Lapatinib for the treatment of advanced and metastatic breast cancer:

a review of the response to the ACD provided by the manufacturer of Lapatinib

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Report by the NICE Decision Support Unit.

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Summary

Following consultation on the preliminary recommendations from the first Appraisal Committee meeting for lapatinib for the treatment of metastatic breast cancer, NICE commissioned the Decision Support Unit (DSU) to comment on new data received from the manufacturer of lapatinib (GSK). Specifically the DSU was requested to comment on the data submitted to estimate the use of trastuzumab following disease progression in the metastatic setting, the methodology used to estimate the relative effectiveness of lapatinib plus capecitabine compared to trastuzumab containing regimens, and the approach to estimating the comparator treatment strategy in the economic analysis. In addition the DSU was asked to confirm that the amendments reported by GSK had been implemented correctly in the economic model, and that the cost-effectiveness of a proposed patient access programme/scheme has been correctly incorporated into the economic model.

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1 BACKGROUND

Lapatinib (Tyverb, GSK Pharmaceuticals), in combination with capecitabine, has a marketing authorisation for the treatment of patients with advanced or metastatic breast cancer whose tumours overexpress ErbB2 (HER2). Patients should have progressive disease following prior therapy which must include anthracyclines, taxanes and therapy with trastuzumab in the metastatic setting. The NICE Appraisal Committee first discussed lapatinib on 22nd January 2008. The Committee's preliminary recommendation was that lapatinib (in combination with capecitabine) is not recommended for the routine treatment of women with advanced or metastatic breast cancer whose tumours overexpress HER2 except in the context of clinical trials.[1] Due to regulatory delays in lapatinib obtaining its marketing authorisation, the Appraisal Consultation Document was issued for public consultation in July 2008.

GSK have submitted the following additional data in response to the ACD.

- Updated efficacy data
- Amendments to the economic model
- Updated market research data on the comparator technologies
- Amendments to the comparators used in the economic analysis
- Details of a proposed 'patient access programme'.

The updated clinical data includes resubmitted clinical data from the main registration trial of lapatinib plus capecitabine compared to capecitabine alone, information from a trial of trastuzumab (with capecitabine) continued beyond disease progression compared to capecitabine alone and results of an updated systematic review. The amendments to the economic model incorporate these data and include corrections made in response to criticisms by the Evidence Review Group.[2] An analysis including an alternative comparator has also been presented. The comparator consists of three treatment regimens, weighted according to proportions reported in updated market research information.

Finally, a patient access programme, whereby the NHS gets reimbursed for up to the first 12 weeks of a patient's lapatinib acquisition costs, has been proposed by GSK and incorporated into the economic analysis.

1.1 *Aim of report*

DSU was requested by NICE to consider the new analysis and data submitted by GSK. Specifically, the aim of this report is to address the following five considerations as requested by NICE.

- To comment on the data submitted to estimate use, in practice, of trastuzumab post progression.
- To comment on the appropriateness of the efficacy estimates, and the indirect comparison methodology, used by the manufacturer to compare lapatinib plus capecitabine versus trastuzumab post progression.
- To establish that the minor corrections to the model and alternative assumptions about dosing (e.g. assumptions about frequency of trastuzumab administration, trastuzumab administration costs assumptions on trastuzumab wastage) have been incorporated into the updated model appropriately.
- To provide a critique on the methodology used for incorporating a weighted "blended comparator" in the economic analysis.
- To establish that the updated model is consistent with new scenarios and patient access programme presented by the manufacturer.

2 UPDATED EFFICACY DATA

2.1 *Trial EGF100151 (lapatinib and capecitabine compared to capecitabine alone)*

GSK report updated overall survival (OS) data from the main registration trial for lapatinib (EGF100151). The cut-off date for original analysis was April 2006. The cut-off date for the most recent analysis of overall survival is September 2007.

These data were presented to the Appraisal Committee at its first meeting, but were not incorporated into the original economic analysis. Updated data were only presented for overall survival.

Details of the trial inclusion criteria and patient characteristics are shown in the Appendix. The results for time to progression (TTP) [time between date of randomisation and the earliest date of either disease progression or death due to breast cancer] and progression free survival (PFS) [the time from randomisation until the first documented sign of disease progression or death due to any cause] are shown in Table 1. Investigator and independent assessments are reported, although the independent assessment of TTP was noted as the primary outcome measure in the trial.

The results of the original and updated analyses for overall survival (OS) are presented in Table 2. There was a light increase in median survival from 15.6 months to 17.1 months for patients in the lapatinib plus capecitabine arm of the trial. However, the hazard ratio also increased to 0.9 (95% CI: 0.71 to 1.12) and was not statistically significant.

The EMEA Assessment Report states that of 39 patients "at risk" for cross over, a total of 36 patients crossed over from monotherapy to combination therapy after April 2006. Of these 36 patients, (at least) 29 crossed over prior to progression on monotherapy. This could potentially reduce the hazard ratio presented for overall survival. A sensitivity analysis is reported in the EMEA Assessment Report that explores the effect of this using alternative methods to reduce the potential for confounding (censoring of cross-over patients at baseline, at time of cross-over, or as time-dependent covariate).[3] The results, presented in diagrammatic form, do not appear to show a statistically significant survival advantage for lapatinib plus capecitabine compared to capecitabine alone in any of the analyses.

The efficacy data for lapatinib plus capecitabine and capecitabine alone used in the original economic analysis submitted by GSK was based on the data for PFS

and OS (April 2006) presented in Tables 1 and 2. The updated economic model includes the data on OS from the Sept 2007 analysis.

