Trastuzumab emtansine for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane: A NICE Single Technology Appraisal

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Abstract

The National Institute for Health and Care Excellence (NICE) invited the manufacturer of trastuzumab emtansine (T-DM1) (Kadcyla®; Roche) to submit evidence of its clinical and cost-effectiveness for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane. The School of Health and Related Research Technology Appraisal Group (ScHARR-TAG) at the University of Sheffield were the independent Evidence Review Group (ERG) who produced a critical review of the company's submission to NICE. The ERG also independently searched for relevant evidence and modified the submitted decision analytic model to produce a revised estimate of cost-effectiveness and examine the impact of altering some of the key assumptions.

The clinical effectiveness data were taken from two randomised controlled trials, which reported a significant advantage in progression-free survival for T-DM1 over lapatinib in combination with capecitabine (EMILIA trial), and over the treatment of physician's choice (TH3RESA trial). A network meta-analysis suggested T-DM1 was the best treatment in terms of both overall survival and progression-free survival compared with: lapatinib in combination with capecitabine; trastuzumab in combination with capecitabine; and capecitabine monotherapy. Adverse event (AE) data were taken from a pooled analysis of additional trials of T-DM1 as a single agent. The most common grade 3 or greater AEs for T-DM1 were thrombocytopenia and hepatotoxicity.

Following the clarification process, the manufacturer reported a deterministic incremental cost effectiveness ratio (ICER) for T-DM1 compared with lapatinib in combination with capecitabine of £167,236, the latter of which was estimated to have an ICER of £49,798 compared with capecitabine monotherapy. The ERG produced similar values of £166,429 and £50,620 respectively. All other comparators were dominated. During the appraisal, the manufacturer offered an analysis of a patient access scheme (PAS), which suggested that T-DM1 had a 0% probability of being cost-effective at an ICER of £30,000 per QALY gained. The NICE Appraisal Committee concluded that whilst the clinical effectiveness of T-DM1 had been proven, it was not likely to represent a cost-effective use of NHS resources and so its use could not be recommended.

Key points for decision makers

- T-DM1 provides a significant advantage in terms of progression-free survival and overall survival compared with alternative treatment options for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane.
- The adverse event profile of T-DM1 is favourable compared with alternative treatment options.
- Given current acquisition costs, T-DM1 does not represent a cost-effective use of NHS resources.

1. Introduction

The National Institute for Health and Care Excellence (NICE) is an independent organisation whose responsibilities include providing national guidance to the NHS in England and Wales on health technologies. The NICE Single Technology Appraisal (STA) process usually covers new single health technologies within a single indication, soon after the UK market authorisation [1]. The manufacturer submits evidence on the clinical and cost-effectiveness of the technology, including a de novo economic model, and an independent Evidence Review Group (ERG) review this submission. The NICE Appraisal Committee (AC) consider the evidence submitted by the company and the ERG, alongside testimony from experts and other stakeholders in order to develop national recommendations for England and Wales reported within a Final Appraisal Determination (FAD). An Appraisal Consultation Document (ACD) is initially produced if the recommendations from the AC are restrictive or additional clarification is required from the manufacturer about their submission. All stakeholders have an opportunity to comment on the ACD before the AC meets again to produce the FAD.

During this assessment, the FAD was subject to an appeal from the company which led to a sixteen month delay in publishing the FAD. This article presents a summary of the ERG report at the time of the assessment and the outcome of the NICE guidance for the STA of trastuzumab emtansine (T-DM1) for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane. This is one is a series of STA summaries being published in PharmacoEconomics. Full details of all relevant appraisal documents can be found on the NICE website [2].

2. The Decision Problem

T-DM1 is licensed for use in people with overexpression of the human epidermal growth factor receptor 2 (HER-2 positive), unresectable locally advanced or metastatic breast cancer whose disease has progressed after treatment with trastuzumab and a taxane (paclitaxel or docetaxel) [3]. Whilst survival has generally improved for breast cancer patients, for this patient group the disease is largely incurable, with the majority dying within three years of progression [4]. In the absence of targeted therapy, HER2-positive metastatic breast cancer is associated with more aggressive disease, including higher recurrence rates, and shorter progression-free and overall survival, than tumours not overexpressing HER-2.

