survival remain non-significant. Conducting cost-effectiveness analyses based on such results are justified, as long as probabilistic sensitivity analyses are performed to assess the impact of model assumptions not principally related to statistical uncertainties.

Sensitivity analyses

Sensitivity analyses are usually carried out in order to estimate the influence of the statistical uncertainties around the model inputs. All studies have performed sensitivity analyses, but there are major differences with respect to their quality. Most studies conducted deterministic sensitivity analyses to assess the robustness of the base case by varying variables with a direct impact on incremental cost within a certain range (e.g. +/- 30%). Clearly described probabilistic sensitivity analyses have been found in three articles. One article used the bootstrapping concept, which differs from probabilistic sensitivity analyses by drawing observations from a data set rather than taking random points in a distribution. However, several studies did not mentioned how the sensitivity analyses were performed neither what parameter have been included. The robustness of the study results can only be shown if sensitivity analyses have taken all variables into account, especially those with a potential impact on the cost-effectiveness ratio. Critical components in a sensitivity analysis were prices and quantities, functional relationships, health related quality of life measure and discount rates.

Perspective of the analysis

Most studies analyzed have taken the health system perspective (77%). These analyses do not take into account indirect costs, although improved cancer survival enhances the overall social surplus (improved labor force potential). However, a huge percentage of breast cancer patients is of working age. Given this, the potential of indirect cost savings and gain in productivity could be considerable and should not be disregarded. Only two articles have taken the societal perspective. There, not only direct and non-direct medical costs but also indirect costs have been included.

Influence of the cost-effectiveness ratio

As shown in this review, the cost-effectiveness of trastuzumab was mainly influenced by factors such as drug cost of trastuzumab, outpatient costs as well as administration costs. The expenditures for administration can be influenced by switching from a weekly administration interval to a 3-weekly schedule. However, as long as the drug intensity remains stable, no improvement in the cost-effectiveness ratio seems to be feasible[33]. From the patient's point of view, a 3-week schedule may yield an enhancement in its quality of life. However, the weekly administration of trastuzumab has been shown as superior compared to the 3-weekly course in terms of median progression-free survival (13.4 month vs. 8.8 months, respectively)[41]. Among conventional chemotherapies, only nab-paclitaxel was studied for different administration schedules. Weekly administration of nab-paclitaxel was associated with more total costs per patient than 3-weekly administration but the improved clinical benefit for the weekly schedule offset these costs.

The drug cost itself was found to be a further variable boosting the economic analysis, especially in the case of trastuzumab[33, 35]. By lowering the cost of a trastuzumab flask by about 200€ ($294), the mean costs per life year gained would equal the ICER achieved by conventional chemotherapy [35]. The standard unit of trastuzumab is a 150mg-vial. It could be argued that providing different vials (10mg, 50mg) could lower the costs by administering only the exact drug dosage needed.

In addition, the duration of the treatment with trastuzumab seems to be a point of discussion. The duration scheme of the targeted therapy in the included studies ranged between 24 weeks (8 cycles)[35] up to one year[34] or until disease progression[34, 35, 37]. Prolonging treatment would be associated with enhanced per-patient costs[42].

Comparability of different studies

Typically, costs-effectiveness ratios for a novel health care intervention range between $50,000/QALY in the United States and £30,000/QALY ($52,200/QALY) in UK [43]. Although those thresholds are generally regarded as acceptable, the true willingness of the society to pay for a new intervention is unknown. It might be reasonable to amend this threshold across higher and lower income countries[44]. The included analyses have been conducted in the US/Canada (38%) or Europe (62%). The limitation of comparing studies from various countries lies not only in striking differences in the cost and resources included. Nevertheless, there are different approaches and factors which have to be considered when using model-based cost-effectiveness analyses across different geographic regions[45]. For the adjuvant treatment with trastuzumab, Essers et al presented a possibility to

transfer a model-based economic study by assessing criteria and limitations of the transferability [46]. However, the main challenge to transfer and compare results from different studies is mainly the transparency of the methods. Given that several studies did not clearly mention how the economic model was performed (states, cycle length, software used), it is very difficult to compare the model results. Hence, one mayor problem to evaluate the quality of the cost-effectiveness analyses is underreporting.