2.2 *Trial GBG-26 (trastuzumab and capecitabine compared to capecitabine alone)*

GSK also report data from a recent trial of trastuzumab and capecitabine compared to capecitabine alone for the treatment of patients with metastatic breast cancer whose disease has progressed following treatment with trastuzumab. The trial was expected to recruit 482 patients up to April 2010, but was closed early due to problems recruiting following the registration of lapatinib. Details of the trial inclusion criteria and patient characteristics are shown in the Appendix.

The trial recruited 156 patients between January 2004 and May 2007. Data from the trial have been reported at two conferences: the 2008 ASCO annual meeting[4;5]; and the 2007 San Antonio Breast Cancer Symposium (SABCS)[6;7]. GSK used data from the 2008 ASCO poster in their updated analysis as it was based on complete follow-up.[4] As data on PFS were not available from this source, data on TTP were used as a proxy for PFS.

Table 3 presents data on TTP and PFS from the trial. The most recent data, from the poster presented at ASCO 2008, show a statistically significant advantage on TTP for trastuzumab plus capecitabine compared to capecitabine alone with a gain in median TTP of 2.6 months. The table also shows results of pooled analyses (see Section 2.3) and an analysis of the TTP data from the GBG-26/BIG 3-05 trial (ASCO 2008) by GSK whereby the hazard ratio for trastuzumab plus capecitabine compared to capecitabine monotherapy was estimated by digitizing Kaplan-Meier curves from the conference poster, and a Weibull distribution fitted.

Table 4 shows the data on OS presented at the two conferences. The gain in overall survival from trastuzumab plus capecitabine compared to capecitabine alone was not statistically significant. The most recent data show a median

survival gain of 5.1 months. The table also shows the results of the analysis of the latest data on OS from the GBG-26/BIG 3-05 trial using the same method as described above for TTP.

The original economic analysis presented by GSK used non-randomised data on TTP pooled from 11 studies. It was assumed that the time following disease progression until death would be the same as that reported for lapatinib plus capecitabine. In the updated basecase economic analysis, the hazard ratios for trastuzumab plus capecitabine compared to capecitabine monotherapy from the GSK analysis of the GBG 26/BIG 3-05 study were used for both TTP and OS.

2.3 *Updated pooled analysis of trastuzumab efficacy*

In the original submission the estimate of trastuzumab efficacy was based on a weighted, pooled estimate of TTP from 11 non-randomised studies. GSK have re-run their original systematic review and provide an updated pooled analysis of 15 non-randomised studies and the trastuzumab arm of the GBG-26 study (total 16 studies). The results are shown in Table 3. The original pooled analysis produced an implied hazard ratio for trastuzumab plus capecitabine compared to capecitabine alone of 0.87. The updated analysis shows a more favourable implied hazard ratio for trastuzumab plus capecitabine of 0.70 (95% CI: 0.61 to 0.81).

Table 1: Time to disease progression (TTP) and progression free survival (PFS) for lapatinib and capecitabine compared to capecitabine alone

	Lap + cap (months)	Cap (months)	Hazard Ratio
TTP (median) Independent assessment	6.25 (4.02 to 11.4)	4.29 (2.1 to 8.52)	0.57 (0.43 to 0.77)
TTP (median) Investigator assessment	5.52 (NR)	4.22 (NR)	0.72 (0.56 to 0.92)
PFS (median) Independent assessment	6.25 (5.56 to 8.52)	4.06 (3.07 to 4.64)	0.55 (0.41 to 0.74)

All figures relate to April 2006 cut-off date in the EGF100151 trial. Figures are medians with 95% confidence intervals in parenthesis. NR = Not reported.

Table 2: Overall Survival for lapatinib and capecitabine compared to capecitabine only

	Lap + cap (months)	Cap (months)	Hazard Ratio
EGF100151 (median) April 2006	15.6 (13.6 to 21.1)	15.4 (11.3 to 17.3)	0.78 (0.55 to 1.12)
EGF100151 (median) Sept 2007	17.1 (15.1 to 19.6)	15.2 (12.3 to 17.3)	0.9 (0.71 to 1.12)

Figures are medians with 95% confidence intervals in parenthesis.

Table 3: Time to disease progression (TTP) and progression free survival (PFS) for trastuzumab and capecitabine compared to capecitabine alone

	Trast + cap (months)	Cap (months)	Hazard Ratio
TTP GBG 26 (ASCO) (median) May 2008	8.2 (7.3 to 11.2)	5.6 (4.2 to 6.3)	0.69 (NR) (p=0.034)
PFS GBG 26 (SABCS) (median) 2007.	8.5	5.6	0.71 (NR)
TTP pooled analysis (mean) – April 2007	5.03 (4.50 to 5.61)	n/a	0.87*
TTP updated pooled analysis (mean) - July 2008	6.23 (5.4 to 7.2)	n/a	0.70* (0.61 to 0.81)
TTP (mean) GSK analysis of GBG 26 – July 2008*	11.17**	8.26**	0.74

Figures are medians with 95% confidence intervals in parenthesis. NR = Not reported.

*Implied vs Capecitabine monotherapy

** Assumes there is a mis-print in the appendix of the GSK response and these figures were presented the wrong way round

Table 4: Overall Survival for trastuzumab and capecitabine compared to capecitabine only

	Trast + cap (months)	Cap (months)	Hazard Ratio
GBG 26 (ASCO) (median) May 2008	25.5 (17.8 to 24.7)	20.4 (17.8 to 24.7)	0.76 (NR) (p=0.26)
GBG 26 (SABCS) (median) 2007	20.3	19.9	0.79 (NR)
GSK analysis of GBG 26 (mean) – July 2008	24.46	22.38	0.870 (NR)

Figures are medians with 95% confidence intervals in parenthesis. NR = Not reported.

