Manufacturer Submission to the National Institute for Health and Clinical Excellence

By

GlaxoSmithKline UK

Submission to address the question of whether and how lapatinib falls within the Supplementary Advice to Appraisal Committees on appraising treatments that extend life at the end of life.

In response to the Appeal Decision relating to the Single technology appraisal of lapatinib for the treatment of women with previously treated advanced or metastatic ERbB2- (HER2) over-expressing breast cancer

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1. Executive Summary - Lapatinib's eligibility for consideration under the Supplementary Advice to Appraisal Committees on appraising treatments that extend life at the end of life

In an appeal by GlaxoSmithKline UK Ltd (GSK) in respect of the FAD issued by NICE for lapatinib, GSK made a number of challenges on the grounds of procedural unfairness and perversity. Following an appeal hearing on 8 June 2009, the Appeal Panel upheld two points under procedural unfairness, and invited GSK and other consultees/commentators to provide submissions on lapatinib's eligibility for consideration under the Supplementary Advice to Appraisal Committees on appraising treatments that extend life at the end of life. This submission addresses the question of whether and how lapatinib falls within the Supplementary Advice, and provides an economic evaluation of lapatinib within that context.

GSK strongly believes that lapatinib in its current indication (treatment of patients with advanced or metastatic breast cancer whose tumours overexpress HER2 with progressive disease following prior therapy including an anthracycline and a taxane, and trastuzumab in the metastatic setting) meets the criteria set out in section 2.1 of NICE's Supplementary Advice on appraising end of life medicines as follows:

The treatment is indicated for patients with a short life expectancy, normally less than 24 months

Once a diagnosis of advanced or metastatic breast cancer is established the average survival time for patients receiving active treatment is 18-24 months. This may be reduced by up to 50% in patients with HER2+ disease (NICE TA no. 34).

Only two randomised, controlled trials (RCTs) in patients with HER2+ advanced or metastatic breast cancer have been conducted in the setting of post-progression on metastatic trastuzumab-based therapy.

The first was the lapatinib pivotal study (EGF100151) supporting the above indication in which the latest (October 2008) median overall survival (OS) for patients in the control arm (capecitabine monotherapy) was approximately 15 months (65 weeks) (see section 3.4.3).

The other is the GBG-26 study conducted in a similar but less heavily pretreated population of patients where median OS in the control arm (capecitabine monotherapy) was 20.4 months (von Minckwitz 2009).

The above studies clearly support the conclusion that the life expectancy in the population indicated for lapatinib plus capecitabine is less than 24 months.

The treatment is licensed, or otherwise indicated, for small patient populations

Lapatinib (in combination with capecitabine) is indicated for the treatment of patients with advanced or metastatic breast cancer whose tumours over express ErbB2 (HER2). Patients should have progressive disease following prior therapy which must include an anthracycline and a taxanes, and therapy with trastuzumab in the metastatic setting. GSK has estimated that the number of patients fulfilling these criteria in the UK is likely to be fewer than 2,000 per year. Full details of how this figure was derived are provided in section 7.2 of GSK's original submission to NICE (GSK submission to NICE for lapatinib, 17 April 2007).

The treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment

The conditional marketing authorisation for lapatinib granted in June 2008 included a stipulation that in order for lapatinib to be granted a full marketing authorisation updated overall survival data from the pivotal study EGF100151 should be provided. Analyses of OS data with a cut-off date of 1 October 2008 have therefore been performed, and are reported in this submission. The last overall survival (OS) analyses provided to NICE for the EGF100151 study were conducted with a cut-off date of 28 Sept 2007, and were provided in GSK's response to the first Appraisal Consultation Document (ACD) on 28 July 2008.

Unadjusted analyses of OS (conducted with 03 April 2006, 28 Sept 2007 and 01 Oct 2008 cut-offs; see sections 3.4.1 and 3.4.2) consistently suggest a survival benefit for lapatinib plus capecitabine compared with capecitabine alone, albeit statistically non-significant. The difference in median OS increased with each data cut, as patient and event numbers increased (0.25 months, p=0.177; 1.86 months, p=0.3; 2.37 months, p=0.210, respectively). However, the ability of study EGF100151 to demonstrate a statistically significant difference in OS between treatment groups was impacted by the premature halt to enrolment resulting in a lower number of patients recruited than planned, and crossover to lapatinib plus capecitabine combination therapy of patients who were originally randomised to capecitabine monotherapy.

The Supplementary Advice specifies that Appraisal Committees should be satisfied that estimates of any extension to life are robust, and can be shown or reasonably inferred from either progression free survival or overall survival, taking account of trials in which cross-over has occurred and been accounted for in the effectiveness review. Since there is no universally accepted methodology to adjust for crossover from control to active treatment in a survival analysis, several approaches have been employed to evaluate this effect using the October 2008 OS data for the ITT population. The methodology and results of these analyses are discussed fully in sections 3.2 and 3.4.2, and summarised below.

The different approaches considered were:

a. Kaplan-Meier analysis excluding all subjects who crossed over
b. Kaplan-Meier analysis censoring crossover patients at time of crossover
c. Kaplan-Meier analysis treating crossover as an event (not conducted as such an analysis would potentially highly favour the lapatinib plus capecitabine arm)
d. Cox regression analysis considering crossover as a time-dependent covariate

    i) Without the inclusion of baseline prognostic variables
    ii) With the inclusion of baseline prognostic variables

e. Weibull survival model

    i) Without the inclusion of baseline prognostic variables
    ii) With the inclusion of baseline prognostic variables

The Cox analysis which adjusts for baseline prognostic factors is considered the most appropriate methodology to adjust for crossover effects, as it controls for the breaking of randomization attributable to crossover, and isolates the pure treatment effects (discussed fully in section 3.2). This analysis is therefore considered as the most reflective of the true survival impact of lapatinib, and has been used to form the base case in the Weibull modelling for the economic evaluation.

The results of analyses a, b, d and e consistently suggest some attenuation of the OS benefit attributable to lapatinib plus capecitabine over capecitabine alone due to the crossover. Each of the Kaplan-Meier and Cox regression methods found a greater reduction in risk for death with the lapatinib combination compared with capecitabine monotherapy (HRs of 0.75 to 0.82) than observed in the unadjusted analysis (HR 0.87).

The increase in median OS for lapatinib plus capecitabine vs. capecitabine alone in the Kaplan-Meier analysis which excluded patients who crossed over was 4.3 months (HR (95% CI): 0.78 (0.62, 0.97), p=0.023). When patients who crossed over were censored at the time of crossover the median survival gain was 2.9 months (HR 0.82 (0.66, 1.02), p=0.074).

In both Cox regression analyses considering crossover as a time-dependent covariate (from which direct estimation of medians is impracticable), the adjusted HRs for the treatment effect demonstrate a clinically relevant reduction in risk of death for patients treated with lapatinib plus capecitabine, with upper limits of the confidence intervals of <1, and p-values that are highly statistically significant (0.75 [0.60, 0.94], p=0.013; 0.80 [0.64,0.99], p=0.043, with and without the inclusion of baseline prognostic factors, respectively.

The Weibull survival model employed in the economic evaluation was used to estimate expected and median OS values using the Cox regression analyses which considered crossover as a time-dependent covariate. Estimates of expected and median OS gains for combination vs. monotherapy adjusted for baseline prognostic factors (which we consider to be the most appropriate estimate of overall survival adjusting for crossover, see section 3.4.2) were 3.8 months (95% CI -0.4, 8.6) and 3.3 months (0.6, 6.8) respectively. The gains in expected and median overall survival without adjusting for baseline factors were 3.0 months (-1.1, 7.8) and 2.7 months (0.1, 6.0), respectively.

Several *post hoc* sub-group analyses of EGF100151 have been conducted to investigate the influence of prior therapy on outcomes:

(i) Subjects treated with 1 or 2 prior regimens, and subjects treated with 3 or more prior regimens (submitted to NICE on 21 January 2009)

(ii) Subjects treated with 1 prior trastuzumab-based regimen in the metastatic setting, and subjects treated with more than 1 prior metastatic trastuzumab-based regimen (new analysis)

(iii) Second-line patients who received trastuzumab in the first-line metastatic setting (new analysis)

These subgroup analyses are summarised in section 4.1 and full details of the methodology and results are given in Appendix 2). Gains in median OS of 7.4 months (HR 0.51, p=0.009), 3.4 months (HR 0.79, p=0.077) and 7.3 months (HR 0.63, p=0.042) were found in sub-groups of patients who had received 1 or 2 prior regimens, 1 prior metastatic trastuzumab-based regimen, and were second-line to a metastatic trastuzumab-based regimen, respectively. Whilst we acknowledge the Appraisal Committee's concern with the robustness of post hoc subgroup analyses which include small patient numbers, it is not unreasonable to conclude that these analyses suggest that less heavily pre-treated patients may experience greater survival benefits from lapatinib, and that the results support those observed in the total trial population.

The above data indicate a survival benefit for lapatinib plus capecitabine over capecitabine alone approximating to or exceeding 3 months. Indeed the estimate which we consider is the most reflective of survival in the indicated population when

crossover is taken into account suggests that the expected overall survival gain would be as high as 3.8 months. Two of the alternative analyses to account for the impact of crossover achieved an OS gain of slightly below 3 months (i.e. simple censoring in a Kaplan-Meier analysis; Cox regression treating crossover as a time dependent covariate without accounting for baseline prognostic factors). However, these methods do not adequately account for the confounding effects of crossover.

It is highly relevant that in the analysis that adjusts for both crossover and baseline prognostic factors, both the expected and median OS estimated using a Weibull survival model were over 3 months.

From the efficacy data presented above it is reasonable to expect that lapatinib, given in combination with capecitabine, offers an extension to life of at least 3 months compared with standard treatment, thereby meeting the requirement set out in NICE's Supplementary Advice.

Economic considerations

In an updated economic evaluation of lapatinib including the most recent survival data, with prices and costs updated to 2008, and including adverse event costs (to reflect the most plausible assumptions as outlined in the FAD), the cost per quality adjusted life year gained (£/QALY) is £86,736, slightly lower than that quoted in the FAD (£93,825/QALY). A modification of the model (detailed in 5.2.2) was undertaken to permit the use of hazard ratios estimated from Cox regression analyses with crossover as a time dependent variable. This modification raised the £/QALY to £93,877, which is similar to the value estimated in the FAD. When overall survival is adjusted to consider crossover as a time dependent covariate, taking into account baseline prognostic factors (the base case analysis), the £/QALY is £77,996 using the Weibull survival model. We believe for reasons stated above that this uses the most appropriate methodology for adjusting for crossover, and is therefore most plausible estimate of lapatinib's cost effectiveness. Implementation of the Tyverb Patient Access Programme (TPAP) in this new base case scenario reduces the £/QALY to £59,441. The TPAP has been approved by the Department of Health as an appropriate patient access scheme to be considered by NICE.

On the basis that lapatinib meets the end of life criteria, a utility weighting was applied such that the extended survival period is experienced at the full quality of life anticipated for a healthy individual of the same age, employing methodology used in previous NICE evaluations of end of life medicines. Without the TPAP the £/QALY was £59,734, falling to £45,524 when the TPAP was applied. In this scenario, the additional weight that would need to be assigned to the QALY benefits in this patient group for lapatinib to be cost effective at a willingness to pay of £30,000/QALY is a factor of 1.5, which is within the range of weightings previously accepted by NICE when considering end of life medicines.

Conclusions

We have demonstrated using the most recent overall survival data available, and using methodologies that take into account the impact of crossover within the study, that lapatinib in its current indication meets each of the criteria for consideration by NICE under the Supplementary Advice for Appraisal Committees, including the requirement for a survival benefit of at least three months. Having met the conditions for consideration, lapatinib's cost effectiveness is within the range of estimates previously accepted by NICE, when appropriate weighting of the estimated quality adjusted survival benefits are applied, and the Tyverb Patient Access Programme is implemented. When considered under the Supplementary Advice to Appraisal

Committees, treatment of this population with lapatinib plus capecitabine should be considered to represent appropriate use of NHS resources.

For this group of relatively young women the additional time without disease progression and prolonged survival afforded by lapatinib can be disproportionately valuable to them and their families, and this would be recognised in part through consideration of lapatinib under the Supplementary Advice. However, there are other factors which are not adequately captured in the cost utility estimates which we believe should be taken into account in reviewing lapatinib in the broader context, e.g. the potential benefits of lapatinib in preventing and treating brain metastases, and the expansion of oral treatment options that this technology represents. Furthermore, whilst we acknowledge the Appeal Decision that any comparison with trastuzumab regimens should be dismissed on the basis that trastuzumab is itself not cost effective, we would still highlight the reality that trastuzumab will continue to be used to a degree in this clinical setting, in the absence of other HER2-targeted therapies available on the NHS. The savings associated with the use of lapatinib plus capecitabine instead of trastuzumab regimens in terms of drug acquisition (particularly in the context of the TPAP), administration costs, and release of capacity in chemotherapy suites, would only serve to improve lapatinib's cost effectiveness in the real world.

We therefore ask NICE to recommend the use of lapatinib plus capecitabine as a new, evidence-based and innovative option for continued HER2-targeted suppression in patients with advanced or metastatic breast cancer who have progressed on trastuzumab, and for whom there are limited treatment options.

