Addendum to GSK's Response to the Lapatinib ACD:
Lapatinib (Tyverb®▼) Patient Access Programme
July 2008

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1. Executive summary

In its Appraisal Consultation Document (July 2008), NICE has proposed that lapatinib should not be used in the NHS except in the context of clinical trials.

On 28 July, GSK submitted a response to the ACD, which addresses issues raised by the Appraisal Committee and Evidence Review Group. This response includes pertinent new evidence that has become available since GSK's original submission and a revised economic analysis. The revised economic analysis suggests an overall ICER for lapatinib plus capecitabine of £60,730/QALY.

In this addendum to GSK's ACD response, the company proposes an access programme for all patients within lapatinib's licensed indication. The effect of this programme is to reduce the overall ICER to £16,384/QALY.

Response to ACD

NICE's draft recommendation that lapatinib should not routinely be used in the NHS was based on three broad conclusions:

- Whilst lapatinib plus capecitabine is acknowledged as being clinically effective in eligible patients, the combination is not cost effective when compared with single agent chemotherapy (as demonstrated by GSK's own analysis).

- It is uncertain to what extent trastuzumab is used beyond disease progression and whether such an approach is based on evidence of clinical effectiveness.
- There is uncertainty around GSK's claim that lapatinib is a cost effective alternative to trastuzumab-containing regimens used beyond progression.

Whilst GSK accepts the first of these conclusions, GSK has presented a robust response to the ACD regarding conclusions 2 and 3 based on significant and pertinent new evidence that has become available since its original submission in April 2007, as highlighted below:

- Submission of new evidence that demonstrates that the majority (around 55%) of patients within the relevant population currently receives treatment with trastuzumab used beyond progression, supporting the evidence provided in our original submission.
- Submission of new evidence from the first randomised controlled trial to demonstrate the clinical effectiveness of trastuzumab used beyond progression.
- Submission of a revised cost effectiveness analysis, using the newly available clinical trial evidence described above, to demonstrate the relative cost effectiveness of lapatinib compared with trastuzumab used beyond progression.
- Addressing the key remaining uncertainties identified within the ACD, based on new evidence, where appropriate, to generate a new 'base case' cost effectiveness analysis.

The results of these revised analyses confirm the finding of GSK's original submission, i.e. that lapatinib plus capecitabine is not a cost effective option when compared with capecitabine alone. However, they also confirm that the combination remains highly cost effective compared with the key trastuzumab-containing regimens (lapatinib dominates, i.e. is more effective and less costly).

Addressing potential equity issues

In its original submission, GSK presented an argument that lapatinib plus capecitabine presents a cost effective alternative to trastuzumab-containing regimens in the subset of patients that is more likely to receive such treatment. This subgroup included patients with progression at an isolated site, patients with few metastases in the soft tissues or bone and patients who experience a previous good response to trastuzumab. However, such an approach presents a number of challenges:

- It is difficult to create clear and unambiguous clinical criteria with which to define such a subgroup, which creates equity issues – a view that has been confirmed by UK medical oncologists
- The only randomised trials to support the use of either lapatinib plus capecitabine (EGF100151) or trastuzumab used beyond progression (GBG 26/BIG 3-05) included a broad population of

ErbB2+ patients that had progressed on trastuzumab, rather than a selected subgroup, such as that described above. Equity issues may therefore be compounded if access to lapatinib plus capecitabine is restricted to a subgroup of patients when data do not exist to support the differential effectiveness of the interventions in this population.

GSK strongly believes that lapatinib offers tangible benefits to a group of patients with limited treatment options. GSK is committed to a solution that ensures access to lapatinib for all patients with the potential to benefit within its licensed indication. To this end, GSK proposes an access programme for lapatinib that will reduce the cost per QALY to a level which is within acceptable limits. The programme aims to facilitate equitable patient access to treatment and maximise value to the NHS by linking payment to clinical benefit.

Assessing overall cost effectiveness

In its response to the Appraisal Consultation Document, GSK has addressed a number of the issues raised by the Evidence Review Group and the Appraisal Committee to create a revised 'base case' analysis of the cost effectiveness of lapatinib plus capecitabine both against single agent chemotherapies (capecitabine and vinorelbine) and trastuzumab-containing regimens (single agent trastuzumab and trastuzumab with either capecitabine or vinorelbine).

Using the revised "base case", as described above, GSK has generated a cost effectiveness estimate for lapatinib plus capecitabine compared with a 'blended' comparator consisting of a weighted average of both the costs and effectiveness of the three main treatment options (capecitabine, trastuzumab plus capecitabine and trastuzumab plus vinorelbine).

To ensure that all patients were represented in the analysis, including those receiving less commonly used interventions identified in GSK's response to the ACD, the less common treatment regimens were re-allocated to the three key intervention groups (see ACD response for methodology), generating final proportions of:

- 44% capecitabine monotherapy
- 29% trastuzumab in combination with capecitabine
- 27% trastuzumab in combination with vinorelbine

The result of the blended analysis estimates the overall ICER for lapatinib plus capecitabine against a blended comparator to be £60,730/QALY.

Whilst GSK strongly believes that this represents a reasonable approach to addressing the question in hand (i.e. the overall cost effectiveness of lapatinib plus capecitabine against options currently employed within the NHS), it recognises that the level of cost effectiveness achieved falls

outside NICE's accepted threshold for cost effectiveness, as judged against its existing criteria and the uncertainty that surrounds some of these estimates. The company also recognises the need to demonstrate clearly the value that lapatinib offers the NHS in order to ensure that all patients can benefit from treatment.

The following sections provide an overview of GSK's proposed access programme and GSK's assessment of its impact on the overall cost effectiveness of lapatinib plus capecitabine.

2. Summary of programme

- Patients with ErbB2+ metastatic breast cancer, as defined by the licensed indication for lapatinib, will receive courses of systemic therapy provided in 3-weekly cycles.
- Clinical response will be assessed after completion of 2-3 cycles (typically at the end of either week 6 or 9 of treatment) and on a regular basis thereafter, in line with current clinical practice.
- Under the terms of the proposed programme, the cost of the lapatinib utilised by the patient during the initial period of treatment, up to a maximum of 12 weeks, will be borne by the company.
- The NHS will bear the cost of continued treatment with lapatinib for any patients beyond week 12.
- A 'cut-off' at the end of week 12 was selected to fit in with usual clinical practice, thus avoiding additional patient management costs, and to achieve cost effectiveness.
- Clear criteria will be defined for entry to the programme, as well as continuation and stopping criteria, to support equity of access and achievement of cost effectiveness.

Supply and rebate

Initial supplies will be made through GSK's normal distribution channels to the NHS Trust treating each patient. NHS Trusts will then apply for a retrospective rebate in the form of a cash rebate at one of the following time points:

1. At point of discontinuation, for patients stopping treatment before 12 weeks.
2. Following clinical review at week 12 for patients continuing to receive treatment at this point.

Under the terms of the programme, the maximum rebate that GSK will provide per patient is equivalent to 12 weeks' treatment with lapatinib (the full cost of treatment with capecitabine would be borne by the NHS). An individual patient would only be eligible under this programme once. GSK will continue to supply lapatinib at the NHS list price under its usual terms and conditions for patients falling outside the eligibility criteria defined by the programme.

It should be noted that a cash rebate has been selected following consideration of advice received from healthcare professionals and policy makers, as well as the requirements of the ABPI Code of Practice for the Pharmaceutical Industry. GSK believes that a cash rebate is both easy to administer and will meet the needs of the vast majority of NHS providers. It should also facilitate relatively straightforward reconciliation of the costs of patient treatment between Acute Trusts and primary care organisations.

An overview of the programme is illustrated in Appendix 1.