2.4 *Comments on updated efficacy data*

Updated estimates from the clinical trials

Based on the most recent data from the trials, neither trastuzumab plus capecitabine nor lapatinib plus capecitabine have been demonstrated to have a statistically significant impact on overall survival compared to capecitabine alone. The median survival gain from the trial of lapatinib is 1.9 months and from the trial of trastuzumab is 4.1 months. The primary outcome measure in both trials was time to treatment progression and the trials demonstrated a statistically significant improvement in TTP for trastuzumab and lapatinib when each was compared with capecitabine alone. The median gain in TTP was 2.6 months for trastuzumab plus capecitabine compared to capecitabine alone, and 2.0 months for lapatinib plus capecitabine compared to capecitabine alone.

Pooled estimate of trastuzumab efficacy [GSK Appendix 2.2]

Table 7 of Appendix 2 in the GSK response displays the results of a pooling of retrospective and prospective comparative and non-comparative studies to derive an estimate of median TTP in weeks. The updated pooled analysis shows a hazard ratio for the effect on TTP of trastuzumab plus capecitabine compared to capecitabine alone that is not dissimilar to the hazard ratio presented in the most recent analysis of the GBG-26/BIG 3-05. However, such a pooling breaks randomisation, i.e. different arms of the same studies are included as independent estimates without the correlation being taken into account, and the weighted analysis uses numbers in each arm rather than the SE of the median.[8] It should be noted that a standard Fixed or Random effects meta-analysis approach produces implied hazard ratios which are considerably larger (that is, less favourable for trastuzumab) than the weighted method adopted. This would have the effect of decreasing the incremental cost-effectiveness ratios of lapatinib plus capecitabine compared to the trastuzumab-containing regimens. In addition an assumption that the TTP follows a lognormal distribution is also made in order that a 95% CI can be calculated for both the median and the implied HR

for T+C vs C (assuming that C+L is a mis-print in Table 8 as only parameters for the associated Weibull distribution are given for C-only). An alternative approach, which would have taken into account the potential for bias in comparisons derived from single arm studies, is that of Begg & Pilote (1991)[9], though a more elegant approach would have been to conduct a Mixed Treatment Comparison (MTC), in which single arm studies are included via a sensitivity analysis with potential adjustment for bias, though it is accepted that this represents a step forward in the manner in which MTC methods have otherwise been applied to date.

Using MTC methods to obtain a hazard ratio HR for trastuzumab plus capecitabine compared to lapatinib plus capecitabine using the results from the Cox model reported in the trial, the hazard ratio for TTP/PFS is 0.96 (95% CI: 0.64 to 1.45) and for OS is 0.84 (95% CI: 0.50 to 1.43). However if the data from the Weibull approximated results are used in the MTC analysis, the results are: HR for TTP/PFS is 1.22 (95% CI: 0.89 to 1.67); and HR for OS is 1.04 (95% CI: 0.76 to 1.44). It should be noted that the confidence intervals around all the estimates are wide and therefore it is difficult to draw firm conclusions about the relative effectiveness of the two treatments.

Estimation of hazard ratio for trastuzumab plus capecitabine compared to capecitabine monotherapy from GBG26/BIG3-05 Study [Appendix 4]

The efficacy estimates for trastuzumab-containing regimens that were used in the economic analysis were based on a reanalysis of the data from the GBG 26/BIG 3-05 study, based on a conference abstract/poster, whereby the Kaplan-Meier curves were digitized and a Weibull distribution fitted for both TTP and OS. Both however show considerable lack-of-fit for the capecitabine-only group (GSK appendix 4, figures 5 and 6). It is also unclear why an Accelerated Failure Time (AFT) Weibull model was used to estimate the hazard ratios when these were available directly from the abstracts. It should also be noted that the hazard ratios using the Weibull model show a larger effect than those reported in the abstract,

and the pooled analysis as reported in Table 8 of Appendix 2 based on the synthesis of trastuzumab plus capecitabine studies/arms (see above). The pooled analysis was then used to derive a hazard ratio for trastuzumab plus capecitabine compared to capecitabine plus lapatinib in a scenario analysis (at least using a standard meta-analysis method – Fixed Effects or Random Effects models – see comments above).

3 Amendments to the economic model

The manufacturer's response to the ACD, along with an additional set of appendices, provides details on a number of changes and corrections made to the re-submitted economic model. These changes are summarised below.

3.1 *Summary of changes*

A summary of the differences between the assumptions and inputs between the original and updated economic models supplied by GSK are presented in Table 5 below.

Table 5: Key efficacy parameters and differences in parameter inputs between original and updated GSK models

Assumption/parameter value or source	**Original model**	**Updated model**
Basecase analysis		
Capecitabine overall survival	April 06 analysis of OS EGF100151 (Weibull regression model)	Sept 07 analysis of OS EGF100151 (Weibull regression model)
Lapatinib overall survival	HR from April 06 analysis of OS EGF100151	HR from Sept 07 analysis of OS EGF100151
Lapatinib PFS	HR from April 06 analysis of PFS EGF100151	No reported change
Trastuzumab overall	Implied from PPS and	Implied HR from GSK

survival	PFS	analysis of TTP GBG 26 (0.87)
Trastuzumab post-progression survival (PPS)	Assumed to be the same as for lapatinib	Implied from difference between OS and PFS
Trastuzumab PFS	HR from pooled analysis of TTP from 11 non-RCTs (0.870)	Implied HR from GSK analysis of TTP GBG 26 (0.74)
Acquisition cost of lapatinib	£11.00 per tablet	£11.49 per tablet
Wastage of trastuzumab	100% of unused trastuzumab is wasted	15% of all trastuzumab is wasted
Dosing schedule for trastuzumab	100% weekly schedule 0% 3-weekly schedule	12% weekly schedule 88% 3-weekly schedule
Discounting of trastuzumab PPS	Discounted PPS same as for lapatinib	PPS discounted taking into account PFS
Disutility for disease progression	31.9% of pre-progression state	32.0% of pre-progression state
Costs of wastage	Calculated using number of vials	Calculated assuming proportion of the final prescription
Additional Sensitivity/scenario analyses		
Trastuzumab PFS (scenarios 2 and 3)	HR from pooled analysis of TTP from 11 non-RCTs (0.870)	HR from pooled analysis of TTP from 11 non-RCTs (0.86396)
Trastuzumab PFS	HR from pooled analysis of TTP from 11 non-	HR from pooled analysis of TTP from 16 non-

(scenarios 4 and 5)	RCTs (0.870)	RCTs (0.70)

3.1.1 Price change

At the time GSK provided their original submission to NICE, the price of lapatinib had not been confirmed. The original basecase analysis assumed an acquisition cost of £11 per lapatinib tablet. The price of lapatinib has since been confirmed at £11.49 per tablet. The model has been amended to include the confirmed price of lapatinib.

