

## A Critical Review of Economic Evaluations of Trastuzumab in the Treatment of Early Stage HER2 Positive Breast Cancer

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### Abstract

Eleven years after Trastuzumab was approved for use in the treatment of early stage human epidermal growth factor receptor positive breast cancer (HER2+) its clinical benefit has been demonstrated in short and long term follow up studies. The cost-effectiveness of the therapy in this context remains the subject of debate with a wide range of Incremental Cost Effectiveness Ratios (ICERs) reported in the literature. While several reviews of the literature have been undertaken these have not provided a critical analysis of the factors that might underlie this heterogeneity. In this review we provide a critical overview of the literature and discuss potential sources of heterogeneity in reported ICERs. We identify gaps in the current literature and provide a rationale for filling these gaps.

**Keywords:** Tumour; Histology; Clinical; Pathological; Disease; Hormone; Health

### Introduction to Breast Cancer

Cancer is a leading cause of morbidity and mortality globally [1,2]. Breast cancer is the second most common type of cancer [1] and is the fifth leading source of cancer death [3]. The disease is more common in Northern Europe and North America than in other part of the world [4]. In the UK, approximately 1 in 8 women will be diagnosed with breast cancer during their lifetime [5]. Major risk factors for breast cancer include: female sex; increasing age; family history; reproductive factors (consisting of early menarche, late menopause, first live childbirth after age 30, nulliparity); long term use of hormone replacement therapy; previous exposure to therapeutic chest wall irradiation; benign proliferative breast disease; increased mammographic breast density; and genetic mutations (such as of the BRCA 1/2 genes) [1,6]. Factors determining treatment decisions include: tumour histology, clinical and pathological characteristics of the primary tumour, metastatic disease status, patient age, hormone receptor (estrogen and progesterone receptors) and HER2 status (human epidermal growth factor receptor 2) [6]. Interventions can be classified as primary, secondary, or tertiary prevention [7]. In the case of breast cancer, primary prevention may include chemoprevention, pre-emptive mastectomy and health education; secondary prevention may include population screening and subsequent treatment as appropriate and tertiary prevention may include chemotherapy, surgery and radiation therapy [8].

While it is common in economic studies of breast cancer to refer to it as if it was one disease, in reality this is not the case. There are up to 21 distinct histological subtypes and at least four different molecular subtypes of breast cancer that are biologically different in presentation, response to therapy and outcomes as well as having distinct risk factors [9-14]. Distinctions between types relate to the hormone receptor status (HR+/HR-) and excess levels of human epidermal growth factor- $\alpha$  growth-promoting protein-receptor 2 status (HER2+/HER2-). The four main molecular subtypes are: Luminal A (HR+/HER2-) (accounting for about 74% of breast cancers which tend to be slow growing and less aggressive than other subtypes) [15,16]; Triple negative (HR-/HER2-) (accounting for about 12% of cancers [16,17]-typically with poorer short-term outcome); Luminal B (HR+/HER+) (accounting for about 10% and tend to be more aggressive than Luminal A breast cancers) [18] and; HER2- enriched (HR-/HER2+) (accounting for about 4% of

breast cancers which tend to be more aggressive than other types of breast cancer and to have had poorer short-term outcomes than other estrogen receptor positive breast cancers though this has changed with the recent emergence of new therapies.

As detection and treatment of breast cancer has improved so too have survival rates [19]. Five-year relative survival rates have improved from nearly 75% between 1975 and 1979 to approximately 90% in 2010 [20] though these vary depending between specific types of breast cancer as well as on stage of diagnosis and access to care [1]. Improvements in survival, increased incidence and the adoption of more expensive therapies has seen the economic burden of breast cancer rise [21,22] both for health services and society more broadly [21]. In high income countries, costs in terms of lost production may be particularly high as the disease tends to affect women when they are often most economically active-aged 35 to 70. While there is a limited research on the economic burden of breast cancer [23], Taylor claim that breast cancer generally accounted for 10-20% of all cancer service costs, or approximately 0.15% of the average GDP in Europe (excluding productivity loss) [21]. In one population-based cost analysis in Europe, breast cancer was estimated to cost €15 billion (12% of total cancer cost) [24] making the second single biggest contribution to overall cancer costs [22]. Studies that have focused on cost that fall outside the health service-productivity losses, out of pocket expenditure, informal carer costs-indicate substantial costs also. For example, it is estimated that a woman with breast cancer missed an average of 68.6 days from work for surgery, radiation and chemotherapy [25]; 20% of employed patients stopped work at 16 months after diagnosis; 12% decreased working time [26]; and mean duration of sick leave was  $104.35 \pm 99.23$  days [27].