Duration of the programme

The programme will come into effect from the date that positive guidance is issued by NICE for use of lapatinib plus capecitabine within its licensed indication. Only patients who commence their first treatment cycle with lapatinib plus capecitabine after this date will be eligible. The programme will continue in operation until the release of updated guidance from NICE.

Eligibility for rebate and continuation/discontinuation criteria

GSK recognises that in order to achieve both equity of access and cost effectiveness, clear criteria are required to define a patient's eligibility to start treatment, and to aid decision-making about when treatment should either continue or stop.

In developing the following continuation/stopping criteria, GSK has made reference to the criteria used to assess clinical response in EGF100151 and the Lapatinib Expanded Access Programme trial (EGF103659), which were based on RECIST[1], as well as its understanding of usual clinical practice in the NHS.

It should be noted that since the more objective measures of clinical response used in breast cancer clinical trials, such as RECIST, are not employed in everyday clinical practice, it may not be possible to generate unambiguous stopping criteria, for example, without significantly adding to the investigations currently employed in usual clinical practice. GSK has therefore presented a balanced approach that reflects both current clinical practice and which it expects could be implemented consistently across the NHS. GSK proposes to test this assumption through further consultation with external experts.

Patient eligibility

All NHS Trusts will be able to sign up to the programme and, thereafter, claim a rebate, as described above, for any NHS patient in England, Wales and Northern Ireland that falls within the initial licensed indication for lapatinib plus capecitabine, subject to NICE approval in that population. Specific eligibility criteria are summarised in Section 2 of the Rebate Application Form (Appendix 2).

Continuation criteria

Patients will be eligible to continue treatment with lapatinib and capecitabine if they are deriving clinical benefit and are able to tolerate the treatment.

Clinical benefit will be determined by the patient's oncologist during routine clinical follow-up, based on clinical and imaging assessments and/or other investigations. Clinical benefit may be characterised by the reduction in size or disappearance of existing lesions (whether measurable or not), stable disease and/or improvement of other response criteria including symptom improvement.

Discontinuation criteria

Patients should discontinue treatment with lapatinib and capecitabine:

1. If there is no clinical response to the treatment at the first planned assessment point
2. If the patient experiences disease progression following an initial response
3. If they are unable to tolerate the combination treatment despite appropriate dose modifications

Clinical progression will be assessed by the patient's oncologist, who will make a judgement concerning the status of the disease and the degree of clinical benefit currently derived based on (i) the increase in size of existing lesions or appearance of new lesions [whether measurable or not] and (ii) symptomatic deterioration.

Costs of implementation

The costs of administering the programme have not been explicitly included in this submission. However, it is anticipated that these would be minimal as the scheme is based on assessments of disease that would be carried out as a normal part of patient care.

3. Impact on overall cost effectiveness

Details of the methodology used to assess the impact of the proposed programme on the overall cost effectiveness of lapatinib plus capecitabine are provided in Appendix 3.

The results of these analyses indicate that the programme can deliver real value to the NHS, improving the overall cost effectiveness of lapatinib plus capecitabine and achieving an ICER of £16,384/QALY.

It has not been possible to perform a specific probabilistic sensitivity analysis on the blended comparison scenario. However, a PSA performed on the individual comparators in the context of the programme suggests

that the likelihood of lapatinib plus capecitabine being cost effective in the £5,000-£20,000/QALY range is over 90% when compared with the key trastuzumab-containing regimens (trastuzumab plus capecitabine, or vinorelbine). The likelihood of being cost effective when compared with single agent chemotherapies is slightly increased, but still remains negligible.

4. Implementation of the programme

In developing the programme, GSK has given consideration to the requirements of the NHS to minimise the administrative burden of access programmes and to operate within existing NHS processes. For example:

- Each claim will be made retrospectively and will require submission of only one application form per patient
- Adoption of the programme will not require any clinical assessments additional to those already employed in normal clinical practice
- Rebates will be made to the NHS Trust that has both purchased the product and treated the patient; as such, the cost of treatment can be reconciled with the relevant primary care organisation, maintaining appropriate financial flows

An overview of how the programme will operate is provided in Appendix 1. Appendix 2 provides a copy of the proposed application form that hospitals/Acute Trusts would use to make each rebate claim. The process of making a claim is described further below.

Input has been sought from a range of healthcare professionals and policy makers during the development of the programme to ensure that its operation will not place an undue additional burden on the NHS and that it implementation will not interfere with usual NHS procedures and practices. Feedback from healthcare professionals is summarised on page 9.

Making and processing a claim

Any hospital (or Acute Trust) that manages eligible patients in England, Wales or Northern Ireland will be eligible to make rebate claims following completion of a standard agreement outlining the terms and conditions of supply. When completing the contract, each hospital/Trust will be asked to confirm the names of individuals authorised to make rebate claims under the terms of the programme.

Rebates relating to valid claims will be made in the form of a cash rebate. At the time of completion of the programme contract, each hospital will also be asked to provide details of how rebates should be made (e.g. hospital bank account details to facilitate BACS transfer). Hospitals treating patients will be encouraged to order directly from one of GSK's logistics service providers (wholesalers) to make it easier for them to reconcile funding flows with the relevant primary care organisation(s).

Following entry into the programme, hospitals will be able to treat eligible patients in the knowledge that they will be able to make rebate claims at the appropriate point. It should be noted that rebate claims will be made retrospectively, leaving hospitals free to obtain supplies of lapatinib and initiate treatment as normal, meaning that there will be no delays to the start of treatment for patients.
As described previously, hospitals will claim a rebate:

1. At point of discontinuation, for patients stopping treatment before 12 weeks.
2. Following clinical review at week 12 for patients continuing to receive treatment at this point.

One application form (claim) will be made per patient. The application form is divided into 4 sections, which will be completed by the applicant:

- Application details (hospital, patient identifier, consultant, etc.)
- Patient eligibility for rebate (based on ErbB2 status, prior therapy, combination with capecitabine)
- Treatment with Tyverb plus capecitabine (date of initiation, treatment duration, adverse events); these data will be used to calculate level of rebate payable
- Authorisation by appropriate NHS personnel

No personally identifiable information relating to individual patients will be disclosed to GSK in submitting an application for rebate, other than a unique patient hospital number, which the hospital will be able to use to identify patients. Upon receipt by GSK, it is anticipated that a unique claim number will be generated for internal use, to facilitate tracking of rebate claims through GSK's financial systems.

An example of the proposed claim form is provided in Appendix 2.

Calculation of rebate

Following receipt of each claim form, GSK's Medical Department will validate claims by confirming that all necessary details have been provided by the hospital and that claims match the predefined patient eligibility criteria.

Once a claim has been validated, GSK will calculate the value of the rebate to be paid. For patients discontinuing before the end of week 12, this will be equal to the cost of the number of whole 3-week cycles of lapatinib (at the licensed dose) initiated at the point of discontinuation for reasons of disease progression or otherwise. For patients who have not progressed and who are continuing treatment beyond the end of week 12, this will be equal to the cost of 4 cycles of treatment with lapatinib (at the licensed dose).

Reporting of adverse events

Adverse events should be reported. GSK will additionally monitor data provided within the application form to identify where patients have experienced an adverse event and follow-up with the physician involved.

Handling data and right to audit

GSK will use data relating to individual applications solely for the purposes of administering the programme and, where appropriate, fulfilling its responsibilities to report notifiable events to regulatory authorities.

Anonymised, aggregated data will be used to identify prescribing patterns and assess the level of uptake of the programme. Where analysis suggests unusual prescribing patterns within any given hospital or Trust in relation to this programme, GSK will reserve the right to request and instigate an independent third party to audit clinical and prescribing records maintained by the NHS, in order to ensure compliance with the terms of the agreement. Hospitals will be required to support necessary applications (such as local Ethics Committee or Trust approvals) where these are required to allow access to patients' records for these monitoring purposes. Furthermore, in developing the detailed processes that will support implementation of the programme, patient confidentiality will be maintained and the potential need to obtain patient consent prior to any third party audit will be addressed.