Role of financial funding

Several health economic studies have been conducted by fundings provided by pharmaceutical companies that market the analyzed drugs [25, 32, 37, 47, 48]. Some others did not declare conflict of interest or funding and had no author affiliated with a pharmaceutical company [21, 23, 33-35, 38, 40]. Although pharmaceutical company sponsorship has not been found to bias individual health economic studies, it has been reported that it is associated with reduced likelihood of reporting unfavorable results[49]. This suggests that pharmaceutical sponsored studies are less likely to publish negative results. In fact, among the economic analyses reviewed in this article that reported negative or borderline results regarding cost-effectiveness ratios were conducted and published by independent research groups[33, 38, 40].

Discussion

During recent years, many studies addressing the issue of cost and effectiveness of various new regimens for metastatic breast cancer have been published. Developments in the understanding of the molecular pathology of breast cancer have enabled the use of targeted therapies for adjuvant and metastatic breast cancer. At the forefront of development among conventional chemotherapies either potentially more potent drugs (docetaxel, ixabepilone) or established drugs with improved drug delivery formulations (nab-paclitaxel) have entered clinical trials and succeeded a role in daily clinical practice. Therapies to target specific cellular pathways expand effective cancer drugs by a systematic patient selection. However, the introduction of new drugs for the therapy of cancer patients normally increases treatment costs. Pharmaco-economic analyses are in great demand in order to obtain a better understanding of the cost-benefit ratio of promising cancer drugs.

Among the new conventional chemotherapy regimens, there are some striking differences in trial design and included patient populations what makes comparisons across the different cost-effectiveness studies difficult. The role of anthracyclines for the adjuvant and metastatic (if not received adjuvantly) treatment of most of the breast cancer types is still not refutable. This is one of the main reasons that most cost effectiveness analysis focus on 2nd line therapy after either metastatic or adjuvant anthracycline-containing regimens. At progression or recurrence after anthracyclines a taxane-containing regimen offers the best response rates and is considered the standard of care. Despite several phase III studies conducted so far, there is still no consent on the best taxane-containing regimen for 2nd line chemotherapy. Docetaxel has been shown to be superior

to paclitaxel every 3 weeks [24], but in a separate trial paclitaxel weekly is more effective than paclitaxel every 3 weeks[26]. On the other hand, docetaxel every week is inferior to docetaxel every 3 weeks[50]. Furthermore, nab-paclitaxel has been compared in a phase II trial to docetaxel and showed superiority[30]. While Phase II trials are not perfect venues to compare agents, docetaxel was outperformed with regard to overall response rate by nab-paclitaxel in this setting. Similarly, the head-to-head comparison of nab-paclitaxel with standard paclitaxel was a comparison employing every 3 week paclitaxel and not the more effective weekly regimen. At present, it seems reasonable to consider all three agents useful for metastatic breast cancer, but difficult to declare a "best" agent on objective grounds. Therefore, cost-effectiveness studies should not omit one of the above three regimens. Unfortunately, paclitaxel weekly has been included as a comparator only in two cost-effectiveness study and resulted not only as the most efficient regimen in one of them but also as the most cost-effective [21].

If economic studies are conducted with poor clinical trial data, this will result in a poor outcome of the cost-effectiveness studies. There is an ongoing debate, whether cost-effectiveness analyses should only be conducted if the difference of clinical effectiveness between two treatment strategies is statistically significant [51-53]. However, if such data are used in economic studies, adequate sensitivity analyses have to be carried out to evaluate if those input parameters have an influence on the base case result. Recently, Chan et al published a review on cost-effectiveness analyses of trastuzumab in the adjuvant setting[54]. Based on the result of the review, the authors concluded that trastuzumab seems to be cost-effective in this setting. Nevertheless, they claimed for further high-quality economic studies with clinical data showing the real efficacy of trastuzumab.