2. Lapatinib regulatory update

Lapatinib is now approved in over 70 countries worldwide.

In the EU, lapatinib is the subject of a conditional marketing authorisation granted to Glaxo Group Ltd by the European Commission via the centralised procedure on 10 June 2008. The indication authorised is:

"Lapatinib, in combination with capecitabine is indicated 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 and taxanes and trastuzumab in the metastatic setting."

A conditional marketing authorisation is granted where the risk-benefit balance of the product is positive but a continued authorisation is dependent on supplying more comprehensive data which confirm this positive risk-benefit. Such a marketing authorisation fulfils an unmet medical need and the benefit to public health of the immediate availability of the conditionally authorised product outweigh the risks inherent in the fact that additional data are still required. In the case of lapatinib, the following conditions are to be met before the product may be granted a 'marketing authorisation not subject to specific obligations'.

1. To perform and submit an updated analysis of survival data for study EGF100151.
2. To conduct a Phase III randomised, controlled clinical study to evaluate the incidence of brain metastases as the site of relapse with a lapatinib-containing therapy compared with an appropriate, trastuzumab-containing control arm.

Condition 1 was fulfilled by supplying overall survival data with an October 2008 cut-off date in the data package submitted to the CHMP as part of a renewal application towards the end of 2008. These data are discussed more fully in sections 3.2 and 3.4.2 of this submission.

A study to fulfil condition 2 is underway and due to report in 2013. The study (EGF111438) is a phase III, randomised, multicentre, open-label study of lapatinib plus capecitabine versus trastuzumab plus capecitabine in patients with anthracycline- or taxane- exposed ErbB2-positive metastatic breast cancer. A number of centres within the UK are participating in this study.

Renewal Application

Conditional marketing authorisations are subject to a re-evaluation of the risk-benefit profile on a yearly basis. This is accomplished by yearly renewal applications to be submitted to the EMEA at least six months prior to the anniversary of licence grant.

In the case of lapatinib, the first renewal application was submitted in November 2008 and authorised by way of Commission Decision on 23 March 2009. The CHMP considered that the risk-benefit profile of lapatinib was unchanged and the Summary of Product Characteristics (SmPC) was not altered.

Clinical Variation Applications

In November 2008, a variation submission was made which updated section 5.3 of the SmPC with animal carcinogenicity data. The Commission Decision for this variation was dated 26 February 2009 and the updated SmPC is provided with this submission.

In March 2009, a variation was submitted which proposed the following new indication for lapatinib:

'Lapatinib in combination with an aromatase inhibitor is indicated for the treatment of patients with hormone receptor-positive metastatic breast cancer which overexpresses the ErbB2 (HER2) receptor'.

This indication is supported by the results of study EGF30008 and is the subject of a proposed NICE multiple technology appraisal (MTA). [redacted]. It is likely that the size of the indicated population is well under 1,000 patients.

Periodic Safety Update Report (PSUR)

A Periodic Safety Update Report for lapatinib covering the period 13 September 2008 to 12 March 2009 was provided to the EMEA on 7th May 2009. A summary is provided in Appendix 1. This confirms that the benefit/risk profile of lapatinib in combination with capecitabine for metastatic breast cancer continues to be favourable.

3. Updated Overall Survival data from EGF100151

Summary points:

- Unadjusted analyses of OS (conducted with 03 April 2006, 28 Sept 2007 and 01 Oct 2008 cut-offs) from EGF100151 consistently demonstrate a survival benefit in favour of lapatinib plus capecitabine compared with capecitabine alone, albeit statistically non-significant, with the difference in median OS increasing with each data cut (0.25 months, p=0.177; 1.9 months, p=0.3; 2.4 months, p=0.210, respectively).
- The ability of study EGF100151 to demonstrate a statistically significant difference in OS between treatment groups has been impacted by the premature halt to enrolment resulting in a lower number of patients recruited than planned and crossover of patients randomised to capecitabine monotherapy to lapatinib combination therapy.
- The results of several analyses conducted to evaluate the effect of crossover (using latest Oct 2008 data) confirm that it has attenuated the OS benefit observed for lapatinib plus capecitabine over capecitabine alone. Each of the Kaplan-Meier and Cox regression methods found a greater reduction in risk for death (HRs of 0.75 to 0.82) than observed in the unadjusted analysis (HR 0.87).
- The adjusted increases in median OS for lapatinib plus capecitabine vs. capecitabine alone in the Kaplan-Meier analyses were 4.3 months (p=0.023; HR 0.78 [0.62, 0.97]) when patients who crossed over were excluded and 2.9 months (p=0.074; HR 0.82 [0.66, 1.02]) when patients who crossed over were censored at the time of crossover.
- The adjusted HRs for the treatment effect in the Cox regression analyses (from which direct estimation of medians is practically unfeasible) demonstrate a clinically relevant reduction in risk of death for patients treated with lapatinib plus capecitabine with upper limits of the CIs of <1 and p-values that are highly statistically significant (0.75 [0.60, 0.94], p=0.013; 0.80 [0.64,0.99], p=0.043, with and without the inclusion of baseline prognostic factors, respectively).
- In analyses based on a Weibull survival model, the gains in expected and median OS for combination vs. monotherapy adjusted for baseline prognostic factors were 3.8 months (95% CI -0.4, 8.6) and 3.3 months (0.6, 6.8) respectively. The gains in expected and median OS without adjusting for baseline factors were 3.0 months (-1.1, 7.8) and 2.7 months (0.1, 6.0), respectively.
- Use of crossover as a time dependent covariate adjusting for baseline prognostic factors is, in GSK's view, the most appropriate method to adjust for crossover. It is highly relevant that the estimated difference in OS is less than three months in one of two analyses where baseline covariates are not included, and when the difference is calculated based on the median.
- Taken together these data indicate a survival benefit for lapatinib plus capecitabine over capecitabine alone approximating to or exceeding 3-months; therefore it is reasonable to expect that lapatinib, given in combination with capecitabine, offers an extension to life of at least 3 months meeting the requirement set out in the Supplementary Advice.

Introduction

The focus of this new submission for lapatinib's consideration under the Supplementary Advice on appraising end of life medicines is the latest overall survival (OS) data (01 October 2008 cut-off) for the ITT population of patients in the pivotal lapatinib study (EGF100151) together with analyses conducted to adjust for the impact of the crossover occurring following the halt to study enrolment. Relevant details of the data provided previously to NICE are summarised in Appendix 2.

Details of several post hoc sub-group analyses of EGF100151 conducted to explore the effect of prior treatment on outcomes are summarised in section 4.1 and

presented in more detail in Appendix 3. Results of one of these sub-group analyses have been provided to NICE previously; the other two have been conducted subsequently to further explore the impact of prior trastuzumab-based regimens.

Efficacy and safety results from the Lapatinib Expanded Access Programme (LEAP; EGF103659) in which lapatinib plus capecitabine was administered to a population similar to the eligible population are summarised in section 4.2 and presented in full in Appendix 4.

3.1 EGF100151 Study background

EGF100151 was a pivotal, phase III, randomised, multicentre, parallel group study evaluating the combination of lapatinib plus capecitabine versus capecitabine alone in women with HER2-positive advanced or metastatic breast cancer who had received prior therapy which included an anthracycline, a taxane and trastuzumab. Trastuzumab must have been administered for at least 6 weeks in the locally advanced/metastatic setting.

Full details of the design and methodology of this trial were provided in section 5.3.1 of GSK's original submission to NICE for lapatinib (17 April 2007).

It is important to note that recruitment to EGF100151 was halted prematurely on the recommendation of the Independent Data Monitoring Committee (IDMC) due to a statistically significant and clinically meaningful improvement in the primary endpoint of independently-assessed time to progression (TTP) seen for patients receiving lapatinib plus capecitabine compared with capecitabine alone at a pre-planned interim analysis, which met the pre-defined stopping criteria.

When the study was stopped on 03 April 2006, 399 patients of a planned 528-patient target had been enrolled in the study. An additional 9 patients who were in screening at this time point were allowed to enrol on the lapatinib plus capecitabine arm. Patients receiving capecitabine alone were offered the option of switching to receive lapatinib plus capecitabine. There was no biased selection in the crossing of capecitabine patients as the majority (36) of 39 patients who were still on capecitabine monotherapy took the opportunity to switch to combination therapy, of whom 26 crossed over prior to disease progression.

Although the study was originally designed with 80% power to detect a 30% increase in median OS between treatment groups, this has been impacted by the early closure resulting in a lower number of patients recruited than planned as well as the confounding effect of the crossover from capecitabine monotherapy to lapatinib plus capecitabine combination therapy

3.2 Methodology for dealing with effect of crossover

As crossover occurred only on the control (capecitabine monotherapy) arm, this has the potential to confound (dilute) the observed effect of treatment on overall survival. A component of the OS benefit attributed to capecitabine may have been influenced by the benefit of lapatinib because, for the purposes of ITT analysis, those patients who crossed over are treated as being in the capecitabine monotherapy group to which they were originally randomised.

Fifty-five percent of patients who opted for crossover had longer exposure to lapatinib plus capecitabine than to capecitabine monotherapy (see section 3.4.3), thereby potentially exacerbating this confounding effect. For 26 patients, crossover was introduced before progression, which may have had an earlier, and perhaps more

profound, effect on the survival results. Additionally with longer follow-up on overall survival, the effect of cross-over is increased.

The Supplementary Advice specifies that Appraisal Committees should be satisfied that estimates of any extension to life are robust, and can be shown or reasonably inferred from either progression free survival or overall survival, taking account of trials in which cross-over has occurred and been accounted for in the effectiveness review. There is no universally accepted methodology to adjust for the confounding effects of crossover from control to active treatment in an analysis of OS from a randomised controlled trial, so several approaches were therefore considered to evaluate the impact of this effect in EGF100151 using the latest OS data (01 October 2008 cut-off).

a. Kaplan-Meier analysis excluding all subjects who crossed over

This is an analysis where any subject who crossed over was removed from the analysis, so the comparison is between subjects randomised to lapatinib plus capecitabine (n=198) and those randomised to capecitabine alone who did not crossover (n=165).

This method may bias outcomes in favour of lapatinib plus capecitabine as it systematically removes longer surviving patients from the capecitabine arm i.e. whilst it excludes any benefit these subjects may have received from combination therapy, it discounts the benefit these subjects may have received from capecitabine alone prior to crossover.

b. Kaplan-Meier analysis censoring crossover patients at time of crossover

This is an analysis where any subject who crossed over is censored at the date of crossover. For all other subjects, OS is measured from time of randomisation to death or last contact.

This analysis reflects the benefits these subjects received from capecitabine monotherapy; however, it is a conservative analysis as it ignores the fact that subjects could have died soon after crossover. Additionally, this analysis does not account for the time on lapatinib plus capecitabine.

Censoring has been used to adjust for crossover and/or post-study therapy in survival analysis (Escudier 2009; Motzer 2009) and has been accepted as an appropriate practice in previous NICE appraisals (TA 169 2009).

c. Kaplan-Meier analysis treating crossover as an event

GSK did not conduct an analysis considering crossover as an event as such an analysis would potentially highly favour the lapatinib plus capecitabine arm.

d. Cox regression analysis considering crossover as a time-dependent covariate

Further analyses were conducted considering cross-over as a time-dependent covariate with and without the inclusion of baseline prognostic factors.

GSK believe that the use of crossover as a time-dependent covariate is the most appropriate methodology to adjust for crossover effects because it accounts for both time on capecitabine as well as time on lapatinib plus capecitabine. Unlike the first analysis (a), it does not exclude the effect of capecitabine on the overall survival of patients who crossed over to the lapatinib combination arm.

It should be noted that it is not practically feasible to obtain directly Kaplan-Meier estimates of median OS from Cox regression models with time-dependent covariates and therefore the treatment effect can only be represented by hazard ratios.

di) Without the inclusion of baseline prognostic variables

This is a Cox regression model where crossover is treated as a time-dependent covariate. This analysis adjusts the hazard ratio for the effect of the crossover. Patients are modelled in one of two states over time: the first state represents the arm to which the patient was randomised; the second states represents crossover to lapatinib plus capecitabine. This model reflects the time at which the patient changed from capecitabine treatment to treatment with lapatinib and capecitabine. The hazard up to the time point of crossover for patients in the capecitabine group is due to capecitabine monotherapy. The hazard from the time the patient crossed over to lapatinib plus capecitabine is due to combination therapy.

dii) With the inclusion of baseline prognostic variables

Because patients in the monotherapy group crossed over, the protocol specified analysis of OS may therefore be confounded. In addition baseline prognostic factors may influence survival outcomes. In order to control for this and isolate the pure treatment effect on OS, a further Cox regression analysis was conducted which included crossover as a time dependent covariate along with a number of baseline prognostic factors. This analysis has therefore been used to form the base case in the economic evaluation because it adjusts for both the confounding effects of crossover and the influence of baseline prognostic factors.