Feedback from healthcare professionals and policy makers

In developing the outline for this programme, GSK has sought advice from a number of healthcare professionals at different stages and on different aspects of its development, either to investigate issues relating to management of access programmes more generally or on specific aspects of the proposal outlined herein. The healthcare professionals consulted include:

- Consultant Oncologists (n=3)
- Acute Trust Chief Pharmacists (n=2)
- Cancer Network Pharmacists (n=2)

In addition, advice has been sought from the Department of Health and reference made to both the position statement issued by the British Oncology Pharmacy Association ('Risk Sharing Schemes in Oncology', March 2008) and the Velcade Response Scheme, which has been well received by the NHS.

Collective feedback suggests that stakeholders recognise the need for programmes that facilitate access to new effective medicines in the oncology therapeutic area by bridging the gap to cost effectiveness. Programmes that are linked to clinical response are generally favoured,

with clear eligibility criteria and, preferably, clear stopping/continuation criteria.

Whilst administration of individual claims may not involve significant additional workload, there is recognition that as the number of such programmes increases (and, correspondingly, the number of patients increases), the collective burden on staff within the NHS will become an increasing concern. Programmes should therefore be easy to administer and, where possible, should not require any steps that would not be considered usual practice (e.g. additional clinical investigations should be avoided). Programmes should also be compatible with the normal financial flows that operate with the NHS.

5. Devolved administrations

Following advice from the Department of Health, GSK will be working via the Department of Health to initiate discussions with the devolved administrations in Wales and Northern Ireland to share details of the programme and address any issues relating to implementation of the programme in these devolved administrations.

In addition, GSK will initiate dialogue with the devolved administration in Scotland with a view to ensuring that consideration of this programme will be possible.

6. Concluding remarks

GSK has generated a cost effectiveness estimate involving a 'blended' comparator achieved by taking a weighted average of both the costs and effectiveness of the key treatment options currently employed within the NHS in the target population. Such an approach aims to demonstrate the overall cost effectiveness of treating a population of patients with lapatinib plus capecitabine as an alternative to existing treatment options.

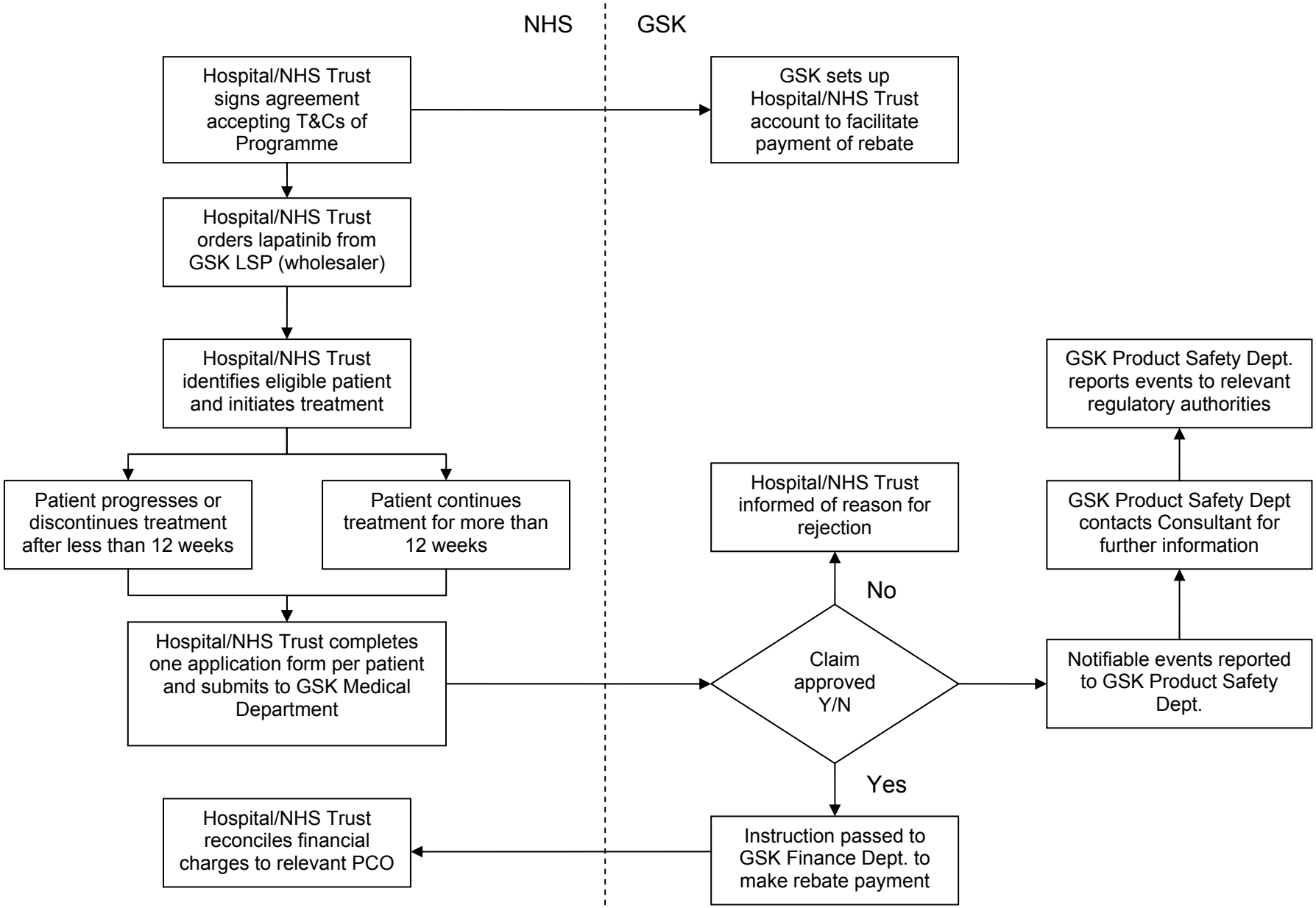
The results of this analysis indicate that adoption of the programme can ensure equity of access for patients and deliver real value to the NHS, achieving cost effectiveness at £16,384k/QALY.

However, it should be noted that adoption of the programme remains dependent on acceptance by NICE of trastuzumab used beyond progression as a valid comparator, as supported by the evidence, and of GSK's approach to demonstrating the overall cost effectiveness of lapatinib plus capecitabine within its licensed indication.

References

1. Response Evaluation Criteria in Solid Tumours (RECIST) Guidelines. Therasse, P et al, Journal of the National Cancer Institute, Vol. 92, No. 3, February 2, 2000.

Appendix 1: Administering the Lapatinib Patient Access Programme



Appendix 2:
Rebate Application Form
Lapatinib Patient Access Programme

This form should be used by NHS Trusts treating NHS patients in England, Wales or Northern Ireland under the terms of the Lapatinib Patient Access Programme. A valid contract ('the Agreement') must be signed by both GSK and the relevant NHS Trust prior to any claim. Terms and conditions are provided within the Agreement.

One application form must be completed per patient. Application forms must be completed in full, as GSK will not be able to authorise incomplete applications.

Completed application forms, signed by an approved authoriser, should be mailed or faxed to GSK as follows:

Address: Lapatinib Patient Access Programme
GlaxoSmithKline UK Ltd
Building 10
Stockley Park West
Uxbridge UB11 1BT
Fax: 020 8990 XXXX

1. Application details

Hospital name: ……..

Hospital postcode: ……..

NHS Acute Trust: ……..

Patient hospital number: ……..

Name of consultant: ……..