Adjuvant treatment with targeted therapies may reduce future incidence of metastatic breast cancer. In our review, we did not include any articles, which assess the impact of adjuvant trastuzumab treatment on the reduced drug usage in the future metastatic indication in those patients[55]. From a health economic point of view, the adjuvant and metastatic setting should be evaluated separately, since these are two separate decisions. If lifetime incidence projections make a distinction between newly diagnosed and previously diagnosed metastatic breast cancer patients, bias may occur due to epidemiological double-counting which leads to overestimating costs and effects of the cancer therapy [37]. On the other hand, most cost-effectiveness studies are based on clinical data of patients naive to the evaluated targeted drug. The developments in clinical practice, however, are shifting the usage of targeted therapies to adjuvant therapy as well. In the case of trastuzumab, for example, the patient population on which the cost-effectiveness analysis of Norum et al[33] is based are virtually non existent any more since literally all of them receive trastuzumab in the adjuvant setting. If these patients develop metastasis, it is not clear to which extent they will benefit from the same targeted treatment and neither which targeted treatment is the most appropriate. Since nowadays many new targeted treatments are gaining market approval for various indications in breast cancer and some of them are also starting to be administered adjuvantly such as in case of trastuzumab and probably soon for lapatinib, cost-effectiveness studies for metastatic breast cancer, according to our review, often do not keep pace with new clinical developments.

Generally, the ICER of targeted non-chemotherapeutics is higher than the rates found in the conventional chemotherapeutic models. Given different comparators and treatment regimens, the lifetime ICER for trastuzumab ranged considerably. The economic models showed some major differences to assess the cost-effectiveness of targeted therapies. A clear description of the economic model used, was only given in some few articles. The two publications focusing on bevacizumab and lapatinib, respectively, showed no favorable ICER. Those two studies were based on clinical trial results and declared clearly the model methodology, the parameters included and the analyses performed. Furthermore, the authors did not receive any fundings from the pharmaceutical industry.

Cost-effectiveness thresholds vary in between countries. Usually, threshold values of $20,000, $50,000 or $100,000 per QALY or life year gained are applied [56]. In the metastatic setting, antibody-based targeted therapies indicated in several studies an unfavourable cost-effectiveness ratio [33, 38, 40]. In spite of this fact, trastuzumab has been established in clinical practice in both the adjuvant and metastatic disease.

There are some limitations of this systematic review. The review excluded articles written in other languages than English. Furthermore, results presented at meeting (abstracts) were not included. In addition to that, the search was limited to the database and the keywords used. This fact might have omitted some cost-effectiveness analyses.

The cost-effectiveness analyses on new therapies of metastatic breast cancer are rarely found in the published literature and high-quality economic models are needed. For agents like bevacizumab or nab-paclitaxel, the clinical benefit in terms of overall survival is still under investigation and it remains to be seen if these new therapies will be established in clinical practice as routine therapies.

Conclusion

We conducted a systematic review of cost-effectiveness studies of chemotherapy and non-chemotherapy regimens for metastatic breast cancer. In this setting, only few studies could be explored both for conventional chemotherapy and targeted therapies. Different conclusions were given. Studies on cytotoxic agents showed mostly favorable cost-effectiveness ratios. Targeted therapies showed both favorable and non-favorable ratios. The cost-effectiveness ratio seems to be dependent on the drug price, the extend of improvement in survival rates, and an altered administration schedule. However, the interpretation of cost-effectiveness studies can not only be limited to the value of the incremental cost-effectiveness ratio achieved. Moreover, the quality of the data and the key modeling parameters included in the analysis have to be taken into account. However, in case of trastuzumab the patient population included in the cost-effectiveness analyses do not reflect anymore the current HER-2 positive metastatic breast cancer patients, since almost all of them have already received trastuzumab adjuvantly nowadays. Many health care systems will have problems with accepting the high cost-effectiveness ratios reached by some expensive cancer treatments. trastuzumab, e.g., is widely justified due to its clinical benefit. The pharmaco-economic decision on the management of new agents like bevacizumab or nab-paclitaxel will arise, as soon as enough clinical evidence is available.

Acknowledgment

We thank Matthias Schwenkglenks, European Center of Pharmaceutical Medicine, University of Basel, Basel, Switzerland, for his valuable comments and his critical review of the manuscript.