The prognostic factors that were included in this analysis (number of metastatic sites; ECOG performance status; presence/absence of liver metastases) had been identified as having a significant impact on OS in the presence of treatment in a previous Cox regression analysis on survival in the EGF100151 study (EMEA, Tyverb EPAR 2008).

e. Analyses based on Weilbull survival model

The model employed in the economic evaluation (see section 5.2) was used to generate estimates of the gain in expected and median OS with lapatinib plus capecitabine combination therapy versus capecitabine monotherapy using HRs obtained from methods d(i) and d(ii) described above to control for confounding by cross-over. To accomplish this, a Weibull survival distribution model was fitted to the 01 October 2008 OS data for the lapatinib plus capecitabine arm using accelerated failure time regression. OS for the capecitabine monotherapy arm was then calculated by applying the estimated HR for monotherapy versus combination therapy (equal to the inverse of the HR for combination therapy versus monotherapy) obtained from analysis (d) described above to the OS for the combination therapy arm. The difference between groups in the estimated mean (i.e. expected) and median OS was then calculated. It should be noted that the Weibull model was fitted to OS for the combination therapy first rather than to the monotherapy arm (as was done in prior analyses) because the combination therapy arm was not confounded by cross-over.

3.3 Baseline characteristics

Baseline characteristics for the two treatment groups in EGF100151 (n=399, as of 03 April 2006) have been provided to NICE previously and are also presented in

Appendix 1 to this submission (Table 1.1). The two groups were well matched in terms of demographic and disease characteristics. The severity of the population is evidenced by the fact that almost all patients had stage IV disease and over 60% had both visceral and non-visceral involvement. Approximately 75% of patients had received multiple (≥3) lines of prior anti-cancer treatments, further demonstrating the late-stage nature of this population.

The addition of the 9 patients (giving a total ITT population, n=408) who were in screening as of 03 April 2006 did not alter the baseline characteristics of the lapatinib plus capecitabine group to which they were then enrolled.

The baseline prognostic factors for patients who crossed over to lapatinib plus capecitabine were generally similar to those of patients on capecitabine alone who did not cross over with some small imbalances (Table 3.1). The group who did not cross over had slightly more patients with visceral involvement, an ECOG PS of 1, liver metastases and hormone receptor negative (HR-) disease and a shorter time from diagnosis than the crossover group.

Table 3.1: Summary of prognostic factors between crossover and non-crossover patients in capecitabine group (ITT population, 01 October 2008 cut-off)

		Capecitabine non-crossover (n=165)	**Capecitabine crossover** (n=36)
Age (years)	Mean (SD)	51.9 (10.45)	49.6 (9.73)
	Median (range)	51.0 (28-83)	51.0 (30-75)
Baseline disease stage, n (%)	Stage IV	158 (96%)	35 (97%)
	Stage IIIb / IIIc	7 (4%)	1 (3%)
Site of baseline disease, n (%)	Visceral	132 (80%)	26 (72%)
	Non-visceral	33 (20%)	10 (28%)
ECOG performance status, n (%)	1	65 (39%)	12 (33%)
	0	93 (56%)	24 (67%)
	unknown	7 (4%)	0
Number of metastatic sites, n (%)	≥ 3	81 (49%)	15 (42%)
	<3	84 (51%)	21 (58%)
Liver metastases at baseline, n (%)	Yes	87 (53%)	15 (42%)
	No	78 (47%)	21 (58%)
Hormone receptor status, n (%)	ER- and/or PR-	85 (52%)	16 (44%)
	ER+ and/or PR+	75 (45%)	18 (50%)
	Unknown	5 (3%)	2 (6%)
Number of prior regimens, n (%)	≥ 3	132 (80%)	32 (89%)
	<3	33 (20%)	4 (11%)
Time from last dose of trastuzumab, n (%)	>8 weeks	67 (41%)	10 (22%)
	≤8 weeks	92 (56%)	25 (69%)
	Unknown	6 (4%)	1 (3%)
Time from metastatic diagnosis (years) , n (%)	Mean (SD)	1.9 (1.65)	2.4 (1.42)
	Median (range)	1.5 (0-8)	2.3 (0-6)
Time from diagnosis (years)	Mean (SD)	4.7 (3.53)	5.9 (3.53)
	Median (range)	3.8 (0-19)	5.3 (1-16)

3.4 Results

3.4.1 Previous OS results

Table 3.2 summarises analyses of OS data conducted with cut-off dates of 03 April 2006 and 28 Sept 2007, both of which have been provided to NICE previously.

Table 3.2: Summary of results for previous OS analyses for EGF100151 (ITT population)

Dataset cut-off date No. subjects/no. events	Description	Median overall survival (weeks) (95% CI)		Difference in median OS (weeks/months)	Hazard ratio (95% CI)	Log rank 2-sided p-value
		Lapatinib + capecitabine N=198	Capecitabine N=201			
03 April 2006 399 / 119	Protocol-specified ITT	67.7 (58.9, 91.6)	66.6 (49.1, 75.0)	1.1 / 0.25	0.78 (0.55, 1.12)	0.177
28 Sept 2007† 408* / 302	Protocol-specified ITT	74.0 (65.3, 84.9)	65.9 (53.4, 75.0)	8.1 / 1.86	0.9 (0.71, 1.12)	0.3

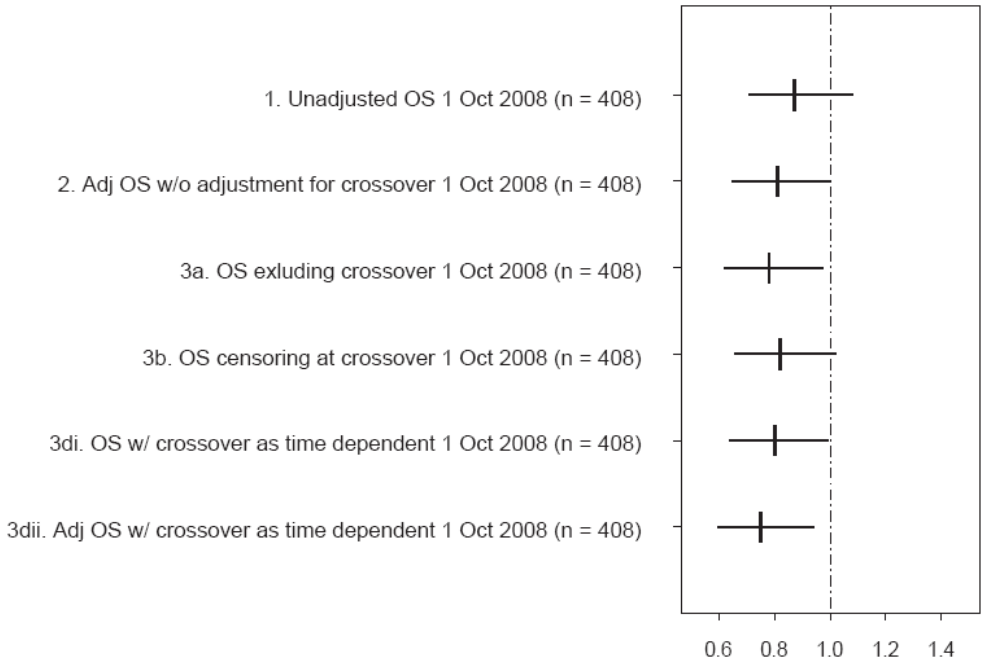
* A total of 408 patients are included in this analysis – an additional 9 patients were in screening at the April 2006 cut-off date; these were all enrolled on the lapatinib plus capecitabine combination.
† n=36 of 39 patients on capecitabine monotherapy at the 03 April 2006 cut-off crossed over to receive lapatinib in addition to capecitabine

3.4.2 Latest OS results (01 October 2008 cut-off)

Analyses of survival data, both unadjusted and adjusted for crossover, updated to a data cut-off date of 01 October 2008 are summarised in the forest plot (Figure 1) and then presented sequentially. (Note: The numbering of each of the analyses on the plot corresponds with their full presentation in this section).

The results are consistent regardless of the methodology and demonstrate some attenuation of the OS benefit seen for lapatinib plus capecitabine versus capecitabine due to the effects of the crossover.

Figure 1: Hazard ratio and 95% CIs for OS analysis adjusting for crossover (01 October 2008 cut-off)



1. Unadjusted OS

As of 01 October 2008, 340 deaths out of 408 patients had been observed, representing 83% of events. The median survival is 64.7 weeks for capecitabine alone compared with 75.0 weeks for lapatinib plus capecitabine, a difference of 10.3 weeks (2.4 months).

Table 3.3: Summary of overall survival (ITT population, 01 October 2008 cut-off)

Outcome Measure	Lapatinib + Capecitabine (N=207)*	Capecitabine (N=201)*	Difference in median OS (weeks/ months)	Hazard Ratio (95% CI)	Log-rank 2-sided p-value
Deaths Censored, follow-up ended Censored, follow-up ongoing	168 (81%) 7 (3%) 32 (15%)	172 (86%) 7 (3%) 22 (11%)	-	-	-
Median Overall Survival† (weeks) (95% CI)	75.0 (65.3, 85.6)	64.7 (53.3, 74.4)	10.3 / 2.37	0.87 (0.71, 1.08)	0.210

Evaluating OS over the sequential data cuts shows a clear upwards shift in the medians for the lapatinib plus capecitabine arm while the medians in the capecitabine arm have decreased slightly, resulting in a 2.4 month difference for the October 2008 cut-off compared with 1.9 months for the September 2007 cut-off and 0.25 months for the April 2006 cut-off. The hazard ratio has improved slightly in the October 2008 analysis compared with the September 2007 analysis, although the difference remains non-significant.

Nevertheless, these analyses consistently suggest a benefit (statistically non-significant) for lapatinib in combination with capecitabine compared with capecitabine alone. As previously explained, whilst the study was powered to detect a significant OS benefit as a secondary endpoint, premature closure to enrolment and crossover of patients who received capecitabine monotherapy has resulted in insufficient power

to demonstrate the planned 30% improvement in OS.

2. OS adjusted for baseline prognostic factors (unadjusted for crossover)

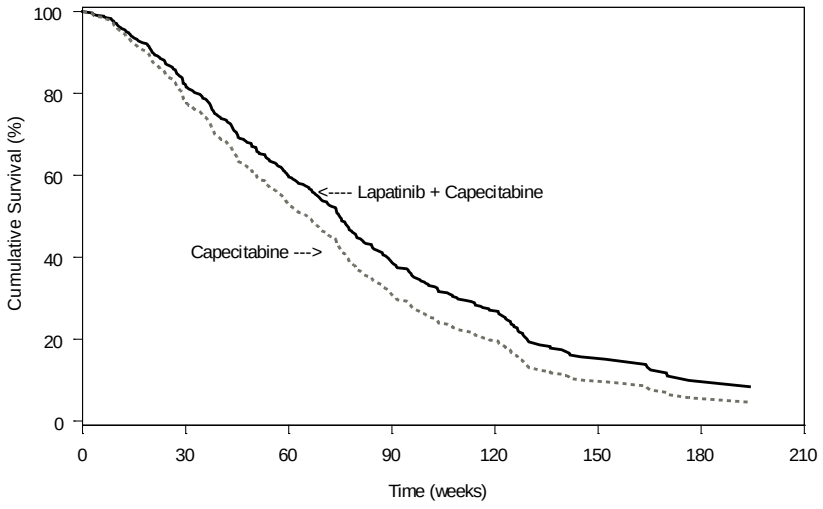
A Cox regression model is a well accepted methodology and has been used to evaluate the effect of various baseline prognostic factors on OS in the EGF100151 study. In addition to retaining the treatment group in the model, the same baseline prognostic factors (i.e. number of sites of disease; ECOG performance status; presence/absence of liver metastases) were identified as having a significant impact on OS in EGF100151 for the 01 October 2008 data set, as for the earlier data sets. The adjusted HR of 0.81 (p=0.051) indicates a 19% reduction in risk of death for patients treated with lapatinib plus capecitabine versus capecitabine alone. The adjusted Kaplan-Meier curves (Figure 2) considering these main effect terms show that the survival benefit is maintained over time in the combination arm.

Table 3.4: Summary of Cox regression model for overall survival (ITT population, 01 October 2008 cut-off)

Covariate	Effect Tested	HR [95% CI]	P-value
Treatment Group	Lapatinib+Capecitabine/ Capecitabine	0.81 [0.65, 1.00)	0.051
Number of Metastatic sites	< 3 sites / ≥ 3 sites	0.64 [0.51,0.79]	<0.001
ECOG Performance Status	0/ ≥1	0.56 [0.45, 0.70]	<0.001
Liver Metastases	No/ Yes	0.52 [0.41, 0.65]	<0.001

HR <1 indicates a lower risk.

Figure 2: Adjusted overall survival curve (ITT population, 01 October 2008 cut-off)



Adjusted for ECOG performance status, number of metaststic sites, and liver metastases

3. Analyses conducted to account for impact of crossover

For patients who crossed over, median time on capecitabine treatment to crossover was 17.7 weeks. Median time on lapatinib plus capecitabine following crossover was 20.0 weeks. Results of the various analyses conducted to adjust for the confounding effect of crossover (see section 3.2 for further details of the methodologies employed) are presented below.