Primary care organisation: ……..

2. Patient eligibility for rebate (eligible for rebate if 'yes' to all)

ErbB2+ metastatic breast cancer:	Yes □	No □
Prior treatment with anthracycline:	Yes □	No □
Prior treatment with taxane:	Yes □	No □
Prior treatment with trastuzumab in metastatic setting:	Yes □	No □
Lapatinib prescribed in combination with capecitabine:	Yes □	No □

3. Treatment with lapatinib plus capecitabine

Date of treatment initiation: …...……..……

Patient completed 12 weeks' treatment and continuing: Yes □ No □

Patient discontinued within first 12 weeks: Yes □ No □

Date of discontinuation (if prior to week 12): …...……..……

Reason for discontinuation (please tick): Progression □

Side effects □

Death □

Other □

If 'other', please specify: …….

Please note: for patients discontinuing before the end of week 12, GSK will reimburse the total cost of lapatinib for the whole number of 21-day cycles initiated prior to discontinuation.

4. Authorisation by NHS Trust

I confirm that the information provided within this form is accurate and correct, and that I am authorised to submit this application under the terms of the Lapatinib Patient Access Programme.

Name (print): ……

Job title: ……

Contact number: ……

E-mail address: ……

Signature: ……

Date: ……

GSK use only:
Date received: ……
Application approved: Yes □ No □
Reason for rejection: ……
Date forwarded to Product Safety Dept. …….....

Appendix 3
Cost-effectiveness evidence submission for Lapatinib (Tyverb®▼) Patient Access Programme

1. Introduction

This submission provides details of the cost effectiveness assessment of the Lapatinib (Tyverb®▼) Patient Access Programme (LPAP). It is an addendum to our ACD response and it therefore refers to that document wherever possible in order to avoid duplication.

The LPAP evaluation is based on a 'revised base case' which was described in our ACD response (Scenario 9). Several changes to the original model, its inputs, and assumptions were implemented in order to generate the revised base case. These are summarised and referenced in Section 2, and their impact on the cost-effectiveness of lapatinib in combination with capecitabine is shown in Table 1, Section 2.

2. Changes to the economic model, inputs and assumptions

2.1. Minor corrections to the original cost effectiveness model

Several minor corrections were made to the economic model to address errors that were discovered after GSK made its original submission. They are detailed in Appendix 3 of the ACD response. These changes had negligible impact on the cost effectiveness results for lapatinib in combination with capecitabine. The impact is shown in Table 1 (Scenario 2).

2.2. Finalisation of list price for lapatinib

The acquisition cost of lapatinib was updated from an assumed £11.00 per tablet used in our original submission, to the current list price, £11.49 per tablet (£804.30 per pack; 17,500mg/pack; Scenario 3 in Table 1).

2.3. Incorporation of evidence on the clinical effectiveness of trastuzumab beyond progression

2.3.1. New randomised data comparing trastuzumab plus capecitabine with capecitabine alone - study GBG 26/BIG 3-05

The ACD highlighted the lack of randomised trial evidence on the use of trastuzumab beyond progression as a significant concern in their consideration of the evidence, concluding that the clinical effectiveness of trastuzumab in patients who have disease progression following treatment with trastuzumab was unproven, and that the unadjusted indirect comparison method used resulted in uncertainty surrounding the cost-effectiveness estimates.

On 3 June 08 the statistical results of the only randomised controlled trial (GBG 26 / BIG 3-05)[1,2] investigating continuation of trastuzumab beyond progression in a setting similar to the current indication for lapatinib (i.e. following progression on trastuzumab administered for metastatic disease), were presented at the American Society of Clinical Oncology Annual Meeting (ASCO).

Section 1.2 of the ACD response describes our rationale for the use of these data in a revised base case as a more robust estimate of trastuzumab efficacy.

Details of changes to model parameters concerning health outcomes for trastuzumab-containing therapies, for incorporation into the economic model, are given in Appendix 4 of this addendum. The impact of these new data is explored in Scenario 6 below.

2.3.2. Additional, uncontrolled trastuzumab studies

Our original systematic review of clinical literature was updated from a cut-off of February 2007 to March 2008. The review identified the GBG 26 study, as well as an additional ten non-randomised studies[4-14] involving the use of trastuzumab beyond progression.

Details of the individual study designs and baseline characteristics can be found in Tables 1 and 2 in Appendix 2 of the ACD response. The main efficacy and safety findings for the new non-randomised studies identified via the systematic review are summarised in Tables 3 to 5 in Appendix 2 of the ACD response. Four of the newly identified uncontrolled studies[4-7] report a time to second progression and these data have been included in an updated pooled analysis (with weighting applied to account for sample size) conducted in a similar manner to that undertaken for our original submission, to estimate a pooled median time to progression (TTP) for trastuzumab-based therapy beyond progression. The GBG 26 study2 was also included in this pooled analysis. The disaggregated and pooled results from these studies can be found in section A2.2 in Appendix 2 of the ACD response. The impact of these new data is explored in Scenario 4 below.

2.4. Incorporation of updated evidence on the clinical effectiveness of lapatinib in combination with capecitabine

The Summary of Product Characteristics (SmPC, section 5.1) now presents a later survival analysis than that presented in our original submission. This updated analysis for overall survival was conducted on 28 September 2007. A comparison of the April 06 and September 07 analyses are provided in Table 1.3, Section 1.3, of the ACD response. As mentioned above, details of changes to model parameters concerning health outcomes for capecitabine and lapatinib in combination with capecitabine, for incorporation into the economic model, are given in Appendix 4 of this addendum. The impact of these new data is explored in Scenario 5 below.

2.5. Addressing additional issues highlighted by ACD/ERG

2.5.1. Three-weekly versus weekly trastuzumab administration

The Evidence Review Group (ERG) scenario analysis assumed that all patients receive trastuzumab on a three-weekly schedule (6mg/kg). Our original assumption was that trastuzumab is administered once-weekly (2mg/kg), in accordance with NICE guidance and the SmPC for trastuzumab treatment of metastatic breast cancer. However, in recognition of the use of the three-weekly administration schedule by some practitioners, despite this schedule being licensed only for use in early breast cancer, we supplied a deterministic sensitivity analysis in our original submission. To further address this issue, as highlighted by the ERG, we tested the assumption in the market research (see Section 1.1.3 of Appendix 1, ACD response).

Respondents fed back that an average of 11.6% of trastuzumab in metastatic breast cancer is given weekly (range 0% to 100%; standard deviation of mean = 29.3%).

Therefore we have applied the figures of 11.6% weekly / 88.4% 3-weekly trastuzumab to the revised base case (see below). The impact of these new data is explored in Scenario 7 below.

2.5.2. Calculation of IV medication use/wastage

Our rationale for revised assumptions regarding treatment wastage is outlined in Section 2.1 of the ACD response. The changes are summarised thus:

For trastuzumab, 15% wastage is assumed, based on independent market research with 24 oncology pharmacists from 17 UK cancer networks (July 2008; Taylor Nelson Sofres) to understand the policies adopted regarding single use vials, and to quantify the proportion of trastuzumab for metastatic breast cancer that is wasted. Further details of this market research are presented in section 1.1.3 of Appendix 1, ACD response). This level of wastage was incorporated into the economic model by setting the automatic 'with wastage' facility to 'No' and inflating the per vial acquisition cost of trastuzumab by 1.18 (100/85).

For vinorelbine, wastage was based on the lognormal distribution of BSA as per the original model, which gives a similar estimate of wastage to that derived using the ERG's methodology (see Section 2.1 of the ACD response for details). The impact of these new data is explored in Scenario 8 below.

2.5.3. Trastuzumab administration costs

The original figure of £245.22 for trastuzumab administration costs has been retained in the revised base case.