3.1.2 Updated overall survival for lapatinib plus capecitabine

GSK have amended the economic model to incorporate the updated analysis on overall survival (see section 2.1 for a description of the updated data). The model has been amended to include the updated overall survival data. Updated data on TTP for lapatinib plus capecitabine and capecitabine alone are not presented.

3.1.3 Updated TTP and overall survival data for trastuzumab

Three separate sets of amendments have been made to the efficacy data for trastuzumab containing regimens and used in separate scenario analyses. These include

- an amendment to a rounding error in the original model (Scenarios 2 and 3).
- results from an updated pooled analysis of efficacy data including the data from GBG-26 and a further 4 new non-randomised studies (Scenarios 4 and 5)
- efficacy data from the GBG-26 study (Scenarios 6 to 9).

The updated efficacy data for trastuzumab have been discussed in Section 2 above.

3.1.4 Wastage of trastuzumab

The assumption in the original GSK model was that unused quantities of trastuzumab in a vial would be discarded. GSK calculated the level of wastage by deriving distributions of weight and body surface area (BSA) from the main trial. The ERG noted that a simpler calculation could have been using data directly from the main trial. In their updated model, GSK amended their estimate to assume that 15% of all trastuzumab is wasted. This was based on a survey of 24 oncology pharmacists conducted on behalf of GSK. The oncology pharmacists were asked to estimate the proportion of trastuzumab under the care of their hospital that they expected to be wasted. They were also asked about their policies on repeated use of single IV vials (not specifically trastuzumab).

The survey found that 11 respondents had a policy that considered all to be single use, 8 had policies recommending consideration of repeated use and 5 had no policy on the issue. The average of responses regarding the amount of trastuzumab that would be wasted was used in the economic model (mean 15%; range 1% to 60%).

3.1.5 Change to trastuzumab dosing schedule:

GSK's original analysis assumed that all patients would receive trastuzumab on a weekly schedule. The rationale for this was that it is compatible with NICE guidance and the SPC for trastuzumab. In the 'Posology and method of administration' section of the SPC for trastuzumab, the recommended dose of trastuzumab is 2 mg/kg, beginning one week after an initial loading dose of 4 mg/kg. The survey of oncology pharmacists conducted on behalf of GSK asked respondents to estimate the proportion of trastuzumab that is administered weekly and 3-weekly. The average across responses from the survey was 12% of trastuzumab is given weekly in combination with capecitabine or vinorelbine and 20% of trastuzumab monotherapy is administered weekly for the treatment of metastatic breast cancer. There was considerable variation in responses (ranging from 0% to 100%).

In their response to the ACD, the manufacturer of trastuzumab (Roche) provided data from an audit of 1064 cases in 2007. Roche state that 92% of patients with metastatic breast cancer who receive trastuzumab, do so in a 3-weekly schedule. No further details of the methodology of the study were provided.

3.1.6 Other amendments

In Appendix 3, the manufacturer details four minor calculation errors which have been corrected.

- Discounting of Post Progression Survival (PPS)
- Disutility for disease progression
- Hazard ratio for PFS with Trastuzumab-based regimens
- Costs of wastage of capecitabine in T+C strategy

These changes do not make a significant difference to the results.

3.1.7 Results

Summary results from the all the amendments and using the efficacy data for trastuzumab containing regimens from the GBG-26 study are presented in Tables 6 and 7 below. These relate to GSK's updated basecase (Scenario 9 of GSK response to ACD). The original results are also presented.

Table 6: Mean life years, progression-free life years, QALYS and costs (GSK original and updated base-case – Scenario 9) (based on PSA results)

	L+C	C-Only	V-only	T-only	T+V	T+C
Original analysis						
Life years	1.488	1.252	1.252	1.282	1.282	1.282
Progression-free life years	0.694	0.426	0.426	0.489	0.489	0.489
Post-progression life-years	0.794	0.826	0.826	0.794	0.794	0.794
QALYs (discounted)	0.857	0.686	0.686	0.714	0.714	0.714
Total Costs (discounted)	£25,678	£11,805	£14,094	£30,131	£26,753	£27,864

Updated analysis						
Life years	1.641	1.436	1.436	1.643	1.643	1.643
Progression-free life years	0.707	0.431	0.431	0.582	0.582	0.582
Post-progression life-years	0.934	1.005	1.005	1.061	1.061	1.061
QALYs (discounted)	0.897	0.748	0.748	0.871	0.871	0.871
Total Costs (discounted)	£26,939	£12,924	£15,212	£26,300	£30,522	£28,013

Table 7: Mean incremental costs and QALYs and ICERS for GSK updated base-case – Scenario 9 (all discounted and compared to lapatinib plus capecitabine)

	C-Only	**V-only**	**T-only**	**T+V**	**T+C**
Original analysis					
QALYs	0.171	0.171	0.143	0.143	0.143
Total Costs	£13,873	£11,584	-£1,075	-£4,452	-£2,186
ICER	£81,251	£67,847	Lapatinib dominates	Lapatinib dominates	Lapatinib dominates
Updated analysis					
QALYs	0.150	0.150	0.026	0.026	0.026
Total Costs	£14,015	£11,726	£638	-£3,583	-£1,075
ICER	£93,825	£78,503	£24,227	Lapatinib dominates	Lapatinib dominates

3.1.8 Comments on amendments to the economic model

The formulae and coding of the amendments has been verified. All of the amendments described above have been implemented as described in the documentation by GSK.