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Given the significant and increasing economic burden of breast cancer-and indeed of healthcare generally-it is not surprising that the relative value for money of alternative therapies has come under increasing scrutiny. Many countries now use economic evaluations to compare the alternative use of healthcare resources in terms of both cost and effect. Relative value for money is often expressed in terms of an Incremental Cost Effectiveness Ratio (ICER) showing the ratio of the additional cost relative to the additional effect of one therapy relative to another (The lower the ICER, the lower the ratio of cost to benefit and the better value for money). Often the effect is expressed in terms of incremental "quality adjusted life years"-QALY. These combine the additional years of life with the quality in which that life is experienced and when related to cost the resulting ICER can be compared against national thresholds as to what is considered an acceptable level of value [28]. In breast cancer, generally early stage interventions are associated with more favorable ICERs than late stage interventions [29,30]. Explanations for this relate both to higher costs typically incurred with late stage treatments and to the better outcomes associated with early stage interventions. For example, late stage interventions tend to involve intensive treatment, including drug use and subsequent intensive monitoring of patients relative to early stage interventions. Similarly, early stage interventions tend to offer a higher potential for QALY gains than late stage disease. In the case of breast cancer, late-stage ICERs were found to be 1.5 to 12 times higher in comparison with the early stage. The National Institute for Health and Care Excellence (NICE) subdivided early breast cancer into two major types, which are in situ cancer, mainly in the form of ductal carcinoma in situ (DCIS), and invasive cancer [31]. Based on the TNM classification of American Joint Committee for cancer, Dipiro et al. claimed that stage I and stage II breast cancer are often referred to as early stage breast cancer [32].

Nearly one in five patients diagnosed with advanced breast cancer are HER2 positive [1,33]. Targeted therapy has proved to be pivotal in the management of HER2 positive breast cancer. In comparison with cytotoxic chemotherapy alone, the addition of HER2-targeted therapies markedly improves response rates, survival outcomes (in terms of Disease-Free Survival (DFS)/Progression-Free Survival (PFS) and Overall Survival (OS)) in patients with HER2-positive breast cancer treated in the neoadjuvant (treatment given to shrink the tumor before the main treatment), adjuvant (treatment given to help the main treatment) or metastatic (when the cancer has spread beyond the breast to other organs) settings [34]. Trastuzumab (Herceptin, Genentech), recombinant humanized monoclonal antibody, was the first medication in this group. Trastuzumab was approved for the treatment of both early stage and metastatic breast cancer in 2006 and 1998, respectively [35]. Several population-based studies reported 4-year survival rates after the first Trastuzumab treatment in patients with Early Breast Cancer (EBC) at nearly 90%, and the 4-year relapse-free survival rate in metastatic breast cancer at 76% [36,37]. Trastuzumab generated 46% relative reduction in the risk of recurrence (Hazard Ratio: 0.54, 95% Confidence Interval: 0.44-0.67) and 24% relative reduction in mortality (Hazard Ratio: 0.76, 95% Confidence Interval: 0.47-1.23) [38]. This review aims to provide a critical overview of economic evaluations of its use in HER2 positive early stage breast cancer.

## Health Economic Evaluation of Trastuzumab in the Treatment of Early Stage HER-2 Positive Breast Cancer

Trastuzumab is expensive, for instance in the UK, to prevent one recurrent case, the estimated cost was £400,000 [39] while in other countries, one year's treatment per patient could cost between \$US60,000 and \$Cdn35,000 to 45,000 [40] (equivalent to \$42,490 to

\$54,630, PPP=1.214-2015) [41]. Its use as an adjuvant chemotherapy has been promising, with it being added in the recently updated Model List of Essential Medicine of WHO [42] despite its expense [40,43]. In fact, it is publicly funded in all Western European and most of Eastern European countries, resulting in significant financial burden on the healthcare system [43]. Given the number of potentially eligible women and the cost of the drug, it is not surprising that its use has been the subject of intense scrutiny especially in countries with publicly funded universal healthcare systems.

Several CEAs of the drug have been published in the light of nearly two decades of clinical study (Table 1) [44]. Assessing its relative value for money with specific regard to early stage disease is complicated by the fact that few evaluations of Trastuzumab in this setting provide clear definitions of what constitutes early breast cancer [39,45-49]. This lack of clarity complicates not only the assessment of its cost effectiveness in this setting but also of understanding the heterogeneity in estimates of its cost effectiveness in this setting.