Conflict of interest

On behalf of all authors we confirm that all potential conflicts of interest have been disclosed.

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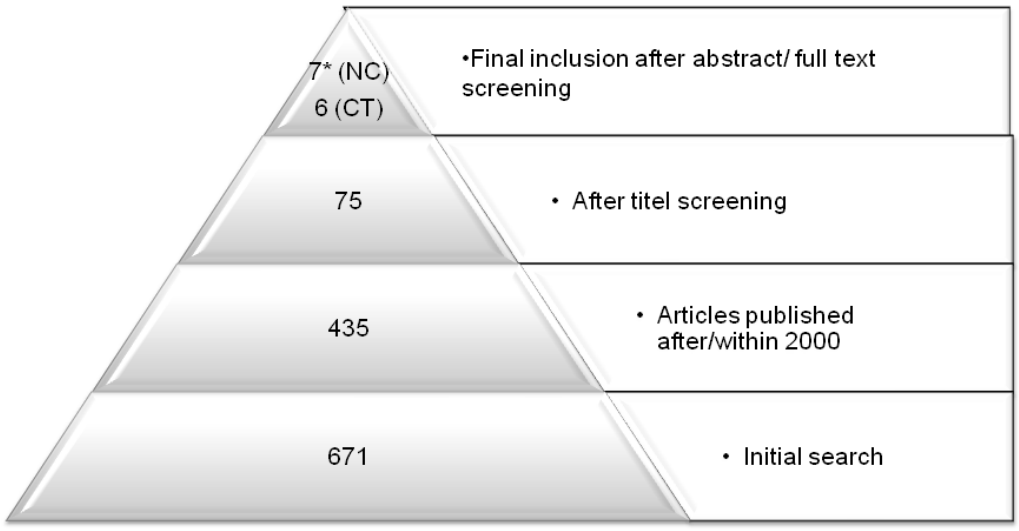
Figure legend

Figure I. Article search



NC: articles on non-chemotherapeutics
CT: article on conventional chemotherapies
*one article was included due to reference search

Tables

Table I. Cost-effectiveness analyses of conventional therapies

Study	Dranitsaris[31]	Maniadakis[21]	Reed[32]	Vu[23]	Benedict[25]	Verma[28]
Year	2009	2009	2009	2008	2009	2003
Country	United Kingdom	Greece	US	Canada	United Kingdom	Canada
Conflict of interest	Yes, manufacturer funded this study	No stated	Yes, manufacturer funded this study	None	Yes, manufacturer funded this study, Co-authorship from manufacturer	Not stated
Management of cancer	nabPac	Pacw, GDoc	Ixb+Cap	Doc	Doc	Cap+Doc
Comparators	Doc	PacCb	Cap	Pac	Pac3w, Pac1w, nabPac3w	Doc
Line of therapy	mostly 2nd line (after anthracyclines)	1st line (after adjuvant anthracyclines)	2nd – 3rd line (after anthracyclines and taxanes)	2nd line (after anthracyclines)	2nd line (after anthracyclines)	2nd lines (after anthracyclines)
Study design	RCT&basic calculations	RCT&basic calculations, multivariate regression	Stochastic decision-analytic model based on RCT,	Retrospective population based	RCT&basic calculations, Markov modelling	RCT& population based study
Population age (range, years)	54	60 (27-84)	52 (25-79)	55 (26-87)	NM	NM
Perspective	Third-payer perspective	Health care system	Health care system	Health care system	Health care system	Health care system
Outcome measure	LYG	QALY	QALY	LYG	QALY	LYG
Time horizon	Life time	34 months	Life time	Life time	10-year horizon	Life time
Overall mean cost results (per patient)	nabPac100mg/m^2: $26,787 nabPac 150mg/m^2: $47,366 nabPac300mg/m^2: $27,508 Doc: $22,486	PacCb : $30,132 GDoc: $28,434 Pacw: $30,250	Ixb+Cap : $60,900 Cap: $30,000	Doc: $9,441 Pac: $2,944	Doc: $30,139 Pac3w: $23,144 Pac1w: $27,793 nabPac: $24,562	Cap+Doc: $13,659 Doc: $12,833
Incremental cost	nabPac100mg/m^2: $4,301 nabPac 150mg/m^2: $24,880 nabPac300mg/m^2: $5,022	Pacw vs PacCb: $118 Pacw vs GDoc: $1,816 PacCb vs GDoc: $1,698	$ 30,900	$6,497	to Pac3w: $6,995 to Pac1w: $2,346 to nabPac: $5,577	$826
Discount rate	NM	3.5%	3%	no	3.5%	no