(a) Kaplan-Meier analysis excluding all subjects who crossed over

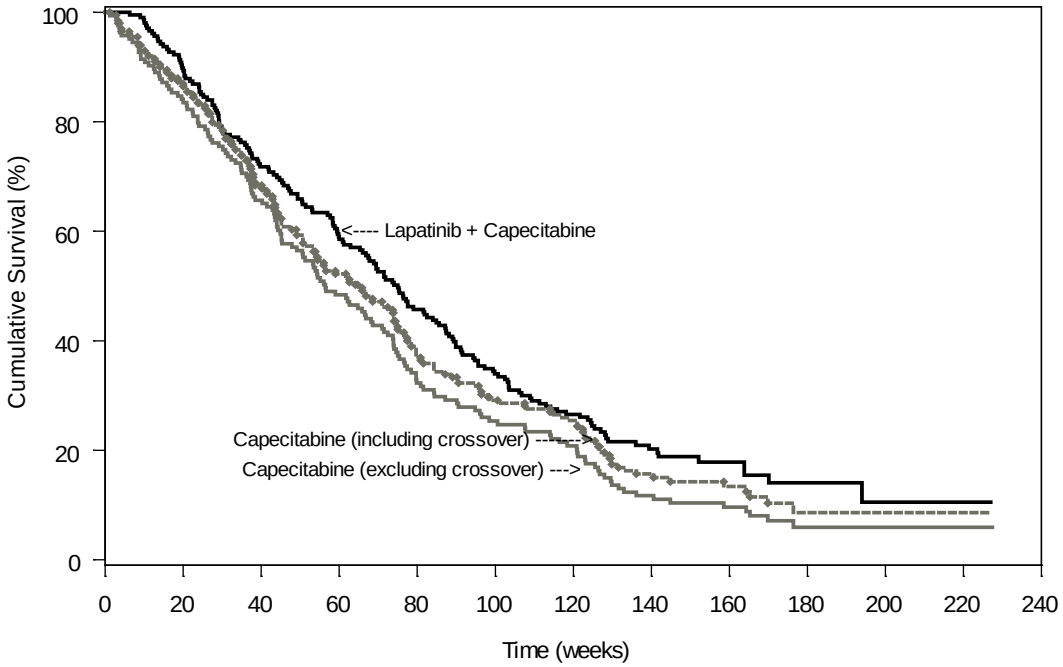
Exclusion of patients from the analysis resulted in a significant 4.3 month-improvement in OS in the combination arm compared with the monotherapy arm (Table 3.5). Figure 3 provides the corresponding Kaplan-Meier curves. These illustrate the confounding effect of the crossover on the OS analysis. The benefit of lapatinib plus capecitabine over capecitabine with respect to OS is demonstrated by the HR of 0.78 (p=0.023).

Table 3.5: Results of OS analysis excluding subjects who crossed over (01 October 2008 cut-off)

Outcome Measure	Lapatinib + Capecitabine (N=207)	Capecitabine (N=165)*	Difference in median OS (weeks/ months)	Hazard Ratio (95% CI)	Log-rank 2-sided p-value
Median Overall Survival (weeks)	75.0	56.4	18.6 / 4.27	0.78 (0.62, 0.97)	0.023

* excludes 36 patients who crossed over to lapatinib plus capecitabine

Figure 3: Kaplan-Meier estimates of overall survival including and excluding the crossover subjects (01 October 2008)



(b) Kaplan-Meier analysis censoring crossover patients at time of crossover

Censoring patients at time of crossover resulted in a trend towards an improvement in OS for patients randomly assigned to lapatinib plus capecitabine compared with capecitabine alone (HR 0.82; p=0.074).

Table 3.6: Results of OS analysis censoring crossover patients at time of crossover (01 October 2008 cut-off)

Outcome Measure	Lapatinib + Capecitabine (N=207)	Capecitabine (N=201)	Difference in median OS (weeks/ months)	Hazard Ratio (95% CI)	Log-rank 2-sided p-value
Median Overall Survival (weeks)	75.0	62.6	12.4 / 2.85	0.82 (0.66, 1.02)	0.074

(c) Kaplan-Meier analysis treating crossover as an event

As explained in section 3.2, this was not conducted due to the potential to highly favour the lapatinib plus capecitabine arm.

(d) Considering crossover as a time-dependent covariate

i) Without the inclusion of baseline prognostic variables

When crossover was used as a time-dependent covariate, the HR for the crossover effect was less than unity (0.63), which indicates that as patients crossed over from capecitabine to lapatinib plus capecitabine their risk of death was reduced (Table 3.7). The HR for the treatment effect indicates a clinically-relevant 20% reduction in the risk of death for patients in the combination arm (p=0.043).

Table 3.7: Summary of Cox regression model for overall survival considering crossover as a time-dependent covariate (ITT population, 01 October 2008 cut-off)

Covariate	Effect Tested	HR [95% CI][1]	P-value
Treatment Group	Lapatinib + Capecitabine/ Capecitabine	0.80 [0.64,0.99]	0.043
Time-dependent Crossover	Crossover/ Not Crossed Over	0.63 [0.41,0.98]	0.042

HR <1 indicates a lower risk

ii) With the inclusion of baseline prognostic variables

The results of the Cox regression model considering crossover as a time-dependent covariate and including the three baseline prognostic factors identified previously are presented in Table 3.8. The adjusted HR for the treatment effect (0.75) demonstrates a survival benefit for the combination with an upper limit of the confidence interval of 0.94 and a p-value which is statistically significant (p=0.013).

Table 3.8: Summary of Cox regression model incorporating effect of crossover as a time-dependent covariate and baseline prognostic factors (ITT population, 01 October 2008 cut-off)

Covariate	Effect Tested	HR [95% CI]	P-value
Treatment Group	Lapatinib + Capecitabine/ Capecitabine	0.75 [0.60,0.94]	0.013
ECOG Performance Status	0/ ≥1	0.55 [0.44,0.69]	<0.001
Liver Metastases	No/ Yes	0.52 [0.42,0.65]	<0.001
Number of Metastatic sites	< 3 sites / ≥ 3 sites	0.64 [0.51, 0.80]	<0.001
Time-dependent Crossover	Crossover/ Not Crossed Over	0.65 [0.41,1.01]	0.054

HR <1 indicates a lower risk

As mentioned in section 3.2, it is not possible to obtain to obtain Kaplan-Meier estimates of median OS from Cox regression models with time-dependent covariates.

(e) Analyses based on Weibull survival model

Results of the analyses conducted with crossover as a time-dependent covariate using a Weibull survival model to estimate the expected and median survival are shown in Table 3.9. The gains in expected and median OS for combination vs. monotherapy adjusted for baseline prognostic factors were 3.8 months (95% CI -0.4, 8.6) and 3.3 months (0.6, 6.8) respectively. The gains in expected and median overall survival without adjusting for baseline factors were 3.0 months (-1.1, 7.8) and 2.7 months (0.1, 6.0), respectively.

Table 3.9: Expected and median OS by treatment group based on economic modelling using a different method to calculate the hazard ratio for lapatinib plus capecitabine vs. capecitabine monotherapy (01 October 2008 data set)

Method to Estimate HR	Adjustment		HR L+C vs C-only	Expected OS (Months)*			Median OS (Months)*		
	Baseline Factors	Cross-Over		L+C	C	Δ (95% CI)	L+C	C	Δ (95% CI)
Cox regression analysis	No	Cross-over as time dependent covariate	0.80	20.7	17.7	3.0 (-1.1, 7.8)	17.5	14.8	2.7 (0.1, 6.0)
Cox regression analysis	Yes	Cross-over as time dependent covariate	0.75	20.7	16.9	3.8 (-0.4, 8.6)	17.5	14.2	3.3 (0.6, 6.8)

* Undiscounted values

It is important to consider the merits of using expected OS as the measure that best reflects overall survival, rather than median survival. Kaplan-Meier estimated median survival is one of the most frequently reported summary statistics in studies of cancer treatments (Michiels 2005). Median survival is often considered a better measure of central tendency than the mean because medians reduce the influence of outliers. However, differences in Kaplan-Meier estimated median survival may not be the most appropriate measure to assess the potential benefits of lapatinib on survival, for several reasons:

It may be practical to use the difference in Kaplan-Meier estimated median survival times to approximate gains in life expectancy, because mean survival estimates from Kaplan-Meier analyses are biased if the last failure time is censored. However, median survival estimated using Kaplan-Meier methods may be imprecise as it does not reflect any survival data beyond the median failure time. Furthermore, Kaplan-Meier estimated median survival times reflect only a single point on the survival distribution curve. Differences in survival times may vary across the percentiles of survival, and approximation of the gain in life expectancy based on the difference in survival times at the median (50th percentile) is arbitrary.

As discussed earlier, use of crossover as a time dependent covariate adjusting for baseline prognostic factors is, in GSK's view, the most appropriate method to adjust for crossover. It is highly relevant that the estimated difference in OS is less than three months only when baseline covariates are not included and when the difference is calculated based on the median.

3.4.3 Other endpoints in EGF100151

Results for all other endpoints for the ITT population in EGF100151 have been provided to NICE previously and are summarised in Appendix 2 of this submission.

3.5 Summary of updated survival data

The trend towards improved survival observed with lapatinib plus capecitabine compared with capecitabine alone in the 03 April 2006 and 28 September 2007 analyses is confirmed in the updated analysis of survival to 01 October 2008. Examining the data sequentially shows an increase in the difference in median OS between treatment groups with time (0.25 months, 1.9 months and 2.4 months, for the respective data sets). There is an improvement in the HR in the Oct 2008 compared with the Sept 2007 dataset, although it remains statistically non-significant. However, these analyses fail to represent the true benefits from treatment with lapatinib plus capecitabine because no account is made for the crossover.

There is no optimal way to adjust for the confounding effects of crossover in survival analysis and several methods were used to evaluate this effect. The Kaplan-Meier and Cox regression analyses demonstrate that crossover does indeed impact survival, as evidenced by the shift in HRs and CIs. Each method found a greater reduction in risk for death with lapatinib plus capecitabine compared with capecitabine alone than observed in the unadjusted analysis (HRs of 0.75 to 0.82 vs. 0.87; Figure 1).

The adjusted increases in median OS with the addition of lapatinib in the Kaplan-Meier analyses were 4.3 months (p=0.023, HR 0.78) when patients who crossed over were excluded and 2.9 months (p=0.074, HR 0.82) when patients who crossed over were censored at the time of crossover.

Estimation of medians directly from Cox regression models with time-dependent variables is practically infeasible. However, in both the analyses with and without the inclusion of baseline factors, the adjusted HRs for the treatment effect demonstrate a clinically-relevant reduction in risk of death for patients treated with lapatinib plus capecitabine with upper limits of the CIs of less than 1, and p-values that are statistically significant (0.75 [0.60, 0.94], p=0.013; 0.80 [0.64,0.99], p=0.043, respectively).

In analyses using a Weibull survival model and HRs based on the Cox model with censoring as a time-dependent variable, the gains in expected and median OS for combination vs. monotherapy adjusted for baseline prognostic factors (which we consider to be the most appropriate estimate of overall survival adjusting for crossover) were 3.8 months (95% CI -0.4, 8.6) and 3.3 months (0.6, 6.8) respectively. The gains in expected and median overall survival without adjusting for baseline factors were 3.0 months (-1.1, 7.8) and 2.7 months (0.1, 6.0), respectively.

The above data indicate a survival benefit for lapatinib plus capecitabine over capecitabine alone approximating or exceeding 3 months. Indeed the estimate which we consider is the most reflective of survival in the indicated population when crossover is taken into account suggests that the expected overall survival gain could be as high as 3.8 months. Whilst the alternative analyses to account for the impact of crossover did not consistently achieve an OS gain of 3 months or more (i.e. simple censoring in a Kaplan-Meier analysis; Cox regression treating crossover as a time dependent covariate without accounting for baseline prognostic factors) these methods do not adequately account for the confounding effects of crossover.

Similarly, the estimate of 4.3 months OS gain from the method of excluding patients who crossed over is not a robust reflection of the impact of crossover.

It is highly relevant that in the analysis that adjusts for both crossover and baseline prognostic factors, both the expected and median OS estimated using a Weibull survival model were over 3 months. It is therefore reasonable to expect that lapatinib, given in combination with capecitabine, offers an extension to life of at least 3 months compared with standard treatment, thereby meeting the requirement set out in NICE's Supplementary Advice.

4. Additional considerations for lapatinib

Summary points:

- A number of *post hoc* subgroup analyses were conducted on EGF100151 to explore the effect of prior treatment on outcomes. These support the findings in the total trial population but also indicate that the efficacy of lapatinib plus capecitabine may be greater when given earlier in the treatment pathway.
- Gains in median OS of 7.4 months (HR 0.51, p=0.009), 3.4 months (HR 0.79, p=0.077) and 7.3 months (HR 0.63, p=0.042) were found in sub-groups of patients who had received 1 or 2 prior regimens (n=66), 1 prior metastatic trastuzumab-based regimen (n=253), and were second-line to a metastatic trastuzumab-based regimen (n=91), respectively, exceeding the 3-month criterion.
- The lapatinib expanded access programme (LEAP) provides evidence of the clinical benefit and tolerability of lapatinib plus capecitabine in a population more inclusive than the EGF100151 population.
- LEAP demonstrates the efficacy of lapatinib plus capecitabine in patients with progressive brain metastases following whole brain radiotherapy and trastuzumab, a population with a very poor prognosis and high unmet need.
- As an all-oral regimen, there is no requirement for patients receiving lapatinib plus capecitabine to attend hospital for treatment. An oral option provides benefits for pharmacy and for IV cancer therapy service capacity.