It has been largely considered to be cost-effective in early-stage breast cancer by the majority of study authors [30,44,50] with estimates ranging from dominant (that is cost saving) [51] to nearly \$135,000/QALY [33,52]-a value whose acceptability will depend on the ICER threshold in the context concerned. ICERs reported from healthcare payers perspective were roughly \$1796/QALY and \$21,830.11 QALY higher than those from societal and hospital perspectives, respectively [33]. However, in comparison with other countries, ICERs reported in Europe and the US studies were more likely to reveal unfavourable thresholds [33]. While the factors underlying these differences have not been explored one might speculate drug acquisition costs, improved understanding of how best to use the drug and select patients for treatment may underlie differences.

Ferrusi et al. indicated that major factors affecting Trastuzumab cost-effectiveness were the choice of testing strategy; drug price and the assumed duration of Trastuzumab benefit [44]. These authors went on to argue that while studies are reported in different countries, the models deployed in those countries often varied little beyond the unit costs used to monetise resource use, calling into question the independence of these studies. That said studies have reported on a range of factors that influence cost effectiveness.

### Duration of use, time horizon and age

The short term use of Trastuzumab appears to generate more favourable ICERs than with its longer term use. For example, some analysis suggest that a 9-week Trastuzumab regimen could result in cost savings compared with 52-week therapy [44,53] but this warrants further investigation as the claim is based on a review of other reviews rather than a trial designed to explore this issue. With respect to age, Chan et al concluded that as an adjuvant therapy, Trastuzumab was cost-effective in women aged below 65 over a life-time horizon, but not cost-effective in patients aged over 75 or with a time horizon of less than 10 years [33]. Another study showed that time horizons shorter than 7.8 years compared to more than 7.8 years and patients over 75 compared to younger group resulted in higher incremental cost effectiveness of more than €50,000/QALY [45]. This number could be up to more than €100,000/QALY in patients more than 79 years old compared to the under 79 [45]. While another review reported that Trastuzumab for those over 65 years old was not cost effective [50], care is warranted with this claim given it is based on the interpretation of previous studies the focus of which was not heterogeneity in ICERs related to age. Clearly there exists some uncertainty both as to the role

| S. No. | Authors                  | Year | Country       | ICER estimate Cost/QALY  | ICER estimate Cost/LYG  | Definition of comparator   | Definition of early stage   |
|--------|--------------------------|------|---------------|--|---|--|---|
| 1      | Garrison et al. [56]     | 2007 | USA           | - Payer perspective: Lifetime \$26,417/QALY; 20-year horizon \$34,201/QALY<br>- Societal perspective: Lifetime \$27,637/QALY | - Payer perspective: Lifetime \$24,435/LYG; 20-year horizon \$32,361/QALY | Regimen without Trastuzumab Paclitaxel q3w x 4 or Paclitaxel qw x 12   | Based upon the definition in the NSABP B-31 and NCCTG N9831 trials  |
| 2      | Norum et al. [40]        | 2007 | Norway        | - €19,176/LYG (OS 20%)<br>- €44,934/LYG (OS 10%)   | - €8,148/LYG (OS 20%)<br>- €30,290/LYG (OS 10%)                           | FEC100 regimen administered for q3w x 6 without Trastuzumab (FEC: fluorouracil, epirubicin, cyclophosphamide)  | N/A   |
| 3      | Millar and Millward [78] | 2007 | Australia     | \$A 22,793/QALY  | \$A 13,730/LYG  | Standard therapy   | N/A   |
| 4      | Liberato et al. [45]     | 2007 | Italy and USA | €15,476 (\$20,211)/QALY<br>Discounted ICER: €14,861 (\$18,970)/QALY  | N/A   | Regimen without Trastuzumab Paclitaxel q3w x 4 or Paclitaxel qw x 12   | Based upon the definition in the NSABP B-31 and NCCTG N9831 trials. |
| 5      | Kurian et al. [62]       | 2007 | USA           | \$39,982/QALY  | N/A   | Doxorubicin+Cyclophosphamide q3w x 4, followed by paclitaxel qw x 12   | N/A   |
| 6      | Dedes et al. [79]        | 2007 | Switzerland   | N/A  | €40,505/LYG (after 10 years)<br>€19,673/LYG (after 15 years)              | Adjuvant treatment after surgical therapy without Trastuzumab  | N/A   |
| 7      | Neyt et al. [53]         | 2008 | Belgium       | Not reported   | €3,383 - €55,518 (15 subgroup analysis)                                   | Standard care  | N/A   |
| 8      | Macedo et al. [80]       | 2010 | Portugal      | €10,595/LYG (direct cost only)<br>€7,789/LYG (indirect cost)   | €10,067/LYG (direct cost only)<br>€7,400/LYG (indirect cost)              | Standard care  | N/A   |
| 9      | Purmonen et al. [46]     | 2011 | Finland       | €12,000/QALY   | €9,300/LYG  | Standard treatment   | Based on FinHER trial   |
| 10     | Hall et al. [64]         | 2011 | UK            | £25,803/QALY (56% probability <£30,000)  | N/A   | Chemotherapy without Trastuzumab   | N/A   |
| 11     | Hedden et al. [60]       | 2012 | Canada        | \$13,095/QALY  | \$15,492/LYG  | Standard chemotherapy  | N/A   |
| 12     | Buendia et al. [47]      | 2013 | Colombia      | \$71,491/QALY  | N/A   | Standard chemotherapy  | N/A   |
| 13     | Aboutorabi et al. [59]   | 2015 | Iran          | \$ 51,302/QALY   | \$54,223/LYG  | Adjuvant chemotherapy alone: Docetaxel, doxorubicin, cyclophosphamide q3w x 6  | N/A   |
| 14     | Lang et al. [49]         | 2016 | Taiwan        | \$51,863/QALY  | N/A   | Commonly used chemotherapy regimen for HER-2+ early breast cancer women without Trastuzumab (such as combination of docetaxel or paclitaxel, doxorubicin and cyclophosphamide) | N/A   |