Outcome results (unit)	nabPac100mg/m^2: 12.8 progression-free months nabPac 150mg/m^2: 12.9 progression-free months nabPac300mg/m^2: 11.0 progression-free months Doc: 7.5 progression-free months	Pacw: 41 (months) PacCb: 29.9 (months) GDoc: 26.9 (months)	Ixb+Cap: 1,01 years Cap: 0.84 years	Doc: 10.9 months Pac: 8.3 months	Doc: 1.18 years Pac3w: 0.85 years Pac1w: 0.89 years nabPac: 0.96 years	Cap+Doc:
Incremental effect	nabPac100mg/m^2: 5.3 months nabPac 150mg/m^2: 5.4 months nabPac300mg/m^2: 3.5 months		32 quality adjusted days	2.6 months	to Pac3w: 0.33 years to Pac1w: 0.29 years to nabPac: 0.22	3 months
Cost-effectiveness result: ICER (Base case)	nabPac100mg/m^2: $9,744 per PF years gained nabPac 150mg/m^2: $37,932 per PF years nabPac300mg/m^2: $17,226 per PF years gained	Pacw vs PacCb : dominance Pacw vs GDoc: $5,286 per QALY PacCb vs GDOC: $10,969 per QALY	$359,000 per QALY	$30,337 per LYG	$20, 936 per QALY to Pac3w $7,974 per QALY to Pac1w $25,568 per QALY to nabPac	$3,691 per LYG
Results of sensitivity analysis	Results robust	Results robust	Univariate sensitivity analyses/ Monte Carlos simulation; >$150,000	Univariate sensitivity analyses: $13,972-$91,724	Probabilistic sensitivity analysis: Cost ratio remains < $34,800	Univariate sensitivity analyses: Results robust
Authors conclusion	nabPac is reasonable alternative to docetaxel	Pw effective and cost-effective regimen	Ixb more expensive than other regimens	Doc is more effecitive than Pac and may considered cost-effective	Doc is cost-effective compared to Pac1w, 3w and nabPac	Cap+Doc is cost-effective

Cap: capecitabine, Doc: docetaxel, Pac: paclitaxel, Pacw: paclitaxel weekly, nabPac: nanoparticle albumin-bound paclitaxel, Cb: carboplatin G: gemcitabine, Ixb: ixabepilone,
LYG: life years gained, RCT; randomized controlled trial; NM: not mentioned; QALY: quality-adjusted life years gained.