In addition to updated survival data for EGF100151 (presented in section 3), new clinical data for lapatinib plus capecitabine in this indication available since GSK's original submission to NICE include a number of *post hoc* sub-group analyses of the EGF100151 study and results of the Lapatinib Expanded Access Programme (LEAP; EGF103659) conducted with a cut-off of 30 September 2008.

4.1 EGF100151 – Sub-group Analyses

Full details and results of exploratory sub-group analyses conducted on the EGF100151 study are presented in Appendix 3 as supportive data and the key points are summarised below.

The vast majority of patients in EGF100151 had received multiple treatment regimens. Pre-treatment history is a well recognised factor in influencing treatment outcome and treatment decisions are often guided by previous treatments received. These analyses were therefore conducted to investigate the effect of the number of prior treatment regimens, including prior trastuzumab regimens, on TTP and OS in EGF100151. The results support the findings from the ITT population, namely that lapatinib plus capecitabine provides statistically significant and clinically meaningful benefits over capecitabine alone.

Although exploratory, unplanned and with relatively small sample sizes, they also indicate that the efficacy of lapatinib plus capecitabine may be greater when given earlier in the treatment pathway. This is consistent with the literature that the clinical benefit seen with cancer treatments can improve when administered in earlier stages of disease. Introducing lapatinib plus capecitabine after 1 or 2 prior lines of treatment or after only 1 line of prior trastuzumab-containing therapy appeared to be associated with a greater magnitude of effect in delaying disease progression than if introduced following at least 3 prior regimens or after more than 1 metastatic trastuzumab-based regimen, respectively. [Tables 3.4 and 4.6, Appendix 4]

In patients who received 1 or 2 prior regimens (n=68), there was a 7.4 month benefit in median OS for patients receiving the lapatinib-containing regimen compared to capecitabine alone, which was highly statistically significant (HR 0.51, p=0.009). In a sub-group of patients who received lapatinib and capecitabine as a second-line therapy to a first-line trastuzumab-based regimen in the metastatic setting (n=91), there was a statistically significant 7.3 month increase in median OS over capecitabine alone (HR 0.63, p=0.042). In a larger sub-group of subjects who received 1 prior metastatic trastuzumab-containing regimen (n=257), there was an improvement in median OS of 3.4 months for the lapatinib combination group, with a trend towards statistical significance (HR 0.79; p=0.077). [Tables 3.5, 3.7, 3.9, Appendix 3, respectively]

The use of lapatinib in combination with capecitabine in these sub-populations clearly meets the requirement for a treatment to offer an extension to life of at least 3 months as stipulated in NICE's Supplementary Advice.

The outcomes in the sub-populations with more than 3 prior regimens and more than 1 prior metastatic trastuzumab-based regimen were consistent with the results in the overall population reflecting the fact that many patients in EGF100151 were heavily pre-treated.

4.2 Lapatinib Expanded Access Programme (LEAP; EGF103659)

The methodology and results of LEAP are presented in Appendix 4 as supportive data and the key findings are summarised below.

LEAP is the largest expanded access programme to have been conducted in breast cancer to date involving more than 4,000 patients. The study demonstrates the clinical benefit and tolerability of lapatinib plus capecitabine in a population of patients with HER2+ metastatic breast cancer more inclusive than the EGF100151 study.

The UK was the second highest recruiter to LEAP in Europe. Although the UK joined LEAP later than other countries, uptake was rapid highlighting the unmet need for patients with HER2+ advanced/metastatic breast cancer that has progressed on or following trastuzumab-based therapy.

Although the design of LEAP does not permit formal hypothesis testing, the efficacy data indicate that the median PFS reported for the global and UK (total and cohort) populations was similar to that reported by investigators in the EGF100151 study (approximately 21 weeks and 24 weeks, respectively).

In a cohort of 162 patients treated at 5 LEAP centres in the UK, an overall response rate to lapatinib plus capecitabine of 21% was reported and a clinical benefit rate of 50%, which compare favourably with the EGF100151 study.

It should be noted that patients in LEAP differed from the EGF100151 population in that they were more heavily pre-treated, were allowed an ECOG performance status of up to 2, and were permitted prior capecitabine therapy. This may partially explain a median OS of approximately 40 weeks reported for both the UK and global LEAP data sets compared with 75 weeks in EGF100151 (latest data).

Approximately 40% of patients in LEAP (both globally and in the UK) had received capecitabine previously. Sub-group analysis showed greater efficacy (longer PFS and OS) in patients with no prior capecitabine exposure than in those with prior exposure. Median PFS in patients who had not received prior capecitabine was 23.9 weeks, which is identical to the investigator-assessed median TTP in EGF100151.

LEAP allowed enrolment of patients with brain metastases receiving steroids up to 1.5mg/day of dexamethasone or equivalent whereas only patients with stable metastases (asymptomatic and untreated) were permitted to enter EGF100151. Median TTP and response rates in a subset of 34 patients with brain metastases from 5 lead recruiting centres in UK were comparable to those seen in the whole 162-patient cohort. A clinical benefit rate of 48% is particularly impressive given that 94% of these patients had progressed following whole brain radiotherapy and for most of whom there would have been no further CNS treatment options. These data compare very favourably with previous studies of lapatinib in patients with HER2+ metastatic breast cancer and progressive brain metastases (Lin 2008; Lin 2009).

The safety profile of lapatinib observed in LEAP was consistent with that seen in EGF100151 and other lapatinib clinical trials. The most frequently reported SAEs were gastrointestinal (diarrhoea, nausea and vomiting). The estimated incidence of decreased LVEF was 0.5% which is less than the overall incidence seen in the lapatinib clinical trials programme (1.0%). The incidence of 0.2% for pulmonary events is consistent with the overall incidence across the lapatinib clinical programme. The incidence of serious hepatobiliary events associated with lapatinib was estimated at 0.4%, less than the 1.0% cumulative incidence of such events in the overall trials programme.

Since LEAP was conducted in the context of considerable use of trastuzumab beyond progression, it is possible that implementation of the recent NICE clinical guideline on the management of advanced breast cancer means that trastuzumab may be less readily available to these patients, and lapatinib treatment may be considered at an earlier point in the treatment pathway for the indicated population.

In conclusion, LEAP confirms that lapatinib plus capecitabine is an effective and well tolerated treatment in patients with HER2+ advanced/metastatic breast cancer that has progressed following trastuzumab-containing regimens, including patients with brain metastases, for whom therapeutic options are currently very limited.

Lapatinib offers further benefits which should be considered in the broader context in appraising its suitability for use on the NHS.

4.3 Brain metastases and HER2+ breast cancer

The development of brain metastases – a condition associated with substantial morbidity, mortality and healthcare costs (Pelletier 2008) – is a particularly widespread problem in patients with HER2+ metastatic breast cancer (Lin 2004; Lin 2007). Historically, approximately 10-16% of women with metastatic breast cancer developed clinically apparent brain metastases (Lin 2004). However, between 28 and 43% of patients receiving trastuzumab in the metastatic setting have been reported to relapse with brain metastases (Bendell 2003; Lin 2004), often as first site of progression (Yau 2006). This apparent increase may reflect the inability of trastuzumab, a monoclonal antibody, to pass through the blood-brain barrier (Burstein 2005; Lin 2007; Stemmler 2006). Hence, while trastuzumab effectively controls non-central nervous system (CNS) disease, the CNS becomes a ‘sanctuary site’ (Clayton 2004; Lin 2007).

Conventional treatment for brain metastases has been whole brain radiation therapy (WBRT) or stereotactic radiosurgery (SRS); however, these are associated with significant neurocognitive deficits (Patel 2007). Effective systemic therapy for patients with CNS progression is extremely limited and represents a major challenge and an urgent medical need (Lin 2009). As a small molecule, lapatinib is able to cross the blood-brain-barrier and penetrate the CNS (Van den Abbeele 2006; Gril 2008) and

there is some evidence that it has activity in both treating (Lin 2008; Lin 2009) and the incidence of brain metastases as a first site of relapse (Cameron 2008).

In a post hoc analysis of the EGF100151 study, lapatinib plus capecitabine was found to reduce the incidence of first relapse within the CNS compared with single-agent capecitabine (p=0.0445) (see Appendix 2, section 2.1.4). In the Lapatinib Expanded Access Programme (LEAP), a sub-population of patients with progressive brain metastases following whole brain radiotherapy and trastuzumab within a UK cohort showed favourable response rates to lapatinib plus capecitabine with times to disease progression identical to the whole cohort (see Appendix 4, section 4.4.3).

4.4 Oral regimen

Lapatinib plus capecitabine offers the convenience of an all-oral regimen which can be self-administered by the patient at home, reducing time spent in hospital and the expense and inconvenience of hospital attendance, when compared with intravenous (IV) therapies. This is in line with one of the key themes set out in the Department of Health's recent 'Next Stage Review' report (DoH 2008) that patient care should be provided closer to, or at home, and supports the recommendations in an earlier White Paper: *Our Health, Our Care, Our Say: A New Direction for Community Services* 2006 (DoH 2006), which noted that more care for cancer patients should be provided outside the hospital setting, including in the home where appropriate. The importance of being able to spend time outside of hospital with family and friends cannot be underestimated for these patients whose life expectancy is short.

As an orally-administered regimen, lapatinib plus capecitabine should also help to reduce pressure on hospital-administered IV cancer therapy service capacity as well as on pharmacy workload since there is no need for reconstitution prior to administration. In addition, it presents an option for the administration of an HER2-targeted agent when venous access is difficult and may avoid some of the complications associated with IV cancer therapies.

4.5 Tyverb Patient Access Programme (TPAP)

GSK has made lapatinib available via a patient access programme, designed to facilitate equitable patient access to treatment and to maximise value to the NHS by linking payment for lapatinib to clinical benefit. This was discussed in detail in an addendum to GSK's response to the first Appraisal Committee Decision (ACD) on the Single Technology Appraisal (STA) for lapatinib in this indication in July 2008 and reviewed by the Decision Support Unit (DSU report, 7 September 2008). The TPAP was approved by the Department of Health as an appropriate patient access scheme to be considered by NICE

Under the terms of the patient access programme, the initial cost of lapatinib, up to a maximum of 12 weeks, is borne by GSK. For patients continuing to derive clinical benefit beyond 12 weeks the cost should be funded by the NHS.

GSK believes that the Lapatinib Patient Access Programme should be considered carefully as an additional factor to be taken into account alongside the published criteria when appraising lapatinib.

5 Pharmaco-economic evaluation

Summary Points:

- In the FAD issued by NICE in February 2009 the incremental cost effectiveness ratio for lapatinib plus capecitabine in comparison with capecitabine monotherapy was £93,825 per quality adjusted life year gained (QALY).
- This new economic evaluation incorporates more recent survival data, updated costs, adverse events costs and an improved method to account for the patient crossover in the EGF100151 clinical trial.
- In the new base case analysis the most plausible estimate of cost-effectiveness is £77,996 per QALY for lapatinib plus capecitabine compared with capecitabine monotherapy.
- In accordance with the Supplementary Advice, a utility weighting was applied based on the assumption that the extended survival period is experienced at the full quality of life anticipated for a healthy individual of the same age as the patient population. The cost utility estimate in this scenario is £59,734/QALY.
- The application of the Tyverb Patient Access Programme (TPAP) in addition to the higher utility weighting results in a cost per QALY of £45,524.
- In the above analysis the additional QALY weight required for lapatinib to be cost-effective at a willingness to pay of £30,000 per QALY is a factor of 1.5.
- This factor of 1.5 is within the range previously accepted by NICE when considering end of life medicines.

5.1 Introduction

Within this submission it is shown that lapatinib satisfies the criteria set out in the NICE Supplementary Advice on appraising end of life treatments (sections 1 and 3.5). GSK therefore believe that lapatinib should be considered in the context of the supplementary advice implemented by NICE on 5th January 2009 and updated in July 2009.

The primary impact of the supplementary advice is that it recognises the need for a greater QALY weighting to be applied to the later stages of terminal diseases. The principle is that as patients come towards the end of their life, the value that they attribute to an extension of their life is higher than would be predicted from the calculated QALY. The effect on the cost-effectiveness analysis is that the utility applied to the extended survival period is the same as that anticipated for a healthy individual of the same age. The guidance also includes an evaluation of the additional weighting (i.e. multiplier) that would need to be assigned to the QALY for the cost-effectiveness of the technology to fall within the current ICER threshold range of £20,000 to £30,000.

5.1.1 Presentation of methods and results

The health economics model is similar in construction and methodology to that used by GSK to develop the most plausible estimate of the ICER for the NICE final appraisal determination (FAD) on lapatinib. Modifications that have been made to the model are described in more detail below. They include limiting the comparator to capecitabine monotherapy, updating the costs to 2008 levels, adding the costs of grade 3 plus adverse events in the base case, using the most recent survival data, and modifying the methods used to estimate survival to permit the use of HRs for OS estimated using Cox proportional hazards regression with crossover to lapatinib as a

time-dependent covariate, in order to adjust for the impact of crossover. Some of these modifications were implemented by GSK to address some of the comments made in the FAD.