The effect of all the amendments to the assumptions regarding cost of treatment has been to reduce the cost difference between lapatinib/capecitabine compared to trastuzumab containing regimens. The individual effects of the changes to the

effectiveness estimates are more complex as there have been significant changes to the assumptions underpinning their inclusion in the model. In particular, one of the key assumptions in the original model was that the length of survival post-disease progression would be the same for lapatinib/capecitabine and the trastuzumab containing regimens. This has been amended in the updated analysis so that the PPS of patients treated with trastuzumab containing regimens is longer than that for those treated with lapatinib/capecitabine.

The QALY gain for lapatinib/capecitabine compared to trastuzumab containing regimens has decreased substantially in the updated analysis compared to the original analysis. The updated model predicts similar overall survival for patients treated with trastuzumab containing regimens (mean 1.643 life years) compared to lapatinib and capecitabine (mean 1.641 life years). The main reason that predicted quality adjusted life years (QALYs) are higher for trastuzumab is that the predicted progression free survival is lower for trastuzumab containing regimes (6.98 months) compared to lapatinib and capecitabine (8.49 months).

The methods used to derive estimates of clinical effectiveness, i.e. hazard ratios, have a number of methodological failings. Most notable of these are breaking of randomisation and reliance on distributional assumptions which are either not assessed or which appear to represent a lack-of-fit to the data (all analyses) and inappropriate weighting of estimates in meta-analyses (pooled scenario analysis) and which at least on initial inspection appear to be over elaborate when either a more appropriate Mixed Treatment Comparison could have been undertaken or sole use of the two relevant RCTs (CBG 26/BIG 3-05).

The effect of assumptions about the amount of trastuzumab wastage reduces the estimated treatment costs of trastuzumab; however the change in assumptions does not make trastuzumab-combination therapies less costly than the lapatinib/capecitabine regimen. The information on the amount of trastuzumab that is discarded and the frequency of administration was provided from a survey of oncology pharmacists. The sample size for the survey was small (n=24) and it is unclear how representative the results are of practice in the NHS. The results

showed a substantial amount of variation in practice between respondents for the responses to questions about wastage and frequency of administration. For illustrative purposes only and based on all the assumptions in the GSK updated analysis, if the amount of all trastuzumab wasted was assumed be 10% rather than 15%, lapatinib/capecitabine would still dominate the trastuzumab-combination therapies, however the cost difference would be substantially reduced (-£478 for trastuzumab/capecitabine; -£2,986 for trastuzumab/vinorelbine). Under these assumptions the ICER for lapatinib/capecitabine compared to trastuzumab monotherapy would increase to £47,630.

Similarly the data underpinning the assumptions regarding trastuzumab dosing schedules show considerable variation in current practice. Using the data supplied by Roche on the frequency of administration instead of the estimates provided by GSK and keeping all other assumptions the same, lapatinib plus capecitabine still dominates trastuzumab in combination with vinorelbine or capecitabine, however the difference in costs is reduces slightly (-£952 for trastuzumab/capecitabine; -£3,460 for trastuzumab/vinorelbine). The ICER is just under £30,000 compared to trastuzumab monotherapy.

3.2 *Cost-effectiveness analysis of lapatinib compared to a combined comparator*

The Appraisal Consultation Document reports that the Appraisal Committee did not consider trastuzumab to be an appropriate comparator for lapatinib. In the updated analysis, lapatinib plus capecitabine has been compared to a combined comparator of capecitabine monotherapy, trastuzumab in combination with capecitabine and trastuzumab in combination with vinorelbine. The proportions in which the predicted costs and QALYs of each treatment strategy have been weighted are based on updated market research data conducted on behalf of GSK.

The NICE Methods Guide 2004[10] and the recently updated Methods Guide 2008[11] state that consideration should be given to routine care and best

alternative care by those submitting evidence to the technology appraisals programme. This technology appraisal is being conduced in accordance with the 2004 version of the Methods Guide. There is no statement in that guide regarding the consideration of unlicensed technologies as comparators. However, the Methods Guide 2008 states that relevant comparator technologies may include those that do not have a marketing authorisation but are used routinely in the NHS for that indication. The Guide does not state a definition of 'routine practice' or how well established those technologies must be in clinical practice, implying that this is left to the judgement of the Appraisal Committee. Therefore, for trastuzumab, as an unlicensed technology for this indication, to be considered as an appropriate comparator it must be considered to represent routine practice, and either routine or best practice in accordance with standard approaches to NICE Technology Assessment.

3.2.1 Summary of amendments to comparator in the updated analysis

In the updated analysis, GSK have weighted the cost and QALY estimates of three of the comparators used it the original analysis (44% capecitabine, 27% trastuzumab and vinorelbine and 29% trastuzumab and capecitabine). The percentages for each of the three comparators included in the analysis were based on data from the updated IMS oncology survey data supplied by GSK. The data relating to the other trastuzumab or bevacizumab containing therapies were split across trastuzumab plus vinorelbine and trastuzumab plus capecitabine (at a ratio of 49:51). The data relating to the other non-trastuzumab containing therapies were allocated to the capecitabine alone group. The results of the combined comparator analysis show that the mean ICER is £60,730 for lapatinib plus capecitabine compared to the weighted comparator.