Trastuzumab administration costs in GSK's original submission (£245.22) were taken from NHS Reference Costs 2006,[15] the most current available at the time. The cost includes the cost of an outpatient chemotherapy consultation £207.22 (interquartile range £171 to £277). In addition the handling cost of a complex IV infusion (£38) was added.[16]

We believe that this represents the more robust costing for this variable than that suggested by the ERG; see Section 2.2 of the ACD response for the rationale.

2.6. Impact of the above changes on the cost effectiveness of lapatinib in combination with capecitabine

A range of scenarios was analysed to evaluate the impact of the above changes on the cost-effectiveness of lapatinib in combination with capecitabine. These scenarios are described below, and the cost effectiveness results for the scenarios summarised in Table 1.

Scenario 1 (original base case; original model):
- Lapatinib list price £11.00 per tablet
- Overall survival data April 2006 cut-off
- Efficacy for trastuzumab comparator regimens from original pooled analysis (11 studies)

Scenario 2 (original base case; corrected model):
- Lapatinib list price £11.00 per tablet

- Overall survival data April 2006 cut-off
- Efficacy for trastuzumab comparator regimens from original pooled analysis (11 studies)

NB. All the following scenarios use the corrected model.

Scenario 3 (*incorporating current list price*)
- Lapatinib list price £11.49 per tablet
- Overall survival data April 2006 cut-off
- Efficacy for trastuzumab comparator regimens from original pooled analysis (11 studies)

Scenario 4 (incorporating updated pooled trastuzumab data)
- Lapatinib list price £11.49 per tablet
- Overall survival data April 2006 cut-off
- Efficacy for trastuzumab comparator regimens from updated pooled analysis (16 studies)

Scenario 5 (incorporating most recent cut-off of lapatinib overall survival data)
- Lapatinib list price £11.49 per tablet
- Overall survival data September 2007 cut-off (most recent data cited in SmPC)
- Efficacy for trastuzumab comparator regimens from updated pooled analysis (16 studies)

Scenario 6 (fully updated price and clinical results)
- Lapatinib list price £11.49 per tablet
- Overall survival data September 2007 cut-off
- Efficacy for trastuzumab comparator regimens from GBG 26/BIG 3-05 study

Scenario 7 (fully updated price and clinical results; addressing rate of 3-weekly trastuzumab)
- Lapatinib list price £11.49 per tablet
- Overall survival data September 2007 cut-off
- Efficacy for trastuzumab comparator regimens from GBG 26/BIG 3-05 study
- 88.4% patients receive 6mg/kg trastuzumab 3-weekly; 11.6% receive 2mg/kg trastuzumab weekly

Scenario 8 (fully updated price and clinical results; addressing IV medication wastage)
- Lapatinib list price £11.49 per tablet
- Overall survival data September 2007 cut-off
- Efficacy for trastuzumab comparator regimens from GBG 26/BIG 3-05 study
- Trastuzumab wastage at 15%; vinorelbine wastage as per original modelling

Scenario 9 (revised base case - fully updated price and clinical results; addressing rate of 3-weekly trastuzumab; addressing IV medication wastage)
- Lapatinib list price £11.49 per tablet
- Overall survival data September 2007 cut-off
- Efficacy for trastuzumab comparator regimens from GBG 26/BIG 3-05 study
- 88.4% patients receive 6mg/kg trastuzumab 3-weekly; 11.6% receive 2mg/kg trastuzumab weekly
- Trastuzumab wastage at 15%; vinorelbine wastage as per original modelling

The ERG reports that trastuzumab monotherapy is rarely used in this setting, which is consistent with the recent market research data reported in Appendix 1 of the ACD response. Therefore the trastuzumab monotherapy comparison is included in Table 1 overleaf for completeness, but is shaded in the table to allow focus on the most relevant comparator regimens – single agent chemotherapies and trastuzumab in combination with either capecitabine or vinorelbine.

Table 1. Summary of impact of changes to the economic model, inputs and assumptions

Scenario	Incremental cost per QALY gained for lapatinib plus capecitabine versus comparators				
	Capecitabine	**Vinorelbine**	**Trastuzumab plus vinorelbine**	**Trastuzumab plus capecitabine**	**Trastuzumab monotherapy**
Scenario 1 (original base case)	£81,251 (QALYs = +0.17, costs = +£13,873)	£67,847 (QALYs = +0.17, costs = +£11,584)	Dominant (QALYs= +0.14, costs = -£4,452)	Dominant (QALYs= +0.14, costs = -£2,186)	Dominant (QALYs= +0.14, costs=-£1,075)
Scenario 2 (original base case, corrected model)	£81,239 (QALYs = +0.17, costs = +£13,872)	£67,836 (QALYs = +0.17, costs = +£11,584)	Dominant (QALYs= +0.14, costs = -£4,662)	Dominant (QALYs= +0.14, costs = -£2,555)	Dominant (QALYs= +0.14, costs = -£1,261)
Scenario 3 (incorporating current list price)	£84,330 (QALYs = +0.15, costs = +£14,400)	£70,927 (QALYs = +0.17, costs = +£12,111)	Dominant (QALYs= +0.14, costs=-£4,134)	Dominant (QALYs= +0.14, costs = -£2,027)	Dominant (QALYs= +0.14, costs = -£733)
Scenario 4 (incorporating updated pooled trastuzumab data)	£84,330 (QALYs = +0.15, costs = +£14,400)	£70,927 (QALYs = +0.17, costs = +£12,111)	Dominant (QALYs= +0.05, costs = -£9,958)	Dominant (QALYs= +0.05, costs = -£7,246)	Dominant (QALYs= +0.05, costs = -£5,712)
Scenario 5 (incorporating most recent cut-off of lapatinib overall survival data)	£93,825 (QALYs = +0.15, costs= + £14,015)	£78,503 (QALYs = +0.17, costs = +£11,726)	Dominant (QALYs= +0.05, costs = -£9,961)	Dominant (QALYs= +0.05, costs = -£7,249)	Dominant (QALYs= +0.05, costs = -£5,714)
Scenario 6 (fully updated price and clinical results)	£93,825 (QALYs = +0.15, costs = +£14,015)	£78,503 (QALYs = +0.17, costs = +£11,726)	Dominant (QALYs= +0.03, costs = -£8,958)	Dominant (QALYs= +0.03, costs = -£6,450)	Dominant (QALYs= +0.03, costs = -£4,993)
Scenario 7 (88.4% 6mg/kg trastuzumab 3-weekly)	£93,825 (QALYs = +0.15, costs = +£14,015)	£78,503 (QALYs = +0.17, costs = +£11,726)	Dominant (QALYs= +0.03, costs = -£4,141)	Dominant (QALYs= +0.03, costs = -£1,632)	Dominant (QALYs= +0.03, costs = -£288)
Scenario 8 (15% wastage)	£93,825 (QALYs = +0.15, costs = +£14,015)	£78,503 (QALYs = +0.17, costs = +£11,726)	Dominant (QALYs= +0.03, costs = -£6,610)	Dominant (QALYs= +0.03, costs = -£4,101)	Dominant (QALYs= +0.03, costs = -£2,968)
Scenario 9 (*Revised base case: 88.4% 6mg/kg trastuzumab 3-weekly and 15% wastage)*	£93,825 (QALYs = +0.15, costs = +£14,015)	£78,503 (QALYs = +0.17, costs = +£11,726)	Dominant(QALYs= +0.03, costs = -£3,583)	Dominant (QALYs= +0.03, costs = -£1.075)	£24,227 (QALYs= +0.03, costs = +£638)

It is clear from the results of Scenarios 1-6 that incorporating the most recent and robust data sources into the cost effectiveness evaluation confirms the results of our original base case: lapatinib in combination with capecitabine remains highly cost effective compared with the key trastuzumab-containing regimens in this setting; lapatinib is not cost effective when compared with single agent chemotherapies (capecitabine or vinorelbine). Of these scenarios we believe that Scenario 6 provides the most robust estimate of cost effectiveness as it is based on randomised trial data. However, if Scenario 5 was preferred (using efficacy for trastuzumab comparator regimens from the updated pooled analysis) it is clear from the decrease in incremental costs that the estimates would further favour lapatinib; therefore the use of Scenario 6 provides the more conservative approach.