**Table 1:** Summarizing the cost effectiveness analysis of Trastuzumab in the treatment of early stage HER2 positive breast cancer.

of age where care is warranted given the extrapolation of estimates from other studies.

### Study perspective

Other factors that have been shown to influence the cost effectiveness of Trastuzumab include the perspective adopted for the study [2]. Most studies evaluated direct cost from a third party payer perspective [47,51,54,55]. This decision likely reflected access to data, details of resource use and reimbursements by third party payers being generally more readily available than details of out of pocket expenditures or where costs relate to absenteeism or presenteeism. In studies adopting a societal perspectives, many included this as part of an analysis undertaken from the payer's perspective [40,56,57]. From the payer's perspective, most studies included as costs HER-2 testing, drug acquisition and drug administration costs, as well as supportive medications [47,54,55], cardiac monitoring [47,55], costs of palliative Trastuzumab [51,54,55], cost of local and distant cancer recurrences

[47,51,54,55] as well as the cost of different chemotherapy-related adverse events [47]. In studies reporting from a societal perspective studies reported productivity losses [51,56-58], transportation costs [56,57], out-of-pocket payments [43]. Assessing non-care costs is not straightforward. With respect to lost production, for example, as it is in general easier to calculate time off work during treatment, compared to the potential opportunity cost of future production, most studies scrutinized the former issue and made no reference to the latter. How appropriate this approach is, is open to debate [40]. Finally, unit cost is another crucial factor to take into account when trying to interpret cost effectiveness study. Unit costs are not available in all countries and the value accorded these can vary depending inter alia on the accounting procedure used to generate them, the structure, efficiency and bargaining power of the healthcare system from which they originate. These are again factors that can complicate the comparative analysis of ICERs even in instances where models differ ostensibly only in terms of the unit costs they apply to resource consumption.

## Modelling

The use of Trastuzumab in early stage breast cancer is relatively recent and it is not surprising therefore to find that most of the studies evaluating its cost effectiveness in this setting are model based given the paucity of data on longer term follow-up [33,40,50]. Modelling, however, often involves the use of many assumptions often based on adjustments of findings from earlier studies [40,47,55,59,60]. The reasonableness of these assumptions, however are central to the quality of model and the validity of its predictions. There is evident heterogeneity in the model based evaluations reported in the literature. For example, different studies use different modelling approaches, while most use a Markov modelling approach (including health-state transition model [47,61,62], life-long state transition model [63], a discrete-state time dependent semi-Markov model [64]), others use dynamic models (dynamic life-cycle model [35]). The number of states modelled also varies markedly from 3 to 10 states of disease [45,47,51,55,59,64], the variation reflecting in part the focus of the authors (such as cardiac toxicity, recurrence or relapse, HER2 testing and Trastuzumab regime) and the willingness of authors to balance complexity with transparency in models. How models are populated also varies though the relatively small number of trials relating to use of Trastuzumab in early stage breast cancer has served to limit heterogeneity here. Data from the HERceptin Adjuvant (HERA) [53,54,65,66] trial has become the most commonly used source for evaluations of treatment in an early stage setting. Differences regarding DFS rates (disease-free state), duration of treatment effect, disease recurrence, cardiac toxicity, mortality, transition probability between trials will lead to significant differences in model parameters and choices in which outcomes to focus on can influence estimated ICERs even when these are derived from the same trial. As new studies report it is probable that cost effectiveness of Trastuzumab could change when new RCTs will be published.

