1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG believes that all trials relevant to the decision problem with available data were included within the MS. 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.

Within the MTC, T-DM1 was the best treatment in terms of both OS and PFS. 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 was associated with a reduction in the hazard of death of 32% and in the hazard of progression or death of 35% compared to lapatinib in combination with capecitabine (the next best option).

1.4 Summary of cost effectiveness submitted evidence by the manufacturer

The manufacturer identified no existing economic evaluations of T-DM1. A *de novo* cohort state transition model was developed which adheres to the NICE Reference Case. The model has three health states: progression-free survival; post-progression; and death, and follows weekly cycles. The model was based upon the EMILIA trial comparing T-DM1 with lapatinib in combination with capecitabine. The trial data was extrapolated (with a range of approaches being tested within sensitivity analyses) and hazard ratios were applied for all other comparators based upon the MTC. A utility was assigned to each health state according to a published mixed model analysis. Costs applied to the health states included: the treatment options; their administration; treatment of a selection of AEs; supportive care; and treatment within the post-progression state.

Following the clarification process, the manufacturer's 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 effectiveness with the same or higher cost, or more costly with the same or lower effectiveness) than these treatment options.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The *de novo* model developed is appropriate for the decision problem defined in the final scope and was generally well described within the report. The model structure was considered by the ERG to be clinically appropriate. 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. However, this produced a very similar revised base case Incremental Cost-Effectiveness Ratio (ICER) to the manufacturer's of £166,429, since not all changes acted upon the ICER in the same direction.

Table 11: AEs of grade 3 or higher, table adapted from MS

Adverse Event	% patients with grade 3 or higher event			
	EMILIA Lapatinib in combination with capecitabine n=488	**EMILIA T-DM1 N=490**	**TH3RESA TPC n=184**	**TH3RESA T-DM1 n=403**
Diarrhoea	20.7	1.6	4.3	0.7
Hand-foot syndrome	16.4	0		
Vomiting	4.5	0.8		
Neutropenia	4.3	2	15.8	2.5
Hypokalaemia	4.1	2.2		
Fatigue	3.5	2.4	2.2	2.0
Nausea	2.5	0.8		
Mucosal inflammation	2.3	0.2		
Thrombocytopenia	0.2	12.9	1.6	4.7
Increased AST	0.8	4.3	2.2	2.2
Increased ALT	1.4	2.9		
Anaemia	1.6	2.7	2.7	2.7
Abdominal pain			2.7	1.2
Asthenia			2.2	1.0
Cellulitis			2.2	0.5
Pulmonary embolism			2.2	0.5
Dyspnoea			1.6	2.0
Febrile neutropenia			3.8	0.2
Leukopenia			2.7	0.2

There were a number of fatalities due to AEs while on study treatment, although percentages were considered low on both arms given the advanced cancer and associated ill health of the patients; EMILIA T-DM1 n=1 (0.2%) (metabolic encephalopathy); EMILIA lapatinib in combination with capecitabine n=4 (0.8%) (coronary artery disease, multi-organ failure, coma, hydrocephalus); TH3RESA T-DM1 n=5 (1.2%) (pneumonia, sepsis, hepatic encephalopathy, subarachnoid haemorrhage and pneumonitis); TH3RESA TPC n=3 (1.6%) (clostridium bacteremia, non-cardiogenic pulmonary oedema and pulmonary embolism).

5.2.9 Cost effectiveness results

In the initial submission, the manufacturer did not present a full incremental analysis, although this was corrected in the response to clarifications. These results are replicated in Table 18. Only deterministic results were presented within the clarification response. These are similar to the probabilistic results re-run by the ERG; however, the uncertainty around the model inputs was inadequately characterised (see Section 5.2.10).