Probabilistic sensitivity analysis (PSA) was performed on Scenario 6 (see Section A5.2, Appendix 5 of the ACD response) with the same probability distributions, means and standard errors as used in our original submission. In summary these analyses suggest that the likelihood of lapatinib plus capecitabine having an incremental cost-utility ratio lower than £20,000/QALY when compared with capecitabine or vinorelbine monotherapies is negligible (under 1%); (2-6% for a threshold of £30,000/QALY). The likelihood that lapatinib plus capecitabine has an incremental cost-utility ratio lower than £20,000/QALY when compared with trastuzumab-containing regimens is over 90% (from 85-93% for the £30,000 threshold).

The results of Scenarios 7 and 8 show that revised assumptions concerning intravenous wastage, and the frequency of administration of trastuzumab, do not materially affect the cost effectiveness of lapatinib plus capecitabine when compared with single agent chemotherapies or trastuzumab regimens. However, they do increase the incremental costs of lapatinib plus capecitabine when compared with trastuzumab-containing regimens. When the two sets of assumptions are combined (Scenario 9) lapatinib remains a highly cost effective option (dominant) when compared with the key trastuzumab-containing regimens; when compared with trastuzumab monotherapy, which we agree is rarely used in this setting, this generates a cost utility ratio of around £24,000/QALY. Therefore, in our revised base case, which accounts for the evolving evidence base, as well as addressing concerns raised by the ERG, the cost effectiveness profile of lapatinib in combination with capecitabine remains broadly similar to the base case submitted in April 07.

Probabilistic sensitivity analysis performed on Scenario 9, the revised base case, suggests that the likelihood of lapatinib plus capecitabine being cost effective in the £20,000-£30,000/QALY range is just over 60% when compared with trastuzumab plus capecitabine; the likelihood of being in this range when compared with trastuzumab plus vinorelbine is 78%-82% (Section A5.3, Appendix 5 of ACD response).

3. Blended analysis

GSK strongly believes that lapatinib offers tangible benefits to the group of patients within its licensed indications which has limited treatment options. GSK is committed to a solution that ensures access to lapatinib for all patients with the potential to benefit within its licensed indication. To this end, we have performed an analysis to demonstrate the overall cost effectiveness of lapatinib plus capecitabine against the three major existing therapeutic options currently employed within the NHS (capecitabine monotherapy, and trastuzumab in combination with capecitabine or vinorelbine).

Using the revised base case, as described above (Scenario 9), GSK has generated a cost effectiveness estimate for lapatinib plus capecitabine compared with a ‘blended’

comparator consisting of a weighted average of both the costs and effectiveness of the three key treatment options. To ensure that all patients, including those receiving less commonly used interventions identified in the IMS Oncology Analyzer study (described in Appendix 1 of the ACD response) were represented in the analysis, the less common treatment regimens were re-allocated to the three key intervention groups (see Appendix 1 of the ACD response for underlying evidence and methodology), generating final proportions of:

- 44% capecitabine monotherapy
- 29% trastuzumab in combination with capecitabine
- 27% trastuzumab in combination with vinorelbine

3.1. Cost effectiveness results – blended analysis

Central estimates of cost-effectiveness for lapatinib plus capecitabine versus a 'blended' comparator consisting of a weighted average of both the costs and effectiveness of the three key treatment options (capecitabine monotherapy, trastuzumab plus vinorelbine, trastuzumab plus capecitabine), for Scenario 3 (assumptions and data from original submission), Scenario 6 (modelling including updated clinical results for lapatinib plus capecitabine and trastuzumab regimens), and Scenario 9 (revised base case) were presented in Section 4 of our ACD response, which addressed equality issues. These results show that, using the original and the updated clinical data, with GSK's original assumptions regarding wastage and dosing schedule for trastuzumab, incremental cost effectiveness ratios for lapatinib plus capecitabine are £30,474/QALY (Scenario 3) and £23,463/QALY (Scenario 6), when compared with a 'blended' comparator broadly representing current clinical practice. However, in addressing uncertainties raised in the ACD it is clear that issues such as drug wastage and dosing schedules for trastuzumab have an impact on the cost effectiveness results, and this is reflected in the higher ICER of around £61,000 when these are taken into account in the blended comparator analysis (Scenario 9). The disaggregated results for Scenario 9 are shown in Table 2 of this submission (below). Note that the weighting in the blended comparator calculations use only the three key intervention groups, therefore only the results for these interventions are shown.

In recognition of the need to address the risks associated with the above uncertainties, and to demonstrate clearly the value that lapatinib offers the NHS, in this addendum GSK is proposing the Lapatinib (Tyverb®▼) Patient Access Programme, which aims to facilitate equitable patient access to treatment and maximise value to the NHS. The economic assessment of this scheme is described in Section 4.

Table 2. Revised base case: Results based on current lapatinib price, updated effectiveness data, and wastage based on 15% waste for trastuzumab, waste for vinorelbine based on lognormal distribution of body surface area

	Costs and effects of different treatment strategies				Incremental costs and effects of lapatinib plus capecitabine versus:			
	Lapatinib plus capecitabine	Capecitabine	Trastuzumab plus vinorelbine	Trastuzumab plus capecitabine	Capecitabine	Trastuzumab plus vinorelbine	Trastuzumab plus capecitabine	Blended comparator
Life years*	1.574	1.384	1.575	1.575	0.190	-0.001	-0.001	0.083
Progression-free life years*	0.694	0.426	0.573	0.573	0.268	0.121	0.121	0.186
Post-progression life years*	0.880	0.958	1.002	1.002	-0.078	-0.122	-0.122	-0.103
QALYs*	0.897	0.748	0.871	0.871	0.149	0.026	0.026	0.080
Cost, study meds*	14,648	2,168	14,029	13,150	12,480	619	1,498	6,093
Cost, administration*	227	84	4,189	2,560	144	-3,962	-2,333	-1,683
Cost, monitoring*	461	0	381	381	461	80	80	248
Treatment specific AE costs*	0	0	0	0	0	0	0	0
Other progression free costs*	4,122	2,529	3,403	3,403	1,593	719	719	1,103
Other post progression costs*	7,481	8,143	8,519	8,519	-663	-1,039	-1,039	-873
Total Costs*	26,939	12,924	30,522	28,013	14,015	-3,583	-1,075	4,887
Cost / life year gained					73,650	3,117,672 †	935,102 †	58,825
Cost / progression free life year					52,247	dominant	dominant	26,301
Cost / QALY					93,825	dominant	dominant	**60,730****

* Costs and effects discounted by 3.5%; ** Please note that the blended cost/QALY in this scenario differs slightly from that shown in the ACD response (£61,088/QALY) which was derived from rounded figures; † Lapatinib+capecitabine is less costly and less effective

4. Economic assessment of the Lapatinib (Tyverb®▼) Patient Access Programme (LPAP)

4.1. Modifications to the model to assess LPAP (up to 12 weeks free)

Under the terms of the proposed LPAP programme, the acquisition cost of the lapatinib utilised by the patient during the initial period of treatment is refunded up to the point of discontinuation, to a maximum of 12 weeks. Therefore in order to assess the cost-effectiveness of the scheme, the acquisition costs of lapatinib treatment were simply removed from the economic analysis for each patient, up to the point they cease treatment (if this occurs before 12 weeks), or for a maximum of 12 weeks (for those patients continuing on treatment beyond this point).