5.1.2 Outline of primary and secondary analyses

The base case uses the latest data cut-off (October 2008) for overall survival (OS) and progression free survival (PFS) (April 06) from the EGF100151 study. There has been no change to the PFS data since the FAD. The base case analysis includes an adjustment for the effect on OS of patient crossover in the EGF10151 trial and uses a Cox regression model with crossover as a time dependent covariate (including baseline prognostic factors). The other primary analyses are the inclusion of the Tyverb Patient Access Programme (TPAP) to the base case and the application of a higher utility in line with the NICE Supplementary Advice. The secondary analyses are a deterministic sensitivity analyses to explore the impact of using alternative methodologies to account for patient crossover and a cost-effectiveness evaluation of two subgroup populations. One subgroup was patients treated with one or two prior regimes and the other group was patients treated with one prior trastuzumab-based regimen in the metastatic setting.

5.2 Modelling the cost-effectiveness of lapatinib plus capecitabine in the treatment of HER2+ metastatic breast cancer following progression on trastuzumab

5.2.1 Overview of the model

A detailed description of the model is given in the GlaxoSmithKline submission to NICE for lapatinib, 17 April 2007. (There was a subsequent correction to the model as detailed in the addendum to GlaxoSmithKline's response to the lapatinib ACD July 2008.)

5.2.2 Changes to the model

The health economics model used in this submission is similar to that used in the previous submission (GlaxoSmithKline's response to the lapatinib ACD July 2008.) Changes that have been made to the model are as follows:

1) The model used in the previous submission compared the cost-effectiveness of lapatinib plus capecitabine with capecitabine monotherapy, vinorelbine monotherapy, trastuzumab plus capecitabine, and trastuzumab plus vinorelbine, as well as a combined treatment strategy reflecting a weighted average of results for all comparators. The current model considers only capecitabine monotherapy as a comparator.
2) The previous model included the costs of adverse events associated with lapatinib and capecitabine only in a sensitivity analysis. The current model includes the costs of grade 3 plus adverse events associated with these treatments in the base case. This change was in response to concerns raised in the FAD regarding the sensitivity of the analysis to the costs of adverse events.
3) The previous model used 2006 prices and costs. The current model uses 2008 prices and costs. Updated cost estimates are provided in Table 5.1**.** A comparison of the updated costs with those used in the previous submission is included in Appendix 5**.**

4) In the previous model, OS was estimated using data from the September 2007 data cut-off of the EGF100151 trial; the current model uses data from the October 2008 data cut-off.

5) In the previous model, PFS and OS for patients receiving lapatinib plus capecitabine and capecitabine monotherapy were estimated by using parametric accelerated failure time (AFT) regression to fit a proportional hazards (PH) Weibull model to patient-level failure time data for both treatment groups from the EGF100151 trial ('PH Weibull Model'). In the analysis of OS, capecitabine monotherapy patients who crossed over to lapatininb were censored as of the date of crossover.

   While the use of Weibull AFT regression was considered a reasonable approach for estimating expected PFS and OS with combination therapy and monotherapy in EGF100151 in the original submission, this approach is limited in that, unlike Cox regression analysis for which methods for the analysis of time-dependent variables are well established, the validity of methods for the estimation of AFT regressions with time-dependent covariates has not been extensively examined and their implementation has been limited. These methods have only recently been reported (Sparling YH et al: Biostatistics 2006). An effort was made to adapt these algorithms to the EGF100151 data but these attempts failed to yield meaningful parameter estimates. It was therefore deemed unfeasible, within the available timeframe, to estimate a PH Weibull model for OS using a time-dependent covariate to account for patient crossover in the EGF100151 trial.

   To develop projections of OS with crossover included as a time dependent variable, a modification to the model was required ('Modified Model').

   OS for patients receiving combination therapy was obtained by fitting a Weibull survival model to patient-level failure time data for these patients in EGF100151. OS for the monotherapy arm was then calculated by applying to the OS for the combination therapy arm to the estimated HR for monotherapy vs. combination therapy (equal to the inverse of the HR for combination therapy vs. monotherapy) using the following formula: OSM[t]= OSC[t] HR MvC. The HR for monotherapy versus combination therapy was obtained from an adjusted Cox proportional hazards regression analysis with crossover to lapatinib plus capecitabine entered as a time-dependent covariate and baseline prognostic factors (performance status, number of metastatic sites, and presence of liver metastases) included as covariates (HRMvC =1.33, 95%CI 1.06 to 1.67 [HRCvM =0.75, 95%CI 0.60 to 0.94], p=0.013).

   The use of the adjusted Cox model was considered appropriate because crossover to lapatinib was not randomised and comparison of randomised groups controlling for crossover might be confounded by patients' baseline characteristics. For consistency, PFS was estimated using a similar method, although the PFS curve for monotherapy was used as a reference, and PFS for combination therapy was estimated by applying to that the HR for combination therapy vs. monotherapy.

Table 5.1 Summary of model cost parameters

Cost/resource parameter	Phase of treatment		Distribution assumed	Source (year)
	Progression-free – mean cost (standard error)	Post-progression – mean cost (standard error)		
Unit cost lapatinib (per tablet)	£11.49	n/a	n/a	BNF 57 (2009)
Unit cost of capecitabine (per tablet)	£2.46	n/a	n/a	BNF 57 (2009)
Pharmacy costs lapatinib (per day of use)	£0.61 (n/a)	n/a	n/a	Derived from Tappenden (2006a)
Pharmacy costs capecitabine (per day of use)	£0.92 (n/a)	n/a	n/a	Derived from Tappenden (2006a)
Monitoring costs for lapatinib (per month)	£70.66 (£9.01)	n/a	Lognormal	NHS reference cost (2007-2008)
Other medications to manage adverse events (per month)	£61.81 (£7.88)	£71.88 (£9.17)	Lognormal	Remak and Brazil (2004)
Clinical consultation/Visits (per month)	£94.74 (£12.08)	£291.64 (£37.20)	Lognormal	Remak and Brazil (2004)
Hospitalisation (per month)	£64.28 (£8.20)	£179.88 (£22.94)	Lognormal	Remak and Brazil (2004)
Diagnostics (per month)	£260.13 (£33.18)	£88.88 (£11.34)	Lognormal	Remak and Brazil (2004)
Radiotherapy (per month)	£22.60 (£2.88)	£20.34 (£2.59)	Lognormal	Remak and Brazil (2004)
Other special interventions (per month)	£33.43 (£4.26)	£116.18 (£14.82)	Lognormal	Remak and Brazil (2004)
Standard errors (for use in probabilistic sensitivity analyses) are reported in parentheses.				

5.2.3 Reconciliation of base case data

Since the FAD for lapatinib was issued in February 2009, there have been several changes to the model as described in section 5.2.2. To demonstrate how the model has changed and to assist in the interpretation of the revised base case results, a number of analyses were performed and are summarised in Table 5.2.

Scenario R1 is the base case analysis reported in the FAD. There are six consecutive changes, one per analysis which changes the base case from scenario R1 to the new base case scenario R7. These six changes are highlighted in Table 5.2 and listed below.

R1 Base case analysis reported in the FAD

R2 Addition of AE costs.

R3 Updating the costs from 2006 to 2008 levels.

R4 Update the OS data set from the September 2007 to the October 2008 data cut-off.

R5 Modifying the model to permit the use of HR estimates from the Cox regression model.

R6 Adjusting for crossover using Cox regression model with crossover as a time dependent covariate

R7 Adjusting for baseline prognostic factors.

Table 5.2 Summary of reconciliation of the base case

Scenario	Adjustment for Baseline prognostic factors	Method used to adjust for crossover	Method for estimating PFS and OS	OS data set	Base year costs	Adverse Events costs included
R1	No	Censoring	PH Weibull Model	September 2007	2006	No
R2	No	Censoring	PH Weibull Model	September 2007	2006	**Yes**
R3	No	Censoring	PH Weibull Model	September 2007	**2008**	Yes
R4	No	Censoring	PH Weibull Model	**October 2008**	2008	Yes
R5	No	Censoring	**Modified Model***	October 2008	2008	Yes
R6	No	**Crossover as a time dependent variable**	Modified Model†	October 2008	2008	Yes
R7	**Yes**	Crossover as a time dependent variable	Modified Model†	October 2008	2008	Yes

* Model modified to permit the use of HR estimates from the Cox regression model (PFS for C-only and OS for L+C from Weibull; HR for PFS and OS from log rank)

† Adjusting for crossover using Cox regression model with crossover as a time dependent covariate (OSL+C[t] from Weibull model; OSC-only[t] = OSL+C[t]HRC-only vs L+C HR from Cox model)

5.2.4 Methods to account for crossover

On reviewing the most recent overall survival data (October 08), several approaches were considered to adjust for the confounding effects of patient crossover in the EGF100151 clinical trial. The different approaches considered are listed below and described in detail in section 3.2.

a. Kaplan-Meier analysis excluding all subjects who crossed over
b. Kaplan-Meier analysis censoring crossover patients at time of crossover
c. Kaplan-Meier analysis treating crossover as an event (not conducted as such an analysis would potentially highly favour the lapatinib plus capecitabine arm)
d. Cox regression analysis considering crossover as a time-dependent covariate
    i) Without the inclusion of baseline prognostic variables
    ii) With the inclusion of baseline prognostic variables
e. Weibull survival model
    i) Without the inclusion of baseline prognostic variables
    ii) With the inclusion of baseline prognostic variables

In the health economics model the hazard ratios from the Cox regression analysis are used in a Weibull survival model (Modified Model) to generate cost-effectiveness estimates. These estimates take into account patient crossover in the EGF100151 trial by treating the crossover as a time-dependent covariate. Although this approach forms the basis of the primary analyses a sensitivity analysis was performed to investigate the impact of using alternative methods to account for crossover (section 5.3.3).

5.2.5 Primary economic analysis

The base case is the 'intent to treat' (ITT) population in which the latest overall survival (October 08) and progression free survival (PFS) (April 06) data from the lapatinib pivotal study (EGF100151) is incorporated into the analysis, and crossover is accounted for using a Cox regression model with crossover as a time dependent covariate (including baseline prognostic factors). The utility applied (0.694) is consistent with quality of life estimates for patients with the disease and was derived from the EGF100151 clinical trial data, as per our original submission in April 2007.

The model was used to calculate the cost per QALY gained with lapatinib plus capecitabine versus capecitabine monotherapy for the base case and three alternative scenarios which estimate the impact of applying a weighting such that life years gained were assigned a utility value equal to that for a healthy woman of the same age as those in EGF100151 trial (mean age 53 years), as well as the impact of implementing the Tyverb Patient Access Programme (TPAP).

5.2.5.1 End of life utility weighting

The utility weighting assumption was 0.85, based on the UK population norm for the EQ-5D among women 50-54 years of age reported in the York MVH Study, a nationally representative survey of 3,395 men and women age 18 years or older in the UK (Kind P, et al. 1999). This study has been used previously in the NICE

Special Health Authority Update on the Application of the End of Life Supplementary Advice in Health Technology Appraisals to estimate the utility for healthy individuals in the evaluations of sunitinib (1st-line), sorafenib (2nd-line) and temsirolimus (1st-line) for advanced and/or metastatic renal cell carcinoma, and for sunitinib for gastrointestinal stromal tumours.

5.2.5.2 Tyverb Patient Access Programme (TPAP)

Full details of the TPAP, in which up to the first 12 weeks of treatment Tyverb is free, are given in the addendum to GlaxoSmithKline's response to the lapatinib ACD July 2008 and have been reviewed by the Decision Support Unit (DSU report, 7 September 2008).

5.2.5.3 Summary of primary analyses

(i) **Base case** – The assigned quality of life value is equal to that for patients with breast cancer (utility 0.694 for PFS and PPS). No TPAP

(ii) **Base case with TPAP** – The assigned quality of life value is equal to that for patients with breast cancer (utility 0.694 for PFS and PPS). TPAP implemented.

(iii) **End-of-Life (EOL) case** – The assigned quality of life value is equal to that of a healthy individual (utility 0.85 for PFS and PPS). No TPAP

(iv) **End -of -Life case (EOL) with TPAP** – The assigned quality of life value to that of a healthy individual (utility 0.85 for PFS and PPS). TPAP implemented.

For each analysis the cost per QALY gained with lapatinib plus capecitabine versus capecitabine was calculated. The relative utility weights that would be required to achieve ICERs of £20,000 and £30,000 were also calculated.

5.2.5.4 Deterministic sensitivity analyses

Deterministic sensitivity analyses for the above scenarios were undertaken to explore the impact on the incremental cost-effectiveness of using alternative methods to account for patient crossover, in particular the impact of treating crossover as a time dependent covariate, and the impact of adjusting for baseline prognostic factors. The cost-effectiveness of the lapatinib plus capecitabine versus capecitabine monotherapy was calculated using the following methods:

(i) **PH Weibull model with censoring, no adjustment for prognostic factors** – Use of the PH Weibull models for PFS and OS and censor monotherapy patients who crossed over to lapatinib plus capecitabine in analyses of OS with no adjustment for baseline prognostic factors.

(ii) **PH Weibull model with censoring and adjustment for prognostic factors** – Use of the PH Weibull models for PFS and OS and censor monotherapy patients who crossed over to lapatinib plus capecitabine in analyses of OS with an adjustment for baseline prognostic factors.

(iii) **Modified Model excluding for crossover, no adjustment for prognostic factors** - Use of the HR for OS for the combination therapy versus capecitabine monotherapy obtained by excluding monotherapy

patients who crossed over (HR=0.78). No adjustment for baseline prognostic factors.