Table 18: Replicated deterministic revised incremental cost-effectiveness analysis results from manufacturer's clarifications

Technologies	Totals			Incrementals			
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	ICER (Cost per QALY gained)
Capecitabine	£13,173	1.87	1.03				
Vinorelbine	£18,874	1.87	1.03	£5,701	0.00	0.00	Dominated
Lapatinib and capecitabine	£34,170	2.53	1.45	£15,296	0.66	0.42	£49,798
Trastuzumab and capecitabine	£37,629	2.27	1.31	£3,459	-0.26	-0.14	Dominated
Trastuzumab and vinorelbine	£39,047	2.27	1.31	£1,418	-0.26	-0.14	Dominated
T-DM1	£111,162	3.16	1.91	£72,115	0.89	0.60	£167,236

It should be noted that the mean hazard ratio from the MTC for lapatinib in combination with capecitabine versus trastuzumab in combination with capecitabine is close to 1 for both PFS and OS, suggesting similar efficacy between these treatment options. However, estimating PFS and OS based upon the Kaplan-Meier data from EMILIA, the model predicts that lapatinib in combination with capecitabine is substantially more efficacious. Since the cost of trastuzumab in combination with capecitabine is greater than that for lapatinib in combination with capecitabine, even if PFS and OS were the same for these two treatment options, trastuzumab in combination with capecitabine would remain dominated.

5.2.10 Sensitivity analyses

The manufacturer undertook PSA and several univariate sensitivity analyses. However, both analyses have flaws.

5.4 Conclusions of the cost effectiveness section

The MS did not identify any existing economic evaluations of T-DM1. The *de novo* model developed is appropriate for the decision problem defined in the final NICE scope and was generally well described within the report. The model structure is clinically appropriate. Following the clarification process, the manufacturer's 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 alone. The ERG has identified two key errors in implementation and four key assumptions which are methodologically weak which have been revised for the ERG's base case, although these do not impact substantially upon the model results (see Section 6).

The uncertainty around the model parameters for the PSA is inadequately characterised and the PSA results are not tabled within the MS. The one way sensitivity analysis provided by the manufacturer does not establish the robustness of the model results or determine the key drivers of the ICERs because T-DM1 is compared with capecitabine only.

6. IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

6.1 ERG's base case ICER

The ERG's base case ICER is developed in stages in Tables 21 – 26. As in the manufacturer's base case, vinorelbine, trastuzumab in combination with capecitabine, and trastuzumab in combination with vinorelbine are dominated. Whilst the revised drug costs increase the ICER associated with T-DM1 compared with lapatinib in combination with capecitabine, the other changes reduce the ICER, resulting in an incremental cost per QALY of £166,429, which is very similar to that submitted by the manufacturer within the clarification responses. All tables show a full incremental analysis. The results have been presented in order of ascending effectiveness rather than costs, as opposed to the manufacturer's, to avoid changing the order of the interventions within the tables due to the costs of lapatinib in combination with capecitabine and trastuzumab in combination with capecitabine being similar.

Table 21: Manufacturer's base case

Technologies	Totals			Incrementals			
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	ICER (Cost per QALY gained)
Capecitabine	£13,173	1.87	1.03				
Vinorelbine	£18,874	1.87	1.03	£5,701	0.00	0.00	Dominated
Trastuzumab and capecitabine	£37,629	2.27	1.31	£18,755	0.40	0.28	Dominated
Trastuzumab and vinorelbine	£39,047	2.27	1.31	£1,418	1.87	1.03	Dominated
Lapatinib and capecitabine	£34,170	2.53	1.45	-£4,877	0.26	0.14	£49,798
T-DM1	£111,162	3.16	1.91	£76,992	0.63	0.46	£167,236

Table 22 shows the model results when the resource use for all adverse events with over 2% incidence in either treatment arm of EMILIA is included correctly and the weekly cost of AEs is multiplied by the proportion of patients in PFS rather than the proportion of patients on treatment. This does not impact substantially upon the base case results.

Table 22: Correcting the cost of AEs

Technologies	Totals			Incrementals			
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	ICER (Cost per QALY gained)
Capecitabine	£13,274	1.87	1.03				
Vinorelbine	£18,975	1.87	1.03	£5,701	0.00	0.00	Dominated
Trastuzumab and capecitabine	£37,802	2.27	1.31	£18,827	0.40	0.28	Dominated
Trastuzumab and vinorelbine	£39,220	2.27	1.31	£1,418	1.87	1.03	Dominated
Lapatinib and capecitabine	£34,332	2.53	1.45	-£4,888	0.26	0.14	£49,942
T-DM1	£111,320	3.16	1.91	£76,989	0.63	0.46	£167,229

Table 23 shows the model results when the cost of AEs is corrected as above, in combination with correcting the code for the cost of administration of trastuzumab in combination with vinorelbine and calculating weekly costs in the progressed disease state independently for each treatment option. Again, this does not impact substantially upon the base case results.