The costs of administering the LPAP have not been explicitly included in this submission. However, it is anticipated that these would be minimal as the scheme is based on assessments of disease that would be carried out as a normal part of patient care.

4.2. Cost-effectiveness results – LPAP

Central estimates of cost-effectiveness of lapatinib plus capecitabine versus the 'blended' comparator described above, in the context of the Lapatinib (Tyverb®▼) Patient Access Programme, are shown in Table 3 overleaf. The incremental cost utility ratio of £16,384/QALY suggests that lapatinib in combination with capecitabine would be a cost-effective treatment option when implemented in the context of the scheme.The blended cost effectiveness result is influenced by the presence of the capecitabine monotherapy comparison, which counterbalances the highly cost-effective profile for the main trastuzumab regimen comparisons. However, as the ICER is well below the commonly accepted threshold for cost effectiveness (£20,000-£30,000/QALY) we believe that the uncertainties associated with the use of trastuzumab in this setting have been addressed in this evaluation.

4.3. Probabilistic sensitivity analysis (PSA) – LPAP

A summary of the probabilistic sensitivity analysis results for individual comparator therapies is presented in Table 4, and detailed results are presented in Section 4.3.1. Although it has not been possible to perform a specific PSA on the comparison with a blended scenario, it is clear from the individual results that the LPAP increases the probability that lapatinib plus capecitabine is cost-effective when compared with the PSA for the revised base case without the scheme (Scenario 9). Indeed, for the trastuzumab plus capecitabine, and trastuzumab plus vinorelbine comparisons the probabilities are similar with the scheme to those obtained with Scenario 6 - original base case assumptions with updated clinical data (shown in Appendix 5, ACD response).

The probabilistic sensitivity analysis with the LPAP suggests that the likelihood of lapatinib plus capecitabine being cost effective in the £5,000-£20,000/QALY range is over 90% when compared with the key trastuzumab-containing regimens (trastuzumab plus capecitabine, or vinorelbine). The likelihood of being cost effective when compared with single agent chemotherapies is slightly increased, but still remains negligible.

Table 3. Evaluation of Lapatinib (Tyverb®▼) Patient Access Programme (using the revised base case)

	Costs and effects of different treatment strategies				Incremental costs and effects of lapatinib plus capecitabine versus:			
	Lapatinib plus capecitabine	**Capecitabine**	**Trastuzumab plus vinorelbine**	**Trastuzumab plus capecitabine**	**Capecitabine**	**Trastuzumab plus vinorelbine**	**Trastuzumab plus capecitabine**	**Blended comparator**
Life years*	1.574	1.384	1.575	1.575	0.190	-0.001	-0.001	0.083
Progression-free life years*	0.694	0.426	0.573	0.573	0.268	0.121	0.121	0.186
Post-progression life years*	0.880	0.958	1.002	1.002	-0.078	-0.122	-0.122	-0.103
QALYs*	0.897	0.748	0.871	0.871	0.149	0.026	0.026	0.080
Cost, study meds*	11,114	2,168	11,098	13,150	8,947	17	-2,036	2,559
Cost, administration*	192	84	2,899	2,560	108	-2,708	-2,368	-1,719
Cost, monitoring*	461	0	381	381	461	80	80	248
Treatment specific AE costs*	0	0	0	0	0	0	0	0
Other progression free costs*	4,122	2,529	3,403	3,403	1,593	719	719	1,103
Other post progression costs*	7,481	8,143	8,519	8,519	-663	-1,039	-1,039	-873
Total Costs*	23,370	12,924	26,300	28,013	10,446	-2,931	-4,644	1,319
Cost / life year gained					54,895	†2,549,854	†4,040,293	15,870
Cost / progression free life year					38,942	Dominant	Dominant	7,095
Cost / QALY	* Costs and effects discounted by 3.5; † Lapatinib+capecitabine is less costly and less effective				69,932	Dominant	Dominant	**16,384**

Table 4. Summary of PSA results: Evaluation of Lapatinib (Tyverb®▼) Patient Access Programme (using the revised base case)

	Capecitabine monotherapy	Vinorelbine monotherapy	Trastuzumab plus vinorelbine	Trastuzumab plus capecitabine	Trastuzumab monotherapy
ΔCost, £	10,446	8,157	-7,152	-4,644	-2,931
95%CI	(6,597, 14,476)	(4,355, 12,303)	(-16,073, -56)	(-12,801, 1,751)	(-11,213, 4,116)
ΔQALY	0.1494	0.1494	0.0263	0.0263	0.0263
95%CI	(-0.047, 0.338)	(-0.041, 0.341)	(-0.274, 0.287)	(-0.284, 0.289)	(-0.267, 0.266)
ΔCost/ΔQALY, £	69,932	54,610	dominant	dominant	dominant
95%CI	(29,179, Dominated)	(17,890, Dominated)	Undefined	Undefined	Undefined
Quadrant of cost-effectiveness plane					
NE (Cost>0, QALYs>0)	92.5%	93.7%	1.3%	5.8%	10.3%
SE (Cost<0, QALYs≥0, or Costs=0, QALYs>0; dominant)	0.0%	0.0%	53.2%	51.2%	45.5%
SW (Cost<0, QALYs<0)	0.0%	0.0%	44.4%	39.2%	35.6%
NW (Cost>0, QALYs≤0 or Cost=0, QALYs<0 ; dominated)	7.5%	6.3%	1.1%	3.8%	8.6%
Probability Lapatinib preferred | WTP (£) for QALY, %					
5,000	0%	0%	97%	92%	81%
10,000	0%	0%	97%	91%	81%
15,000	0%	1%	96%	89%	80%
20,000	0%	3%	95%	87%	78%
25,000	1%	9%	93%	86%	77%
30,000	9%	24%	90%	82%	75%

4.3.1. LPAP scheme - Detailed probabilistic sensitivity analysis results for individual comparisons

Lapatinib plus capecitabine versus capecitabine monotherapy

Figure 1. Cost-effectiveness plane for lapatinib plus capecitabine versus capecitabine monotherapy