As described by the manufacturer, T-DM1 is part of a new class of drugs, termed antibody-drug conjugates [4]. It has multiple modes of action to specifically target HER-2 positive cancers. T-DM1 is administered intravenously every three weeks, typically within an established oncology unit in a hospital. No additional monitoring for T-DM1 is required compared with alternative existing treatments. To be eligible for T-DM1, patients should have either received prior therapy for locally advanced or metastatic disease or developed disease recurrence during, or within six months of, completing adjuvant therapy [3]. According to the company's calculations there are approximately 1300 eligible patients per year [4].

Treatment options recommended by NICE for this patient population are: trastuzumab in combination with paclitaxel (first line); capecitabine or vinorelbine (plus trastuzumab in central nervous system only progression)

(second line); and vinorelbine or capecitabine or trastuzumab (third line) [5]. However, due to the Cancer Drugs Fund, current practice in England and Wales includes: pertuzumab in combination with docetaxel or trastuzumab in combination with a taxane (first line); lapatinib in combination with capecitabine (second line); and vinorelbine or capecitabine or trastuzumab (third line) [4]. The company proposes T-DM1 as an alternative second line option. Comparators included within the final NICE scope included: lapatinib in combination with capecitabine; trastuzumab in combination with capecitabine; trastuzumab in combination with vinorelbine; capecitabine monotherapy; and vinorelbine monotherapy [2].

3. The Independent ERG Review

The company provided a submission to NICE regarding the clinical and cost-effectiveness of T-DM1 for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane. The ERG report comprised a critical review of the company's submission. In accordance with the process for STAs, the ERG had the opportunity to seek clarification on specific points in the company's submission, resulting in the company providing additional information. The ERG also modified the company's decision analytic model to produce an ERG base case assessment of cost-effectiveness and to assess the impact of alternative parameters and assumptions on the model results. This section summarises the evidence presented in the company's submission and the ERG's review of that evidence.

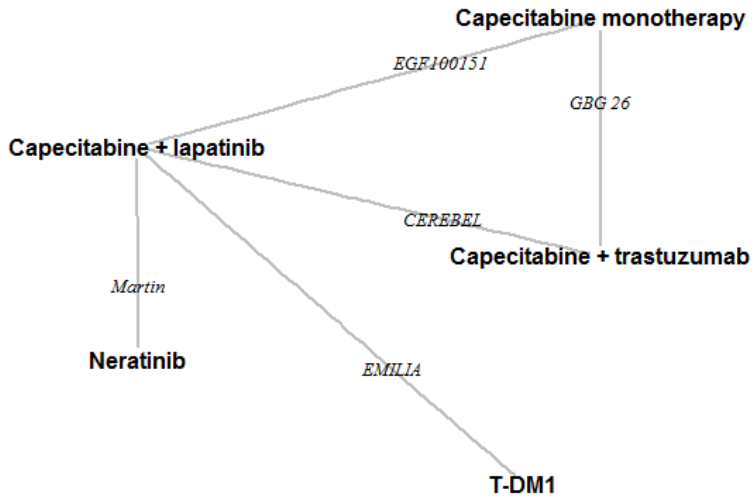
3.1 Clinical Evidence provided by the Company

The clinical effectiveness data were taken from two (EMILIA and TH3RESA) open-label, phase III randomised controlled trials (RCTs) of T-DM1 within its licensed indication [6;7]. Both were international, multi-centre studies, with centres in Europe (including the UK), the United States of America and Asia. The EMILIA trial compared T-DM1 with lapatinib in combination with capecitabine. The comparator within the TH3RESA trial was treatment of physician's choice, of which: 68.5% of patients received chemotherapy plus trastuzumab; 10.3% of patients received lapatinib plus trastuzumab; 1.6% of patients received hormonal therapy plus trastuzumab; 2.7% of patients received chemotherapy plus lapatinib; and 16.8% of patients received single-agent chemotherapy. The RCTs reported a significant advantage in progression-free survival (PFS) for T-DM1 over lapatinib in combination with capecitabine (stratified HR 0.65; 95% confidence interval (CI) 0.55 – 0.77), and over the treatment of physician's choice (stratified HR 0.53; 95% CI 0.42 – 0.66). EMILIA reported a significant advantage in overall survival (OS) for T-DM1 over lapatinib in combination with capecitabine (stratified HR 0.68; 95% CI 0.55 – 0.85), whilst TH3RESA reported a non-significant difference (i.e. did not cross the O'Brien-Flemming stopping boundary) compared with the treatment of physician's choice (stratified HR 0.55; 95% CI 0.37 – 0.83).