3.2.2 Comments on approach to combining comparator technologies

The approach employed by GSK in their combined comparator analysis assumes that all of the treatment regimens are established as routine practice and that it would be appropriate for any or all of the comparators including in the weighted analysis to be potentially displaced by the routine introduction of lapatinib. The implication of this is that it could displace those technologies which, based on GSK estimates, are cost-effective relative to lapatinib/capecitabine (that is, capecitabine and vinorelbine monotherapies) as well as those technologies that may not be considered cost-effective relative to lapatinib/capecitabine (that is, trastuzumab containing regimens).

As mentioned above, the NICE Methods Guide also states that best practice should be considered as a comparator for appraisal of health technologies. If best practice is defined as the current cost-effective treatment option, the standard approach to assessing the cost-effectiveness of lapatinib in this context would be to consider all treatment options in a single incremental analysis (as, for example, described in Drummond et al [12]). This compares the costs and health effects of all potential technologies so that the most cost-effective technology can be identified. The results from the GSK basecase analysis are presented in Table 8 using this approach to analysis. The treatments are ranked in terms of effectiveness and those treatments that are dominated (that is, more costly and less effective than others) are excluded from the analysis.

Of the remaining comparators, compared to capecitabine as the next best alternative, trastuzumab monotherapy has a mean incremental cost effectiveness ratio of £108,728. If trastuzumab monotherapy is ruled out as an appropriate comparator because it is outside of the £20-30K range reportedly considered cost-effective by NICE[10;11] and therefore not considered to be ‘best practice’, the ICER for lapatinib plus capecitabine compared to the remaining alternative, capecitabine monotherapy, is £93,825.

Table 8: Incremental analysis of treatment options (based on GSK updated basecase)

Treatment	Mean cost	Mean QALY	Cost diff	QALY gain	ICER
Lap/cap*	£26,939	0.897	£14,015 (£639)	0.150 (0.026)	£93,825 (£24,227)
Trast/vin	£30,522	0.871	£17,598	0.123	Dominated
Trast/cap	£28,013	0.871	£15,089	0.123	Dominated
Trast mono	£26,300	0.871	£13,376	0.123	£108,748
Vin mono	£15,212	0.748	£2,288	0	Dominated
Cap mono	£12,924	0.748			

*incremental results compared to trastuzumab monotherapy in parenthesis

3.2.3 Market research data on the use of trastuzumab post-progression in the metastatic setting

The original GSK submission included market research data on the use of trastuzumab following disease progression to support their assertion that trastuzumab is an appropriate comparator for lapatinib. The primary source of data was from the Intercontinental Marketing Services (IMS) Oncology Analyzer database (data relate to period Jan 2004 to Sept 2006). Since the first meeting of the Appraisal Committee, GSK have supplied an updated analysis of this database (data relate to period Jan 2004 to Q4 2007) and details of another market research study (Dendrite Doscan Oncology Survey, Aug 06). The manufacturer of trastuzumab (Roche Pharmaceuticals) has also supplied results from a market research study.

The manufacturer of lapatinib reports that the IMS database is the largest commercially available oncology-patient database. The data are obtained from

patient records completed by physicians treating people with cancer. The updated analysis of the IMS database included records of 2815 UK patients with metastatic disease. Of these, 98 patients had been previously treated with a taxane and an anthracycline and had progressed on trastuzumzab therapy, where progression was defined as

- one or more chemotherapeutic agent(s) was added to what was originally trastuzumab monotherapy and/or
- chemotherapeutic switch in a trastuzumab-containing regimen occurred.

GSK submitted results from a survey of physicians conducted by Cegedim Dendrite to support the information from the IMS database. Physicians were asked about the proportions of patients treated with various treatment regimens. It is not clear if clinicians had the opportunity to retrospectively review their patients' records but the information from GSK implies that it was based solely on clinician recall.

Roche Pharmaceuticals also provided results of a market research study, which showed that only 12% of those responding to the survey received any regimen containing trastuzumab post progression. It is not possible to comment further on the data collected as part of this survey as the methods of data collection were not provided.

The results from all the studies are presented in Table 9.

Table 9: Summary of submitted market research data on use of trastuzumab beyond progression

	GSK – IMS 2004-6	GSK – IMS 2004-7	GSK - survey	Roche – survey
N	24	98	92	222
Cap mono	47%	32%	33%	NR
Vin mono	9%	5%	11%	NR
Trast / vin	17%	20%	12%	NR
Trast /cap	17%	21%	23%	NR
Trast mono	7%	2%	2%	NR
Other trast	NR	11%	12%	NR
Other non-trast	NR	9%	7%	NR
Any trast	41%	55%	48%	12%

NR: not reported

Full details of data collection, including the methods of recruitment of respondents, characteristics of respondents/non-respondents and response rates were not available for any of the market research data. Therefore it is not possible to single out a specific source of data as being superior to the others.

GSK highlight that the IMS data are based on patients records, which is likely to be less prone to internal bias than relying on physician recall. The definition of disease progression in this dataset is based on changes in therapeutic approach as a proxy for disease activity.[1]

The Roche dataset is based on the largest number of respondents, however data are not available to judge the generalisability of any of the datasets to patients eligible for treatment with lapatinib in the NHS (estimated at 1,643 new patients

[1] Disease progression was defined in the lapatinib trial as the "appearance of any new lesion not previously identified or increase of > 25% in existent lesions" and in the main registration trials of trastuzumab (in the metastatic setting) it was defined as "an increase of ≥ 25% of any measurable lesion and/or death" and "as a ≥ 25% increase in any measurable lesion or the appearance of a new lesion".

each year in the GSK submission). GSK state that only limited details of the background of respondents submitting data to the IMS database are available, but provide some information for 2006-7 (during which 117 physicians submitted data). They note that 38% of respondents stated they were based in a University hospital, 56% in a non-University and 6% worked in both types of hospital. GSK also provide information on the UK region in which the physicians were based and note that a disproportionate amount come from Greater London but state that this is due to "the relatively larger population of patients and clinicians in this geography" (see GSK Appendix 1, Table 5). It has not been possible to obtain definitive figures on the proportion of patients treated for metastatic breast cancer within a University hospital compared to a non-University hospital.