Table 23: Correcting the code for the cost of administration of trastuzumab in combination with vinorelbine and weekly costs in the progressed state

Technologies	Totals			Incrementals			
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	ICER (Cost per QALY gained)
Capecitabine	£13,445	1.87	1.03				
Vinorelbine	£19,146	1.87	1.03	£5,701	0.00	0.00	Dominated
Trastuzumab and capecitabine	£37,904	2.27	1.31	£18,757	0.40	0.28	Dominated
Trastuzumab and vinorelbine	£44,849	2.27	1.31	£6,945	1.87	1.03	Dominated
Lapatinib and capecitabine	£34,180	2.53	1.45	-£10,669	0.26	0.14	£49,177
T-DM1	£110,926	3.16	1.91	£76,745	0.63	0.46	£166,701

Analysis **(BCV= Base case value)**	**Capecitabine**	**Trastuzumab and capecitabine**	**Lapatinib and capecitabine**	**T-DM1**
Discount rate (costs & outcomes) 6% 0%	 - -	 Dominated Dominated	 £52,852 £47,412	 £174,951 £154,012
Time horizon - 5 years	-	Dominated	£60,284	£217,513
PFS & OS of T-DM1 equivalent to lapatinib and capecitabine after week 72 and 96 respectively	-	Dominated	£50,620	£449,554
Cost of AEs (BCVx2)	-	Dominated	£51,146	£165,858
Fixed dose subcutaneous trastuzumab administration	-	Dominated	£50,620	£166,429

All of these analyses result in an incremental cost per QALY gained for T-DM1 compared with lapatinib in combination with capecitabine in excess of £147,000. The ICER associated with lapatinib in combination with capecitabine compared with capecitabine does not fall below £44,000.

The ICER for T-DM1 compared with lapatinib in combination with capecitabine is reduced by more than 10% by:

- excluding wastage from the drug costs;
- increasing the utility associated with progressed disease from 0.5 to 0.7;
- fitting a weibull distribution to the tail of the PFS curve rather than a lognormal distribution.

For T-DM1 compared with lapatinib in combination with capecitabine, the ICER is increased by more than 10% by:

- assuming consistent utilities across treatment options in PFS/ using utility values from interim results of TH3RESA;
- fitting a weibull distribution for OS rather than a gamma distribution;
- reducing the time horizon to 5 years;
- setting PFS and OS for T-DM1 equivalent to lapatinib in combination with capecitabine after weeks 72 and 96 respectively.

The MTC results show that the comparative effectiveness between treatment options is uncertain (a 16% and 13% chance that T-DM1 is not the best treatment for reduced hazard of death and progression respectively). If any of the comparators were to have equivalent overall survival impacts to T-DM1 then they would dominate T-DM1 due to the higher acquisition costs associated with T-DM1.

8. OVERALL CONCLUSIONS

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, with adverse event data from additional trials. Data from these two RCTs 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. For T-DM1, the most common grade 3 or greater AEs were thrombocytopenia and hepatotoxicity.

There was a lack of head-to-head comparison with T-DM1 for most comparators in the decision problem. Most of the data were from third-line or later therapy, whereas the MS suggests T-DM1 as second-line treatment, and there were only a few patients with ECOGPS2 from one trial providing data. Within the MTC analysis, allowing for heterogeneity between studies increases the uncertainty about the true treatment effect on OS and PFS. 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.

The *de novo* model developed by the manufacturer is appropriate for the decision problem defined in the final scope and was generally well described within the report. The model structure was considered to be clinically appropriate. Following the clarification process, the manufacturer's 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 uncertainty around the model inputs for the PSA was inappropriately characterised within the MS. In addition, the sensitivity analysis provided by the manufacturer does not establish the robustness of the model results or determine the key drivers of the results because T-DM1 is compared with capecitabine only. The deterministic sensitivity analysis undertaken by the ERG suggests 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 progressed disease; 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 one way sensitivity analyses.