The only comparator from the final NICE scope for which there was head-to-head data with T-DM1 was lapatinib in combination with capecitabine. A network meta-analysis (NMA) was therefore undertaken by the company, which included five RCTs allowing a comparison of T-DM1 with: lapatinib in combination with capecitabine; trastuzumab in combination with capecitabine; capecitabine monotherapy; and neratinib [8-12], as shown within Figure 1. The TH3RESA trial was excluded from the NMA due to the large number of differing treatments within the comparator arm which did not fit within the scope of the appraisal [2]. The results

produced by the company's analysis suggested that all hazard ratios (and credible intervals) associated with T-DM1 fall below 1. No RCTs were identified of trastuzumab in combination with vinorelbine or vinorelbine monotherapy within this patient population.

Fig. 1: Network of evidence



Adverse event (AE) data were taken from an integrated safety analysis [13] of additional trials of T-DM1 as a single agent. The data showed fewer AEs of grade 3 or greater for T-DM1 than for lapatinib in combination with capecitabine, or than for treatment of physician's choice. The most common grade 3 or greater AEs for T-DM1 were thrombocytopenia and hepatotoxicity. Limited health-related quality of life (HRQoL) data were identified; although the Functional Assessment of Cancer Therapy for patients with Breast Cancer Trial Outcomes Index – Physical/ Functional/ Breast (FACT-B TOI-PFB) data collected within the EMILIA trial suggested deterioration took longer in the T-DM1 group than the comparator.

3.1.1 Critique of the Clinical Evidence and Interpretation

The ERG believes that all relevant trials with available data were included by the company. The clinical effectiveness data relevant to the decision problem were taken from two large RCTs, both of which were open-label, but otherwise at low risk of bias. The lack of blinding is unlikely to have affected OS, but could bias the HRQoL data. The EMILIA trial had independent outcome assessment of PFS [8]. Although both trials were ongoing at the time of the assessment, they had reached their primary endpoint. Data were available for OS, PFS and AEs. Additionally, AE data were available from a pooled analysis of T-DM1 trials. EQ-5D data is being collected within the TH3RESA trial, however, these outcomes had not been reported within the public domain at the time of the assessment. Most of the data were from third-line or later therapy, whereas the company suggested T-DM1 as second-line treatment. The studies were international, so not all participants would have had prior treatment in accordance with UK practice. The trial populations were broadly similar to populations that would be encountered in UK practice, although only a small proportion of patients had Eastern Cooperative Oncology Group performance status scale 2 whilst in practice this is expected to be a higher

percentage. The ERG's clinical advisors did not expect this to impact upon the relative efficacy of the treatment options.

The only comparator from the final NICE scope for which there was head-to-head data with T-DM1 was lapatinib in combination with capecitabine. The NMA undertaken by the company used a fixed effect model rather than a random effects model which assumes that there is no heterogeneity between trials, which is unlikely to be the case given knowledge of the trials. This is likely to underestimate the uncertainty around the relative efficacy of the treatment options.

3.2 Cost-Effectiveness Evidence provided by the company

The company identified no existing economic evaluations of T-DM1. A de novo cohort state transition model was developed which adhered to the NICE Reference Case [14]. The model has three health states: PFS; progressed disease; and death, and uses weekly time cycles. At each cycle patients can either transition from PFS to progressed disease, remain in the current state, or transition to death. The EMILIA trial data [6] comparing T-DM1 with lapatinib in combination with capecitabine were extrapolated to estimate PFS and OS independently within the model. Hazard ratios were applied for all other comparators based upon the results of the NMA. Within the company's base case, for PFS the Kaplan-Meier curve was applied directly until week 72, after which a lognormal distribution was used to represent the tail of the curve, whilst for OS the gamma distribution was fitted for the entire curve. The decision about which extrapolation approach to use within the base case was based upon cumulative hazard plots, visual fit, external validity and clinical plausibility, as recommended by Latimer within a NICE DSU Technical Support Document [15]. A range of extrapolation approaches were tested within sensitivity analyses.