There is variation between the sources in the estimated proportion of patients receiving trastuzumab containing regimens after progression in the metastatic setting, most notably between the data submitted by GSK and Roche. In addition, there is considerable variation in practice across the NHS as demonstrated by the market research data submitted by GSK (see GSK Appendix 1, Table 9 and Table 10 below). Table 10 shows the variation in the reported provision of trastuzumab after progression in the metastatic setting across the individual cancer networks. The table shows that three cancer networks estimate that no patients receive trastuzumab in this setting and two networks would use trastuzumab in over 90% of its patients in this setting.

Table 10: Number of cancer networks estimating the proportions of patients who receive trastuzumab containing regimens after progression in the metastatic setting (GSK market research survey)

Proportion of patients who receive trastuzumab containing regimens after progression in the metastatic setting	Number of cancer networks reporting percentage range
0%	3
0% > and ≤ 10%	1
10% > and ≤ 20%	2
20% > and ≤ 30%	2
30% > and ≤ 40%	4
40% > and ≤ 50%	4
50% > and ≤ 60%	2
60% > and ≤ 70%	4
70% > and ≤ 80%	2
80% > and ≤ 90%	4
90% > and ≤ 100%	2
TOTAL	30

For illustrative purposes, Table 11 shows the results of exploratory analyses varying the weighting for each of the comparators. An alternative approach to apportioning the updated IMS data was explored in order to include all of the comparators included in the original analysis. In this analysis, data relating vinorelbine and trastuzumab monotherapy were included directly from the IMS data. The remaining data for trastuzumab-containing regimens were split according to the reported proportions of the three trastuzumab containing comparators, and the data for non-trastuzumab-containing regimens were split into the capecitabine monotherapy and vinorelbine monotherapy groups according to their relative proportions. The data from the GSK survey were also incorporated using this same approach. The data supplied by Roche were also

used assuming that all trastuzumab regimens were in combination with either vinorelbine or capecitabine combinations (equal split).

Table 11: Mean incremental cost-effectiveness ratios (cost per QALY) for lapatinib plus capecitabine compared to alternative weighted comparators

	C-Only	V-only	T-only	T+V	T+C	ICER
GSK IMS data (GSK base case)	44%	0%	0%	27%	29%	£ 60,730
Alternative split of IMS data	40%	6%	3%	25%	26%	£ 62,136
GSK survey data	38%	13%	3%	16%	30%	£ 67,050
Roche data	88%	0%	0%	6%	6%	£ 89,545

3.2.4 Guidelines on the use of trastuzumab following progression in the metastatic setting

Summary of Product Characteristics

In the 'Posology and administration' section of the SPC for trastuzumab it states that "*Herceptin should be administered until progression of disease*". As stated above, according to NICE's methods and procedures, technologies that do not have a marketing authorisation for the indication being appraised may be considered as comparators if they are used routinely in the NHS.

NICE Guidance

A draft of the NICE clinical guideline 'Advanced breast cancer: diagnosis and treatment' has recently been issued for consultation. The guideline includes as a key priority for implementation the recommendation that "*Patients who are receiving treatment with trastuzumab should not continue trastuzumab at the time of disease progression outside the central nervous system*."

The full version of the draft guideline provides the following qualifying statement for the recommendation. "*This recommendation is based on the absence of evidence that trastuzumab leads to a better outcome*". The guideline cites evidence from several studies including the abstract of the GBG-26 study presented at ASCO 2008, although it is unclear if the data from the ASCO poster were also available to the Guideline Development Group. The draft guidance further states that "*There is controversy and practice variation about continuing its [trastuzumab's] use when chemotherapy is stopped or changed at the time of disease progression*". The guideline recommends that "*the use of continued trastuzumab in patients with progressive metastatic disease should be investigated as part of a randomised controlled trial*."

SIGN Guideline

The latest guideline from the Scottish Intercollegiate Guidelines Network on the Management of breast cancer in women was published in December 2005. The Guideline recommends the use of combination therapy of trastuzumab with a taxane for women with metastatic breast cancer. This guideline was produced before the availability of data from the GBG 26/BIG 3-05 study and states that no randomised data were available to address the question of duration of therapy and note that trastuzumab was discontinued at time of progression in the main RCT of trastuzumab available at that time. The guideline is currently being considered for review.

4 Proposed 'patient access programme'

GSK have proposed a 'patient access programme' whereby the acquisition costs of lapatinib for up to 12 weeks of therapy would be refunded to the NHS for patients meeting the inclusion criteria.

- For patients stopping treatment before 12 weeks due to disease progression, a lack of clinical response or intolerance to treatment despite

dose adjustments. For these patients the rebate would be equivalent to the cost of the number of 3-week cycles initiated (at the licensed dose).

- For patients continuing treatment beyond 12 weeks, the full 12 weeks therapy would be reimbursed following a clinical assessment. For these patients the rebate would be equivalent to the cost of 4 cycles of lapatinib treatment (at the licensed dose).

The continuation criteria are not tightly defined. Clinical benefit will be determined by the patient's oncologist and may be based on clinical and imagining assessments or other investigations. The proposal states that the programme would apply to NHS patients in England, Wales and Northern Ireland. The programme would not apply to patients currently taking lapatinib.

The scheme has been incorporated into the analysis by removing the acquisition costs of lapatinib for patients treated for less than 12 weeks and removing the costs of 12 weeks of lapatinib treatment for those who continued beyond this point. No additional monitoring costs have been included in the analysis on the grounds that no additional monitoring will be required. The formulae and coding of the patient access programme in the revised economic model has been verified. The amendments described above have been implemented as described in the documentation by GSK.