Since 2010, new RCTs have been published with focus on collating the clinical outcome of Trastuzumab in neoadjuvant setting and in combination with other HER2 targeted medications (including pertuzumab and lapatinib) or other drugs used in breast cancer treatment (docetaxel, aromatase inhibitors, hormonal therapies). Some studies are phase II clinical trials for instance TBCRC 006, EORTC 10054, CHER-LOB [67-69], the others are phase III clinical trials such as the NOAH trial, NeoALTTO, CALGB 40601, NSABP protocol B-41, the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization Trial [70-73]. Such studies have the potential to produce parameters that will inform future modelling exercises.

## Cost- effectiveness thresholds

In deciding whether a particular ICER represents value for money or not, ICERs must be compared with an appropriate threshold that reflects societal willingness to pay for the health gain achieved. Applying different thresholds is entirely reasonable given different countries may have different levels of income, different values for health gain and indeed different values for health gain related to specific diseases. Therefore, it is crucial for the authorities in different settings to be aware of this when interpreting the corresponding ICERs and making decision related to oncological drugs [29,33]. Although thresholds do differ [33] and cost effectiveness acceptability curves provide the opportunity to assess the likelihood of an intervention being deemed to be cost effective at various thresholds, it remains the case that these thresholds are indicative rather than prescriptive when it comes to reimbursement decisions. While, for example, the National Institute for Clinical Excellence (NICE) in the United Kingdom applies the threshold of 20,000 to 30,000 British pounds/QALY gained [74]

in practice interventions including those for early stage breast cancer may be approved for reimbursement above this level. In fact, the importance of the cost-effectiveness threshold in the UK has called for studies to explore. This is an area of research in its own right. Applying the method of estimating the WTP based on the existing value of preventing a statistical fatality, Mason et al. suggested that the WTP for a discounted QALY was nearly £69,000 (without adjustments) and £31,000 (with age adjustment, apply for young adults) [75]. Using the same technique but in Swedish population, Johannesson and Meltzer estimated a WTP per QALY gained of around US \$90,000 [28]. In Australia, George et al. applied revealed preference method to examine the recommendations made by the Pharmaceutical Benefits Advisory Committee from 1991-1996 and revealed that no treatment costing under Au\$39,800 per life year gained was rejected and none over Au\$75,300 was approved [76]. In terms of how the estimated ICER of Trastuzumab actually influences reimbursement decisions in different jurisdiction these and the potential budgetary impact of the drugs reimbursement are clearly important issues.

## Conclusion

There have been numerous economic evaluations of Trastuzumab since it was first approved for use in breast cancer. Despite the fact that it was approved for use in early stage breast cancer in 2006, there have been relatively few evaluations of it in this context. Of those that have reported, most adopt a model based approach that rely heavily on one trial extrapolating from this using a variety of assumptions. This has allowed a number of systematic reviews of the literature to be published on the subject [2,33,44,50]. However, these have focused on comparing the conclusions of studies, in terms of the cost effectiveness ratio reported and some information related to modelling method, providing limited critical analysis of sources of variations or how best to reconcile the apparently conflicting conclusions of these studies. While best practice guidelines on modelling exist, few of the reviews have sought to assess the quality of evidence incorporating the insights these might afford into their analyses.

Three important contributions to the literature now seem timely. First the conduct of a systematic review that critically assesses the cost effectiveness of Trastuzumab in the treatment of early stage breast cancer would be useful. Such a review should assess the quality of model based assessments against established criteria for the production of economic models, heterogeneity in the interpretation of the term "early stage" and seek to identify the source of variation in reported ICERs. Second, some 11 years after the approval for use of Trastuzumab in the treatment of early stage HER2 positive breast cancer, longer term follow up data on cost and survival now exist [77]. A model based analysis that avails of data outside a trial setting with the potential inherent biases this might generate not seems timely. This seems preferable to resorting to assumptions around many parameters with however an extensive sensitivity analysis. Third, a budget impact analysis based on the acquired experience of the drugs deployment to accompany the economic evaluation has the potential to provide valuable insights for those considering its use in this setting or expanding its use to other settings.

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