A utility was assigned to each health state based upon a published mixed model analysis [16]. Costs applied to the health states included: the treatment options; administration regimens; treatment of a selection of AEs; supportive care; and treatment within the post-progression state. Established sources were used for costs including the BNF, NHS Reference Costs and PSSRU [17-19].

Following the clarification process, the company reported a deterministic ICER for T-DM1 compared with lapatinib in combination with capecitabine of £167,236, the latter of which was estimated to have an ICER of £49,798 compared with capecitabine monotherapy. All other comparators were dominated (less effective with the same or higher cost, or more costly with the same or lower effectiveness) than these treatment options. The company results are summarised in Table 1.

Table 1: Company's base-case results

Technologies	Totals			ICER (Cost per QALY gained)
	Costs (£)	LYG	QALYs	
Capecitabine	£13,173	1.87	1.03	-
Vinorelbine	£18,874	1.87	1.03	Dominated
Trastuzumab and capecitabine	£37,629	2.27	1.31	Dominated
Trastuzumab and vinorelbine	£39,047	2.27	1.31	Dominated
Lapatinib and capecitabine	£34,170	2.53	1.45	£49,798
T-DM1	£111,162	3.16	1.91	£167,236

3.2.1 Critique of the Cost-Effectiveness Evidence and Interpretation

The de novo model developed was appropriate for the decision problem and was generally well described within the company's report. The model structure was considered by the ERG to be clinically appropriate and data sources were generally reasonable. The use of hazard ratios for PFS and OS assumes that the treatment effect is constant over time and thus hazards are proportional. However, the extrapolation of both PFS and OS within the company's base case used accelerated failure time models (lognormal and gamma distributions respectively). Although such distributions are theoretically incompatible with hazard ratios, the curves produced were clinically plausible. An error was identified within the calculation of utilities; however, this was not corrected within the ERG's base case because the estimated utilities employed within the model were considered to be externally valid based upon the results of a systematic review and meta-analysis of health state utility values in metastatic breast cancer identified by the ERG [20].

The ERG identified two key errors in implementation and four key assumptions which were methodologically weak which were revised for the ERG's base case. The errors were that the cost of AEs and the cost of administration of trastuzumab in combination with vinorelbine were incorrectly calculated within the model. The four key assumptions which were deemed methodologically weak were that:

(i) a fixed effects model was appropriate for the network meta-analysis rather than a random effects model, which would underestimate the uncertainty between treatments;

(ii) the calculation of post-progression costs was simplified using an approach which was unequal across treatments;

(iii) a 10-year time horizon is sufficient. This does not capture all the expected differences in costs and outcomes between the interventions; and

(iv) the cost of T-DM1, capecitabine and trastuzumab can be estimated using the mean body weight or surface area of patients within the trial, rather than including patient variability. This impacts upon overall vial usage when assuming that vial sharing was not possible.

The uncertainty around the model inputs for the probabilistic sensitivity analysis (PSA) was inappropriately characterised by the company. In addition, the one way sensitivity analysis did not establish the robustness of

the model results or determine the key drivers of the results because T-DM1 was only compared with capecitabine monotherapy in the presented analyses.

3.3 Additional Work Undertaken by the ERG

The ERG repeated the NMA using a random effects model. The central estimates (i.e. medians of posterior distributions) of efficacy were, as expected, similar to those produced by the company. However, allowing for heterogeneity between studies increased the uncertainty about the true treatment effect on OS and PFS. From the ERG's random effects model, T-DM1 is associated with a reduction in the hazard of death of 32% (HR=0.68, 95% credible interval (CrI) [0.37, 1.25]) and a reduction in the hazard of progression or death of 35% (HR=0.65, 95% CrI [0.35, 1.20]) compared to lapatinib in combination with capecitabine. The credible intervals generated by the ERG do not rule out the possibility that T-DM1 is less efficacious than comparators.

The ERG produced a revised deterministic base case ICER to correct the errors and amend the methodologically weak assumptions described within Section 3.2.1. The cost per quality adjusted life year (QALY) gained for T-DM1 compared with lapatinib in combination with capecitabine was estimated to be £166,429, with the latter having an ICER of £50,620 compared with capecitabine monotherapy. These results were very similar to the company's base case following the clarification process. It is noted that not all of the ERG's changes acted upon the ICER in the same direction. All other comparators were dominated by these treatment options.