The results are presented in Table 12. Results using an incremental approach comparable to that presented in Table 8 are shown in Table 13.

Table 12: Summary of mean incremental cost-effectiveness results with patient access programme (all results compared to lapatinib plus capecitabine & discounted)

	C-Only	V-only	T-only	T+V	T+C
QALYs	0.150	0.150	0.026	0.026	0.026
Total Costs	£10,446	£8,157	-£7,152	-£4,644	-£2,931
Cost/QALY	£69,932	£54,610	dominant	dominant	dominant

Table 13: Incremental analysis of treatment options (based on GSK updated basecase including patient access programme)

Treatment	Mean cost	Mean QALY	Cost diff	QALY gain	ICER
Lap/cap*	£23,370	0.897	£10,446 (-£2,930)	0.150 (0.026)	£69,934 (Dominates trast mono)
Trast/vin	£30,522	0.871	£17,598	0.123	Dominated
Trast/cap	£28,013	0.871	£15,089	0.123	Dominated
Trast mono	£26,300	0.871	£13,376	0.123	£108,748
Vin mono	£15,212	0.748	£2,288	0	Dominated
Cap mono	£12,924	0.748			

*incremental results compared to trastuzumab monotherapy in parenthesis

The costs of monitoring and assessing disease progression (included in the original and updated analyses) are based on a study by Remak and Brazil (2004).[13] The study estimated resource-use for the treatment of women with metastatic breast by obtaining information on usual treatment practice from panel of UK cancer physicians. The cost estimates include scans and laboratory tests, however the assumed frequency or types of assessments are not reported. The

cost of scans\tests is reported to be £228 in the active treatment phase and £78 in the supportive care phase.

The patient access programme proposed by GSK does not require any additional form of monitoring. If specific methods or frequencies of assessment were to be required as a condition of the programme, it would be necessary to ensure that the cost estimates reported above sufficiently reflect the form and frequency of monitoring required.

The costs of administering the programme are not included in the analysis.

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Appendix: Summary of inclusion criteria and patient characteristics for trials EGF100151 and GBG-26/BIG 3-05

Table A1: Inclusion criteria for trials EGF100151 and GBG-26/BIG 3-05

EGF100151	GBG-26/BIG 3-05
• Refractory breast cancer, defined as progression in the locally advanced or metastatic setting, or relapse within 6 months of completing adjuvant therapy • Prior therapies must have included, but not been limited to, at least 4 cycles of regimens containing an anthracycline and a taxane (2 cycles if the disease progressed while the women were receiving therapy), administered concurrently or separately in the adjuvant or metastatic setting • Prior treatment must have contained trastuzumab alone or in combination with other chemotherapy for at least 6 weeks in the advanced/metastatic setting • No prior capecitabine	• Patients (pts) with pathologically confirmed, HER2 positive, locally advanced or metastatic breast cancer • No more than one chemotherapy for palliation was allowed. • Left ventricular ejection fraction (LVEF) had to be >= 50% in the prestudy cardiac monitoring. • Stratified by type of previous therapy (taxane and trastuzumab given as adjuvant therapy; taxanes and trastuzumab given as 1st line therapy; trastuzumab given alone or in combination with further chemotherapy as 1st line therapy). • Trastuzumab-free interval before study participation had to be less than 6 weeks.

Table A2: Baseline characteristics of patients in trials EGF100151 and GBG-26/BIG 3-05

	EGF100151 (n=399; 198 L/C, 201 C)		GBG-26/BIG 3-05 (n=156; 78 T/C, 78 T)	
	L/C	**C**	**T/C**	**C**
Median age (years) range	53.6 (26-80)	51.2 (28-83)	52.5 (30-78)	59.0 (33-82)
Karnofsky Index (%) 100 90-80 <80	NR	NR	44.2% 53.2% 2.6%	51.3% 46.0% 2.7%
ECOG performance status – no. (%) 0 1 Unknown	 58% 40% 2%	 60% 38% 2%	NR	NR
Hormone receptor status* negative positive unknown	 50% 48% 2%	 53% 46% <1%	 40.8% 59.2%	 42.1% 57.9%
pT at 1st diagnosis pT1 pT2 pT3/4	NR	NR	28.2% 38.0% 33.8%	42.9% 42.9% 14.2%
pN at 1st diagnosis pN0 pN1	NR	NR	16.9% 83.1%	20.6% 79.4%
Grading at 1st diagnosis G2 G3/4	NR	NR	 43.8% 56.2%	 39.4% 60.6%
M at 1st diagnosis M0 M1	NR	NR	81.7% 18.3%	76.4% 23.6%
Stage of disease (at baseline of trial) – (%) IV visceral IV non-visceral Non-visceral only	 75% 22% 4%	 79% 17% 4%	NR	NR

No. of metastatic sites(at baseline of trial) (%) >=3 2 1	NR	NR	 49% 31% 20%	 48% 30% 22%
Prior trastuzumab exposure – weeks median (range)	44 (3-296)	45 (0-329)	NR	NR
Prior therapy	• 314 pts had anthracyclines • 315 pts had taxanes • 175 pts had flurouracil • 141 pts had vinorelbine • 313 pts had trastuzumab o of which 16 as adjuvant therapy o of which 1 as neoadjuvant therapy o of which 296 for metastatic disease		Anthracyclin containing chemotherapy • 92 pts neoadjuvant/adjuvant • 21 pts 1st-line Trastuzumab therapy • 111 pts had a pre-treatment with a taxane/trastuzumab combination as 1st-line therapy • 42 pts received trastuzumab alone or with a non-taxane containing chemotherapy as 1st-line treatment • 3 pts got taxane and trastuzumab as part of adjuvant treatment.	

*Defined in EGF100151 as ‘ER+ and/or PR+’ and ‘ER- and/or PR-’