(iv) **Modified Model excluding for crossover and adjustment for prognostic factors** - Use of the HR for OS for the combination therapy versus capecitabine monotherapy obtained by excluding monotherapy patients who crossed over (HR=0.78) with an adjustment for baseline prognostic factors.

(v) **Modified Model with censoring, no adjustment for prognostic factors** - Use of the HR for OS for the combination therapy versus capecitabine monotherapy obtained by censoring monotherapy patients who crossed over (HR=0.82). No adjustment for baseline prognostic factors.

(vi) **Modified Model with censoring and adjustment for prognostic factors** - Use of the HR for OS for the combination therapy versus capecitabine monotherapy obtained by censoring monotherapy patients who crossed over (HR=0.82) and including an adjustment for prognostic factors.

(vii) **Modified Model with crossover as a time dependent covariate, no adjustment for prognostic factors –** Use of the HR for OS for the combination therapy versus capecitabine monotherapy obtained by including crossover as a time-dependent covariate but no inclusion of baseline prognostic factors as covariates (HR=0.80).

For each of these scenarios, the analyses were run with and without TPAP, and using the base case utility estimates of 0.694 or the higher utility value of 0.85 for all life years gained. Results of these analyses are presented in Table 5.6.

5.2.5.5 Probabilistic sensitivity analyses

Probabilistic sensitivity analyses were performed according to the methodology previously submitted to NICE.

5.2.6 Secondary economic analyses

To explore the impact of introducing lapatinib at an earlier stage in the treatment pathway three post hoc subgroup analyses were conducted on the EGF100151 trial data (see section 4.1 and Appendix 3 for background, methodology and results). For pragmatic reasons of timing/feasibility, the economic evaluation was restricted to those patients treated with one or two prior regimens (previously provided to NICE) and those treated with one prior trastuzumab-based regimen in the metastatic setting This latter might be considered to most accurately represent the profile of those patients who would be treated once lapatinib were established in clinical practice, i.e. earlier in the treatment pathway than those patients in EGF100151. The clinical data (Appendix 3) for all the subgroups suggests that the efficacy of lapatinib plus capecitabine may be greater when given earlier in the treatment pathway. The two subgroups selected for the evaluation had OS gains that covered the range of values obtained for the three subgroups in which the interventions were given early. The subgroup who had received one prior trastuzumab regimen in the metastatic setting was the largest of the subgroups studied, with 131 patients and 126 patients in the lapatinib combination and capecitabine-only arms, respectively. This may therefore be considered to the most robust of the subgroup analyses.

To model survival for the subgroups a similar approach to that used in the overall population was used: For OS a Weibull curve was fitted to the lapatinib combination arm, and the HR with time-dependent censoring applied, adjusted for baseline factors. For PFS a Weibull curve was fitted to the C-only arm and the HR applied, which was adjusted for baseline factors.

5.2.6.1 Summary of secondary analyses

(i) One or two prior regimens

From an analysis performed on subjects treated with 1 or 2 prior regimens and subjects treated with 3 or more prior regimens, with the regimen defined as any regimen in any setting (see Appendix 3.1).

(ii) One prior trastuzumab-based regimen in the metastatic setting

This was an analysis performed on subjects treated with 1 prior trastuzumab-based regimen in the metastatic setting and subjects treated with more than 1 prior metastatic trastuzumab-based regimen.

5.3 Results

5.3.1 Reconciliation of base case results

The base case estimate reported in the FAD was £93,825 per QALY. To demonstrate the impact of the various changes to the modelling and assumptions making up the base case a series of reconciling analyses were conducted. The results are given in Table 5.3. Full details of undiscounted and discounted estimates of survival are provided in Appendix 6.

The update in the overall survival data from the September 2007 to the October 2008 data decreases the cost per QALY by almost £10,000 from £96,672 to £86,736. The change from the PH Weibull to the 'Modified Model' increases the cost per QALY by £7,141 despite the fact that all other inputs are the same. This means that the estimated cost per QALY with the Modified Model (plus the Oct 2008 OS data) is £93,877 which is a similar value to that reported in the FAD (£93,825) using the PH Weibull model. The positive impact of the improved OS data on the cost-effectiveness analysis is thus diminished by converting to the new model. This result suggests that the ICERs estimated with the Modified Model are conservative.

The use of a Cox regression model with crossover as a time dependent covariate, to account for patient crossover leads to a decrease in the cost per QALY by £5,283 when no adjustment is made for baseline prognostic factors. There is a further reduction by £10,598 to £77,966 when baseline prognostic factors are included in the analysis. This last analysis (R7) provides the new base case estimate.

Table 5.3 Summary of reconciliation of base case results

	Overall Survival				Base-year costs	Cost AEs incl	L+C		C-only		L+C vs C-only		
	Adjusted for BL	Adjusted for XO	Estimation PFS and OS	OS dataset			Costs £	QALYs	Costs £	QALYs	Costs £	QALYs	Cost per QALY £
R1	No	Censored	PH Weibull	Sep-07	2006	No	26,939	0.897	12,924	0.748	14,015	0.149	93,825
R2	No	Censored	PH Weibull	Sep-07	2006	Yes	27,690	0.897	13,478	0.748	14,212	0.149	95,145
R3	No	Censored	PH Weibull	Sep-07	2008	Yes	28,864	0.897	14,424	0.748	14,440	0.149	96,672
R4	No	Censored	PH Weibull	Oct-08	2008	Yes	29,599	0.935	14,727	0.763	14,872	0.171	86,736
R5	No	Censored	Modified model	Oct-08	2008	Yes	29,037	0.927	15,000	0.778	14,037	0.150	93,877
R6	No	XO as TDV	Modified model	Oct-08	2008	Yes	29,037	0.927	14,776	0.766	14,261	0.161	88,594
R7	Yes	XO as TDV	Modified model	Oct-08	2008	Yes	29,037	0.927	14,206	0.737	14,832	0.190	77,996

NB all costs and QALYs are discounted at 3.5% per annum
BL - baseline prognostic factors
XO - crossover
TDCV - time dependent variable

5.3.2 Primary economic analysis results

The base case and scenario analyses described in section 5.2.5.3 are summarised in Table 5.4 and presented in a disaggregated format in Table 5.5 overleaf.

Table 5.4 Summary of the incremental cost-effectiveness for lapatinib plus capecitabine versus capecitabine

	Lapatinib plus capecitabine versus capecitabine			
Incremental	**Base case**	**Base case with TPAP**	**EOL case**	**EOL case with TPAP**
LYGs (disc)	0.292	0.292	0.292	0.292
QALYs (disc)	0.190	0.190	0.248	0.248
Cost (disc)	£14,832	£11,303	£14,832	£11,303
Cost per LYG	£50,774	£38,695	£50,774	£38,695
Cost per QALY gained	£77,996	£59,441	£59,734	£45,524
QALY multiplier for ICER <£30k	2.6	2.0	2.0	1.5

The 'EOL case with TPAP' is the pivotal cost-effectiveness analysis for this submission. It takes into consideration the NICE supplementary advice for end of life treatments by using a higher utility weighting based on healthy individuals of a similar age to those in the EGF100151 trial. It employs an appropriate method to account for patient crossover and includes TPAP which was approved by the Department of Health as an appropriate patient access scheme to be considered by NICE. The additional QALY weight required to bring the ICER for lapatinib plus capecitabine below £30,000 is a factor of 1.5. This is within the range previously accepted by NICE when considering end of life medicines.

Table 5.5 Primary estimates of cost-effectiveness and cost-utility lapatinib plus capecitabine versus capecitabine monotherapy

	Base case			Base case with TPAP			EOL case			EOL case with TPAP		
	L+C	Capecitabine monotherapy	Incremental	L+C	Capecitabine monotherapy	Incremental	L+C	Capecitabine monotherapy	Incremental	L+C	Capecitabine monotherapy	Incremental
Progression-free life years	0.664	0.428	0.236	0.664	0.428	0.236	0.664	0.428	0.236	0.664	0.428	0.236
Post-progression life years	0.988	0.932	0.057	0.988	0.932	0.057	0.988	0.932	0.057	0.988	0.932	0.057
Life years	1.652	1.360	0.292	1.652	1.360	0.292	1.652	1.360	0.292	1.652	1.360	0.292
QALYs	0.927	0.737	0.190	0.927	0.737	0.190	1.404	1.156	0.248	1.404	1.156	0.248
Acquisition costs	£14,056	£2,178	£11,878	£10,565	£2,178	£8,387	£14,056	£2,178	£11,878	£10,565	£2,178	£8,387
Administration costs	£232	£90	£142	£195	£90	£105	£232	£90	£142	£195	£90	£105
Monitoring costs	£563	£0	£563	£563	£0	£563	£563	£0	£563	£563	£0	£563
Adverse events costs	£792	£584	£209	£792	£584	£209	£792	£584	£209	£792	£584	£209
Other progression-free costs	£4,278	£2,760	£1,518	£4,278	£2,760	£1,518	£4,278	£2,760	£1,518	£4,278	£2,760	£1,518
Other post-progression costs	£9,116	£8,594	£522	£9,116	£8,594	£522	£9,116	£8,594	£522	£9,116	£8,594	£522
Total costs	£29,037	£14,206	£14,832	£25,509	£14,206	£11,303	£29,037	£14,206	£14,832	£25,509	£14,206	£11,303
Cost per LYG	-	-	£50,774	-	-	£38,695	-	-	£50,774	-	-	£38,695
Cost per PFLYG	-	-	£62,972	-	-	£47,991	-	-	£62,972	-	-	£47,991
Cost per QALY gained	-	-	£77,996	-	-	£59,441	-	-	£59,734	-	-	£45,524
Weighting to achieve Cost per QALY of £20,000	-	-	3.9	-	-	3.0	-	-	3.0	-	-	2.3
Weighting to achieve Cost per QALY of £30,000	-	-	2.6	-	-	2.0	-	-	2.0	-	-	1.5

NB all costs and effects are discounted at an annual rate of 3.5%

5.3.2.1 Deterministic sensitivity analysis results

Deterministic sensitivity analyses undertaken to explore the impact of using alternative methods to account for patient crossover are reported in Table 5.6. These analyses allow the independent examination of the impact of treating crossover as a time dependent covariate and adjustment for baseline prognostic factors.

The additional weight that would need to be assigned to the QALY benefits in the ITT population of EGF100151 for lapatinib to be cost effective at a willingness to pay of £30,000/QALY is consistently 2 or less when end of life considerations are made, and the TPAP is implemented. Censoring for crossover but using the modified model, which is more conservative than the PH Weibull model, the QALY weighting for a £30,000/QALY ICER is 2.0 without, and 1.6 with adjustment for baseline prognostic factors, when end of life considerations are made, and the TPAP is implemented.

Adjusting for prognostic factors appears to have a greater effect in reducing the incremental cost effectiveness ratio than treating crossover as a time dependent covariate.

Table 5.6 Deterministic sensitivity analyses to explore alternative methods to account for patient crossover on OS (continued overleaf)

	Base case utility			Base case utility with TPAP			EOL case utility			EOL case utility with TPAP		
	L+C†	Capecitabine monotherapy	Incremental	L+C†	Capecitabine monotherapy	Incremental	L+C†	Capecitabine monotherapy	Incremental	L+C†	Capecitabine monotherapy	Incremental
PH Weibull model with censoring, no adjustment for prognostic factors (method i)*												
Costs £	29,055	14,731	14,324	25,526	14,731	10,796	29,055	14,731	14,324	25,526	14,731	10,796
QALYs	0.928	0.764	0.164	0.928	0.764	0.164	1.406	1.204	0.202	1.406	1.204	0.202
Incremental Cost/QALY £			87,237			65,748			71,075			53,568
Multiplier for ICER <£30K			2.9			2.2			2.4			1.8
PH Weibull model with censoring and adjustment for prognostic factors (method ii)												
Costs £	29,037	13,855	15,182	25,509	13,855	11,654	29,037	13,855	15,182	25,509	13,855	11,654
QALYs	0.927	0.719	0.208	0.927	0.719	0.208	1.404	1.124	0.281	1.404	1.124	0.281
Incremental Cost/QALY			72,962			56,005			54,110			41,535
Multiplier for ICER <£30K			2.4			1.9			1.8			1.4
Modified Model excluding for crossover, no adjustment for prognostic factors (method iii)												
Costs £	29,037	14,550	14,487	25,509	14,550	10,959	29,037	14,550	14,487	25,509	14,550	10,959
QALYs	0.927	0.755	0.173	0.927	0.755	0.173	1.404	1.188	0.217	1.404	1.188	0.217
Incremental Cost/QALY			83,962			63,513			66,894			50,602
Multiplier for ICER <£30K			2.8			2.1			2.2			1.7
Modified Model excluding for crossover and adjustment for prognostic factors (method iv)												
Costs £	28,646	14,069	14,578	25,118	14,069	11,049	28,646	14,069	14,578	25,118	14,069	11,049
QALYs	0.907	0.730	0.177	0.907	0.730	0.177	1.368	1.143	0.225	1.368	1.143	0.225
Incremental Cost/QALY			82,283			62,367			64,822			49,132
Multiplier for ICER <£30K			2.7			2.1			2.2			1.6

* All scenarios use "modified model" for PFS; results will not match with reconciliation scenario R4 which uses "original model" for both PFS and OS