The ERG suggested that the following corrections would need to be undertaken as a minimum to provide reasonable probabilistic results:

- Reanalyse the survival data to derive the parametric distributions for PFS and OS;
- Use the joint posterior distribution of (log) hazard ratios for each treatment from the NMA;
- Use informed parameters for the uncertainty around costs and utilities.

Given the substantial resources that would be required in delivering these, the short timeframes for the work and the relatively small expected impact of the PSA upon the mean ICER, the ERG focused upon correcting the deterministic base case analysis and undertaking substantial univariate sensitivity analysis to describe the key drivers of the model results rather than producing robust PSA results.

The deterministic univariate sensitivity analysis undertaken by the ERG suggested that the key drivers of the model results are:

- the relative OS associated with the interventions;
- the distribution employed for extrapolation of PFS and OS;
- whether the treatment effect is assumed to continue beyond the trial data;
- the utility values associated with PFS and post-progression; and
- whether wastage is included within the drug costs.

However, the ICER for T-DM1 versus lapatinib in combination with capecitabine did not decrease below £147,000 within any of the univariate sensitivity analyses.

3.4 Conclusions of the ERG Report

Data from two large RCTs at low risk of bias reported a statistically significant advantage in PFS for T-DM1 over lapatinib in combination with capecitabine, and over the treatment of physician's choice. Data also reported a statistically significant advantage in OS and time to symptom worsening for T-DM1 over lapatinib in combination with capecitabine. There was a lack of head-to-head comparison with T-DM1 for most comparators in the decision problem. Within the NMA, T-DM1 appears to be the best treatment in terms of both OS and PFS. From the ERG's random effects model, T-DM1 is associated with a reduction in the hazard of death of 32% (HR=0.68, 95% CrI [0.37, 1.25]) and a reduction in the hazard of progression or death of 35% (HR=0.65, 95% CrI [0.35, 1.20]) compared to lapatinib in combination with capecitabine. For T-DM1, the most common grade 3 or greater AEs were thrombocytopenia and hepatotoxicity.

The de novo model structure developed by the company is appropriate for the decision problem defined in the final scope and was considered to be clinically appropriate. However, there were errors identified which were corrected by the ERG and the population of the probabilistic model was considered inappropriate. Following the clarification process, the company reported a deterministic ICER for T-DM1 compared with lapatinib in combination with capecitabine of £167,236, the latter of which is estimated to have an ICER of £49,798 compared with capecitabine monotherapy. The ERG produced very similar revised base case values of £166,429 and £50,620 respectively. The deterministic sensitivity analysis undertaken by the ERG suggests that by changing parameters within plausible ranges, the ICER for T-DM1 versus lapatinib in combination with capecitabine is unlikely to decrease below £147,000 per QALY gained. The results from a robust PSA are unknown.

4. Key Methodological Issues

4.1 Model results

In the initial submission, the company did not present results incrementally or probabilistically, both of which are necessary in order to be able to compare treatment options appropriately. Within the clarification process, the request for a full incremental analysis led to the ICER for T-DM1 of £111,095 (compared with capecitabine) increasing to an ICER of £167,236 (compared with lapatinib in combination with capecitabine). The substantial difference in these ICERs highlights the importance of making appropriate comparisons within the analysis, although given these values it would be unlikely to affect NICE's decision.

The company did not tabulate the results of the PSA and the characterisation of uncertainty within the model was insufficient. The company suggests that a fixed effect NMA model was appropriate rather than a random effects model because of the limited number of trials. However, this assumes that there is no heterogeneity between trials which is unlikely to be the case given knowledge of the trials. The ERG believes that use of a random-effects model would therefore more appropriately characterise the plausible uncertainty around relative efficacy.

The characterisation of uncertainty for the PSA generally appears to be arbitrary. For example, many of the mean costs are multiplied by 0.5 and 1.5 to estimate lower and upper bounds respectively. Importantly, the

uncertainty around the hazard ratios did not take into account the joint distribution of treatment effects as generated by the NMA, which indicated lack of understanding of NMA by the company. Additionally, the ERG believes that the regression approach used to estimate the parameters for both PFS and OS produces correlation matrices which are arbitrary rather than appropriately characterising the uncertainty. Furthermore, no relationship is assumed between PFS and OS, which in theory means that estimates of PFS could be greater than estimates of OS within the PSA. Within the company's base case, the effectiveness of lapatinib in combination with capecitabine is based upon the Kaplan-Meier curve from EMILIA until 72 weeks and hence no uncertainty is assumed around the relative efficacy between this treatment and T-DM1 until beyond 72 weeks. However it is highly unlikely that improving the characterisation of uncertainty within the PSA would reduce the mean ICER for T-DM1 to the range of cost per QALY gained values quoted within the NICE Guide to the Methods of Technology Appraisal as representing cost-effective use of resources. [14].