Table II. Cost-effectiveness analyses of targeted therapies

Study	Norum[33]	Perez-Ellis[34]	Poncet[35]	Hornberger[48]	Garrison[37]	Dedes[40]	Le[38]
Year	2005*	2002*	2002*	2002**	2009**	2008*	2007*
Country	Norway	France	France	UK	USA	Switzerland	USA
Conflicts of interest	Not stated	Not stated (French Ministry of Health/ French League against Cancer funded study)	Not stated (French Ministry of Health funded study)	Not stated (Co-authorship from manufacturer)	Not stated (Unrestricted grant from manufacturer)	None	None
Management of cancer	T + Doc, AC or P	T or T+Tax	T + Pac	T + Pac	T + Pac	Pac + Bev	L + C
Comparators	SC (Doc, AC or Pac)	SC (Tax and/or A-based)	SC (Doc or Doc+Epi)	Pac	Pac	Pac weekly	C
Line of therapy		1st	1st line	1st line, 2nd line (T only after progression)	1st line	1st line	2nd line
Study design	RCT (literature) & basic calculations	Before-and-after design study & bootstrapping method	Open controlled prospective study & basic calculations	RCT & statistical matching methods/ Gompertz function	Dynamic life-cycle modeling	Markov modelling based on RCT	Markov modelling based on RCT
Population age (mean, range, in years)	T: 25-80 SC: 24-79	T: 51 (27-73) SC: 55 (26-75)	51 (30-77)	NM	Five age groups (<21, 21-29, 40-54, 55-65, >65)	27-85	53
Perspective	Third party payer	Payer perspective	Hospital perspective (France)	UK National Health Service	Payer and Social perspective	Payer perspective	Societal perspective
Outcome measure	LYG	LYG	LYG	QALY (months)	QALY	QALY	QALY
Time horizon	Life time	Life time (or until date of patients last news)	Life time	5 years	18 years	Life time	Life time
Overall mean cost results (per patient)	T: $64,968	T: $58,222 SC: $18,809	T+Pac: $48,908 SC: $16,598	T+Pac: $50,373 Pac: $18,479	T+SC: $87,728 SC: $40,000	Pac+Bev: $101,492 Pac: $42,149	L + C: 66,499$ C: 46,869$
Incremental cost		$39,415	$32,310	$31,894	$47728	$59,342	19,630$
Discount rate	5% (only for benefits)	NM	NM	NM	3%	No	3%
Treatment duration	40 weeks (36 doses T)	T for max. one year or until disease progression	24 weeks (8 cycles) or until disease progression/ death	NM	Until disease progression	Pac+Bev: 7.1 months (followed by 3 month Bev-monotherapy) Pac: 5.1 months	NM
Outcome results (unit)	T: 25.8-30.5 months	T: 37.02 months	T+Pac: 2.4 LYG	T+Pac: 12.3 QALY-months	T+SC: 1.26 QALYs	Pac+BEV: 0.90 QALYs	Not stated

	SC: 21.1 months	SC: 18.98 months	SC: 0.97 LYG	Pac: 6.4 QALY-months	SC: 0.70 QALYs	Pac: 0.69 QALYs	
Incremental effect	3.7-8.4 months = 0.3-0.7 LYG	18.04 months	1.43 LYG	5.9 QALY-months = 0.49 QALY	0.56 QALY	0.21 QALYs	0.12 QALYs
Cost-effectiveness result: ICER (base case)	$101,742-$238,753 per LYG	$40,413 per LYG	$22,594 per LYG	$65,250 per QALY	$85,676 per QALY	$278,458 per QALY	$166,113 per QALY; $120,184 per LYG
Results of sensitivity analysis	Results sensitive to reduced drug cost and further improvement in survival	Cost ratio remains >$11,760 per LYG and < $29,400 per LYG	Threshold analysis: trastuzumab flask should be $634 to achieve an equivalent ICER in both groups	Montecarlo simulation to assess distribution of cost-effectiveness	Deterministic sensitivity analysis: ICER ranged from $21,210 to $52,842	One-way and probabilistic sensitivity analysis: WTP of $88,200 was never reached	One-way and probabilistic sensitivity analysis(95% confident limits): ICER $158,000-$215,000 per QALY
Authors conclusion	T not cost-effective in MBC	Despite huge unit price, T should be considered as cost-effective treatment for MBC patients	Additional costs seem affordable and justified the use for HER2+ patients	First-line treatment with T+Pac increases overall survival and QALYs. This approach is cost-effective	Average ICER can increase or decrease for different indications during the life-cycle of a compound	Addition of Bev is expensive given QALYs gained	Addition of L to C treatment is not clearly cost-effective

A: Anthracycline; AC: Anthracycline+Cyclophosphamide; BEV: bevacizumab; C: capecitabine; Doc: Docetaxel; Epi: Epirubicine; L: Lapatinib; Pac: paclitaxel; SC: standard chemotherapy; Tax: taxane; T: trastuzumab; V: Vinorelbine
LYG: life year gained; NM: not mentioned; OS: overall survival; RCT; randomized controlled trial; WTP: willingness to pay; * year of monetary value; ** year of publication