Table 5.6 continued. Deterministic sensitivity analyses to explore the impact of using alternative methods to account for patient crossover

	Base case utility			Base case utility with TPAP			EOL case utility			EOL case utility with TPAP		
	L+C†	Capecitabine monotherapy	Incremental	L+C†	Capecitabine monotherapy	Incremental	L+C†	Capecitabine monotherapy	Incremental	L+C†	Capecitabine monotherapy	Incremental
Modified Model with censoring, no adjustment for prognostic factors (method v)												
Costs £	29,037	15,000	14,037	25,509	15,000	10,509	29,037	15,000	14,037	25,509	15,000	10,509
QALYs	0.927	0.778	0.150	0.927	0.778	0.150	1.404	1.229	0.175	1.404	1.229	0.175
Incremental Cost/QALY £			93,877			70.281			80,161			60,012
Multiplier for ICER <£30K			3.1			2.3			2.7			2.0
Modified Model with censoring and adjustment for prognostic factors (method vi)												
Costs £	29,037	14,321	14,716	25,509	14,321	11,188	29,037	14,321	14,716	25,509	14,321	11,188
QALYs	0.927	0.743	0.184	0.927	0.743	0.184	1.404	1.167	0.238	1.404	1.167	0.238
Incremental Cost/QALY			79,869			60,720			61,921			47,075
Multiplier for ICER <£30K			2.7			2.0			2.1			1.6
Modified Model with crossover as a time dependent covariate, no adjustment for prognostic factors (method vii)												
Costs £	29,037	14,776	14,261	25,509	14,776	10,733	29,037	14,776	14,261	25,509	14,776	10,733
QALYs	0.927	0.766	0.161	0.927	0.766	0.161	1.404	1.209	0.196	1.404	1.209	0.196
Incremental Cost/QALY £			88,594			66,675			72,864			54,836
Multiplier for ICER <£30K			3.0			2.2			2.4			1.8

† L+ C refers to lapatinib plus capecitabine therapy
The base case utility is 0.694. The EOL case utility is 0.850

5.3.2.2 Probabilistic sensitivity analysis results

The results of the probabilistic sensitivity analysis for the base case (with and without TPAP and end of life considerations) are summarised in Table 5.7. The cost-effectiveness planes and cost-effectiveness acceptability curves are given in Appendix 7.

Table 5.7 Summary of probabilistic sensitivity analysis

	Lapatinib plus capecitabine versus capecitabine			
PSA results	**Base case**	**Base case with TPAP**	**EOL case**	**EOL case with TPAP**
Predominant quadrant	NE	NE	NE	NE
% in predominant quadrant	94.5	95.3	94.7	95.5
Probability ICER <£20k	0.00	0.02	0.01	0.07
Probability ICER <£30k	0.07	0.19	0.16	0.34

The data in Table 5.7 shows that the majority of sample estimates of the incremental costs and QALYs for lapatinib plus capecitabine fall in the North-East quadrant of the cost-effectiveness plane which means that this intervention is more effective and more costly than capecitabine monotherapy. In approximately 95% of the simulations, lapatinib plus capecitabine is expected to produce more QALYs at a greater cost than capecitabine monotherapy. As expected, without the application of a QALY multiplier the cost-effectiveness acceptability curve data suggest that the probability that lapatinib plus capecitabine has an incremental cost-utility ratio that is lower than £30,000 is low (approximately 0.07 to 0.34) when compared with capecitabine monotherapy. The probability that lapatinib plus capecitabine has an incremental cost-utility ratio that is lower than £20,000 is approximately 0.0 to 0.07 when compared with capecitabine monotherapy. The probabilities of falling within the NICE accepted cost-effectiveness range are higher for those analyses that include TPAP.

5.3.3 Secondary economic analysis results

Cost-effectiveness analyses were conducted for two of the subgroup populations described in section 5.2.6.1. The cost-effectiveness results are summarised in Tables 5.8 and 5.9 and the PSA results are given in Appendices 8 and 9.

For the subgroup population exposed to one or two therapies prior to the EGF1000151 treatment (preliminary data for which were submitted to NICE on 21 January 2009), the estimated cost per QALY varies from £32,440 for the 'end-of-life case with TPAP' to £54,575 for the base case.

In the case of the larger subgroup population exposed to one prior line of trastuzumab in the metastatic setting, who had a median survival gain on lapatinib plus capecitabine of 3.4 months (HR=0.79, p=0.077), the estimated cost per QALY is in the range of £44,688 for the end-of-life case with TPAP (QALY multiplier 1.5) to £70,474 for the base case (QALY multiplier 2.3).

The PSA data for the subgroups given in Appendices 8 and 9 show that for these populations the probability that lapatinib plus capecitabine has an incremental cost-utility ratio that falls within the NICE accepted cost-effectiveness range are higher than those for the base case ITT population (section 5.3.2.2).

These subgroups were less heavily pre-treated prior to enrolment on the EGF100151 trial than the general ITT population. The results of this cost-effectiveness analysis suggest that there is a higher probability that lapatinib plus capecitabine will be cost-effective if it is introduced earlier in the treatment pathway.

Table 5.8 Analyses for patients treated with one or two prior regimens

	Base case			Base case with TPAP			EOL case no TPAP			EOL case with TPAP		
	L+C†	Capecitabine monotherapy	Incremental	L+C†	Capecitabine monotherapy	Incremental	L+C†	Capecitabine monotherapy	Incremental	L+C†	Capecitabine monotherapy	Incremental
Progression-free life years	0.909	0.388	0.521	0.909	0.388	0.521	0.909	0.388	0.521	0.909	0.388	0.521
Post-progression life years	1.044	0.872	0.172	1.044	0.872	0.172	1.044	0.872	0.172	1.044	0.872	0.172
Life years	1.953	1.260	0.693	1.953	1.260	0.693	1.953	1.260	0.693	1.953	1.260	0.693
QALYs	1.050	0.636	0.414	1.050	0.636	0.414	1.660	1.071	0.589	1.660	1.071	0.589
Acquisition costs	£18,096	£1,842	£16,254	£14,653	£1,842	£12,811	£18,096	£1,842	£16,254	£14,653	£1,842	£12,811
Administration costs	£304	£71	£233	£268	£71	£197	£304	£71	£233	£268	£71	£197
Monitoring costs	£771	£0	£771	£771	£0	£771	£771	£0	£771	£771	£0	£771
Adverse events costs	£1,079	£692	£387	£1,079	£692	£387	£1,079	£692	£387	£1,079	£692	£387
Other progression-free costs	£5,859	£2,500	£3,359	£5,859	£2,500	£3,359	£5,859	£2,500	£3,359	£5,859	£2,500	£3,359
Other post-progression costs	£9,633	£8,048	£1,585	£9,633	£8,048	£1,585	£9,633	£8,048	£1,585	£9,633	£8,048	£1,585
Total costs	£35,741	£13,153	£22,588	£32,262	£13,153	£19,109	£35,741	£22,588	£14,832	£32,262	£13,153	£19,109
Cost per LYG	-	-	£32,595	-	-	£27,574	-	-	£32,595	-	-	£27,574
Cost per PFLYG	-	-	£43,336	-	-	£36,661	-	-	£43,336	-	-	£36,661
Cost per QALY gained	-	-	£54,575	-	-	£46,169	-	-	£38,347	-	-	£32,440
Weighting to achieve Cost per QALY of £20,000	-	-	2.7	-	-	2.3	-	-	1.9	-	-	1.6
Weighting to achieve Cost per QALY of £30,000	-	-	1.8	-	-	1.5	-	-	1.3	-	-	1.1

All costs and effects are discounted at 3.5% per annum

† L+ C refers to lapatinib plus capecitabine therapy

Table 5.9 Analyses for patients treated with one prior trastuzumab-based regimen in the metastatic setting

	Base case			Base case with TPAP			EOL case no TPAP			EOL case with TPAP		
	L+C†	Capecitabine monotherapy	Incremental	L+C†	Capecitabine monotherapy	Incremental	L+C†	Capecitabine monotherapy	Incremental	L+C†	Capecitabine monotherapy	Incremental
Progression-free life years	0.780	0.438	0.342	0.780	0.438	0.342	0.780	0.438	0.342	0.780	0.438	0.342
Post-progression life years	0.854	0.818	0.036	0.854	0.818	0.036	0.854	0.818	0.036	0.854	0.818	0.036
Life years	1.635	1.256	0.378	1.635	1.256	0.378	1.635	1.256	0.378	1.635	1.256	0.378
QALYs	0.946	0.691	0.255	0.946	0.691	0.255	1.389	1.068	0.321	1.389	1.068	0.321
Acquisition costs	£16,287	£2,145	£14,141	£12,743	£2,145	£10,597	£16,287	£2,145	£14,141	£12,743	£2,145	£10,597
Administration costs	£268	£88	£180	£230	£88	£142	£268	£88	£180	£230	£88	£142
Monitoring costs	£662	£0	£662	£662	£0	£662	£662	£0	£662	£662	£0	£662
Adverse events costs	£952	£529	£424	£952	£529	£424	£952	£529	£424	£952	£529	£424
Other progression-free costs	£5,029	£2,825	£2,204	£5,029	£2,825	£2,204	£5,029	£2,825	£2,204	£5,029	£2,825	£2,204
Other post-progression costs	£7,880	£7,547	£333	£7,880	£7,547	£333	£7,880	£7,547	£333	£7,880	£7,547	£333
Total costs	£31,078	£13,134	£17,943	£27,496	£13,134	£14,362	£31,078	£13,134	£17,943	£27,496	£13,134	£14,362
Cost per LYG	-	-	£47,458	-	-	£37,985	-	-	£47,458	-	-	£37,985
Cost per PFLYG	-	-	£52,468	-	-	£41,995	-	-	£52,468	-	-	£41,995
Cost per QALY gained	-	-	£70,474	-	-	£56,406	-	-	£55,833	-	-	£44,688
Weighting to achieve Cost per QALY of £20,000	-	-	3.5	-	-	2.8	-	-	2.8	-	-	2.2
Weighting to achieve Cost per QALY of £30,000	-	-	2.3	-	-	1.9	-	-	1.9	-	-	1.5

All costs and effects are discounted at 3.5% per annum

† L+ C refers to lapatinib plus capecitabine therapy

5.4 Overall cost effectiveness discussion and conclusions

Results of this pharmaco-economic evaluation show that with the implementation of the Tyverb Patient Access Programme, TPAP, (which allows all eligible NHS patients to receive up to the first 12 weeks of treatment free), and using utility weights for life years gained equal to those for healthy women of the same age as those for whom the treatment is indicated, the cost per QALY gained with lapatinib plus capecitabine compared to capecitabine monotherapy is £45,524. Given this estimate the relative QALY weight required to obtain a cost-effectiveness ratio within the acceptable range (<£30,000 per QALY) is 1.5. This value is less than the corresponding value accepted by the NICE Appraisal Committee in its assessment of first line sunitinib in metastatic renal cell carcinoma using Committee's preferred assumptions (and no restriction on time of administration of IFN) (value=1.58), although we acknowledge the differences in the decision making context for this appraisal. These results suggest that based on the same criteria as have been employed previously, the relative QALY weight required for lapatinib to be considered cost-effective is acceptable. Lapatinib should therefore be recommended for use on the basis that it meets the criteria for assessment as a life extending end of life treatment and all other base case model assumptions and parameter estimates are acceptable.

Patients with ErbB2-positive advanced or metastatic breast cancer, who progress on or following treatment with trastuzumab, represent a population with an unmet clinical need who have very few therapeutic options available to them other than continued use of trastuzumab, which is unlicensed for use in this setting. As metastatic breast cancer is essentially incurable, effective treatment options that can delay progression or extend survival without negatively impacting quality of life and adding unacceptably to the toxicity burden are greatly needed in this patient group. For these women, who are relatively young, with good performance status, the modest gains associated with medicines at this stage of breast cancer can be disproportionately valuable.

GSK believe that the estimates of cost-effectiveness in this evaluation may be conservative given that the comparator was capecitabine monotherapy and approximately 50% of the patient population in England and Wales for this indication are treated with more costly trastuzumab combination therapies (GlaxoSmithKline's response to the lapatinib ACD July 2008).

The introduction of lapatinib plus capecitabine, as an oral combination regimen, has the potential to reduce the need for IV administration of chemotherapy and/or trastuzumab in the hospital setting, thereby releasing capacity for deployment elsewhere in chemotherapy services. The impact on capacity is difficult to quantify because the introduction of a new intervention will affect many areas within the treatment pathway, across the whole of cancer services, and not just within the field under consideration (i.e. breast cancer). Furthermore there is enormous local variation in the organisation and implementation of cancer services.

Quality of life is a major consideration in patients who develop brain metastases. The condition is associated with substantial morbidity, mortality and healthcare costs (Pelletier 2008) and systemic treatment options are particularly limited. Lapatinib is able to cross the blood-brain-barrier and penetrate the CNS (Van den Abbeele 2006; Gril 2008) and there is some evidence that it has activity in both treating (Lin 2008; Lin 2009) and preventing brain metastases (Cameron 2008). Whilst the impact of lapatinib on brain metastases cannot be readily modelled with the data available, the potential benefit of the intervention on this condition should be considered by the Appraisal Committee.

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