4.2 The Cancer Drugs Fund

The introduction of the Cancer Drugs Fund means that the budget for health technologies is likely to be allocated more inefficiently as relatively expensive cancer drugs are being funded in preference to drugs which represent a more cost-effective use of public funds within other disease areas. The opportunity cost associated with such drugs would be the primary reason for NICE to have produced 'negative' guidance where these drugs have been appraised. During the NICE appraisal process for T-DM1, the drug was made available by the Cancer Drugs Fund. T-DM1 costs on average £76,000 per year per patient, with the annual cost rising to over £100,000 for patients weighing more than 100kg. Health economic evaluation suggests that T-DM1 does not produce the QALY gains required to be commensurate with this price. Whilst the availability of T-DM1 is beneficial to HER-2 positive metastatic breast cancer patients, there are a greater number of patients with other diseases who could produce greater QALY improvements than that seen by T-DM1 for the same monetary expense. In addition, cancer treatments which are not recommended by NICE are representing current practice within England and Wales which may lead to trials being run which are not reflective of NICE guidance, thus increasing uncertainty about the relative efficacy of new cancer drugs.

Where current practice differs from NICE recommendations due to the Cancer Drugs Fund, the ERG believes it is appropriate to include all relevant comparators within the economic analysis and use the efficiency frontier to assess cost-effectiveness, as has been done by the ERG within this STA. However, if NICE were to consider the appropriate comparator within a STA to be current practice within England (rather than limiting to those treatments recommended by NICE), there may be a situation where a new drug would be recommended because it was considered to be cost-effective in comparison to a non-cost-effective treatment option. This will also lead to inadequate clinical guidance when the Cancer Drugs Fund ceases.

5. NICE Guidance

Following NICE's provisional decision not to recommend T-DM1 within this patient population after the first Appraisal Committee meeting, the company offered a patient access scheme (PAS) to discount the price of the drug. The level of discount was designated as commercial in confidence and, due to concerns over backward calculation of the PAS, the ICER of T-DM1 compared with lapatinib in combination with capecitabine was also

marked as commercial in confidence. The analysis with the PAS, undertaken by the company, suggested that T-DM1 has a 0% probability of being cost-effective at an ICER of £30,000 per QALY gained. The ERG were not asked to undertake any additional analysis around the PAS. The Appraisal Committee discussed whether T-DM1 met the end of life criteria and concluded after deliberation that it did. However, they agreed that even after adjusting the weights applied to the QALY benefits, T-DM1 would not be considered a cost-effective use of NHS resources. The company appealed against the FAD on the basis that the 2014 Pharmaceutical Price Regulation Scheme (PPRS) should have been taken into account. The PPRS is a voluntary agreement between the Department of Health and the pharmaceutical industry to control the prices of branded drugs sold to the NHS. Whilst the Appeal Panel agreed that the 2014 PPRS should have been considered within the appraisal, the Committee concluded that the 2014 PPRS did not affect its recommendations about TDM-1. The Final Appraisal Determination (FAD) states that T-DM1 is not recommended for treating adults with HER2-positive, unresectable locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane.

6. Conclusions

The evidence suggests that T-DM1 is an effective option for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane. However, the ICER reported by both the company and the ERG was in the region of £167,000 per QALY gained compared with lapatinib in combination with capecitabine. Although the company provided a PAS, T-DM1 was not considered to be a cost-effective use of NHS resources by NICE.

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Author Contributions

HS and MS drafted the manuscript. ES, RH and JS revised the manuscript for important intellectual content. All authors have given their approval for the final version to be published.

Conflicts of interest

The authors, Hazel Squires, Matthew Stevenson, Emma Simpson, Rebecca Harvey and John Stevens, have no potential conflicts of interest.

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