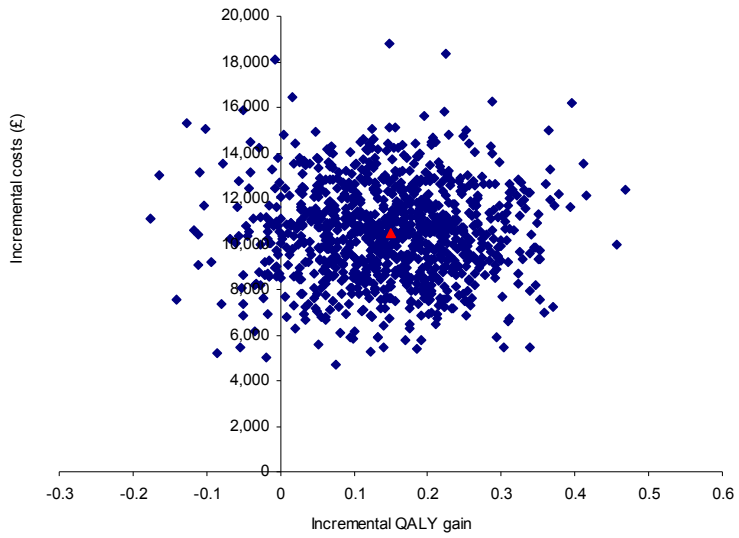
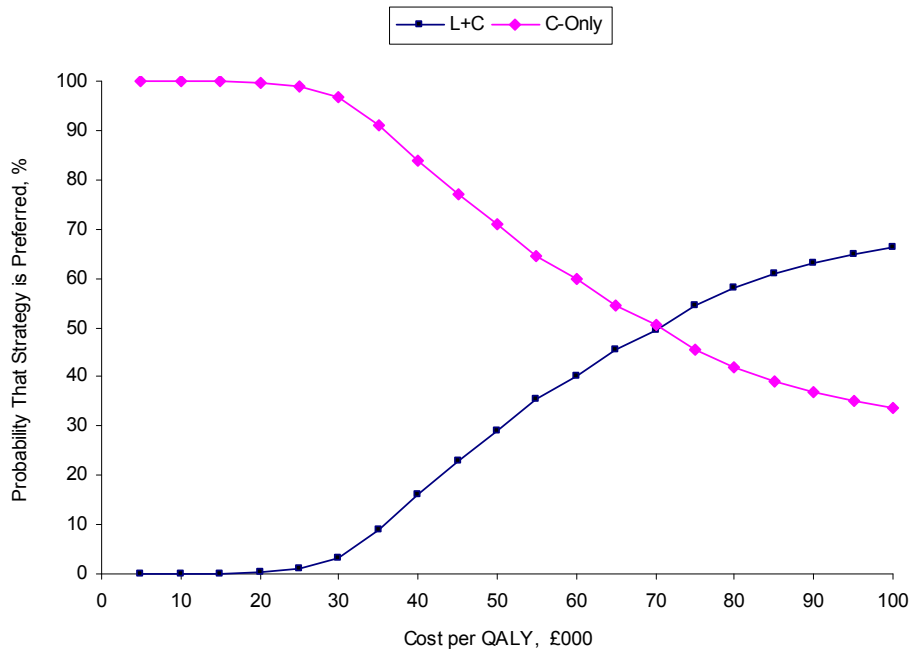


Figure 2. Cost-effectiveness acceptability curves for lapatinib plus capecitabine versus capecitabine monotherapy



Lapatinib plus capecitabine versus vinorelbine monotherapy

Figure 3. Cost-effectiveness plane for lapatinib plus capecitabine versus vinorelbine monotherapy

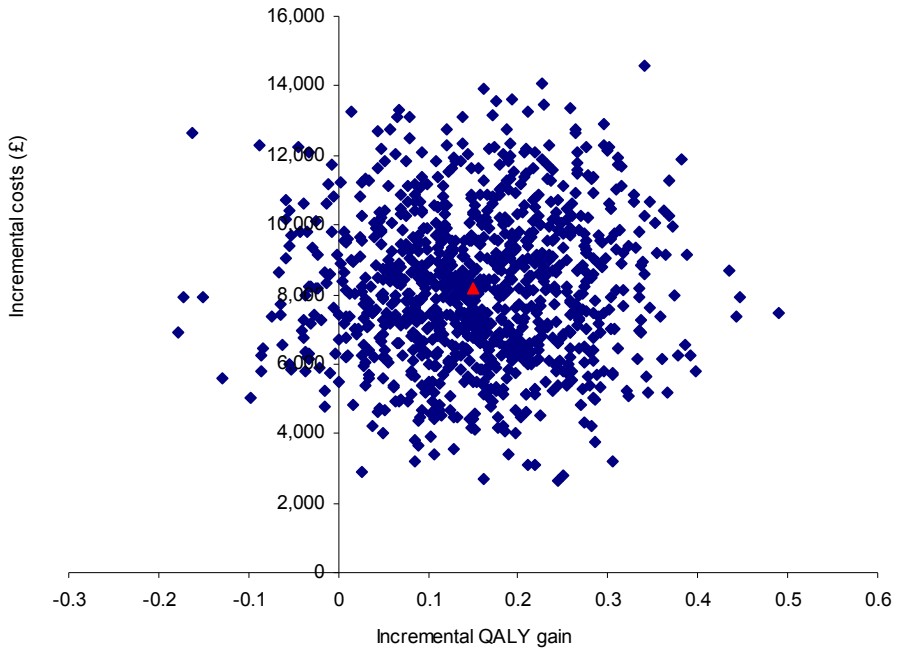
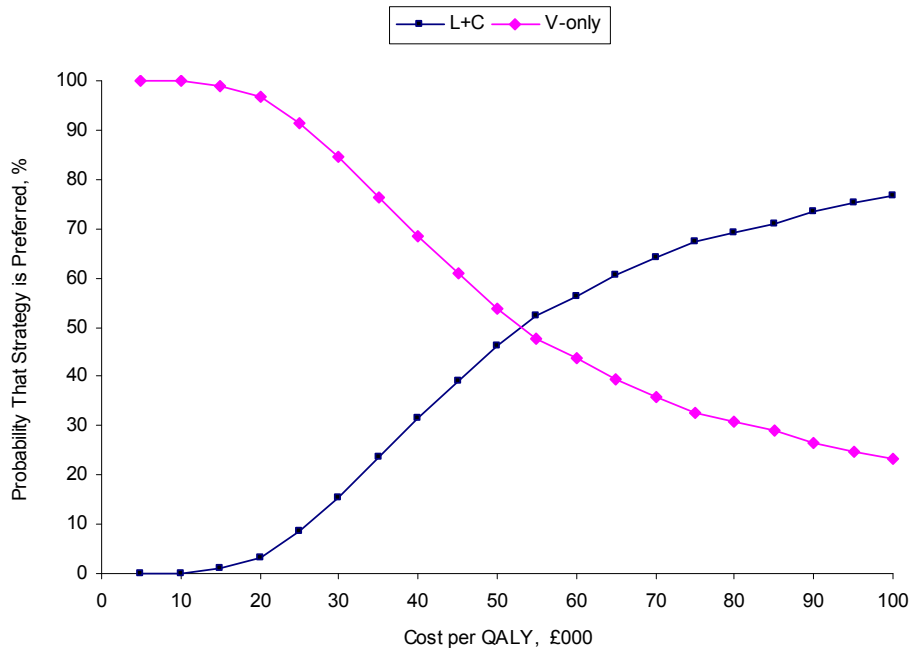


Figure 4. Cost-effectiveness acceptability curves for lapatinib plus capecitabine versus vinorelbine monotherapy



Lapatinib plus capecitabine versus trastuzumab plus vinorelbine

Figure 5. Cost-effectiveness plane for lapatinib plus capecitabine versus trastuzumab plus vinorelbine

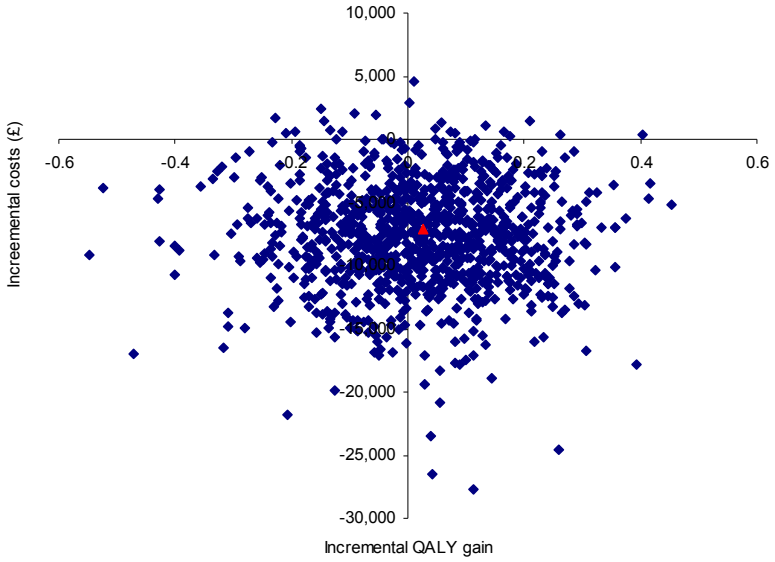
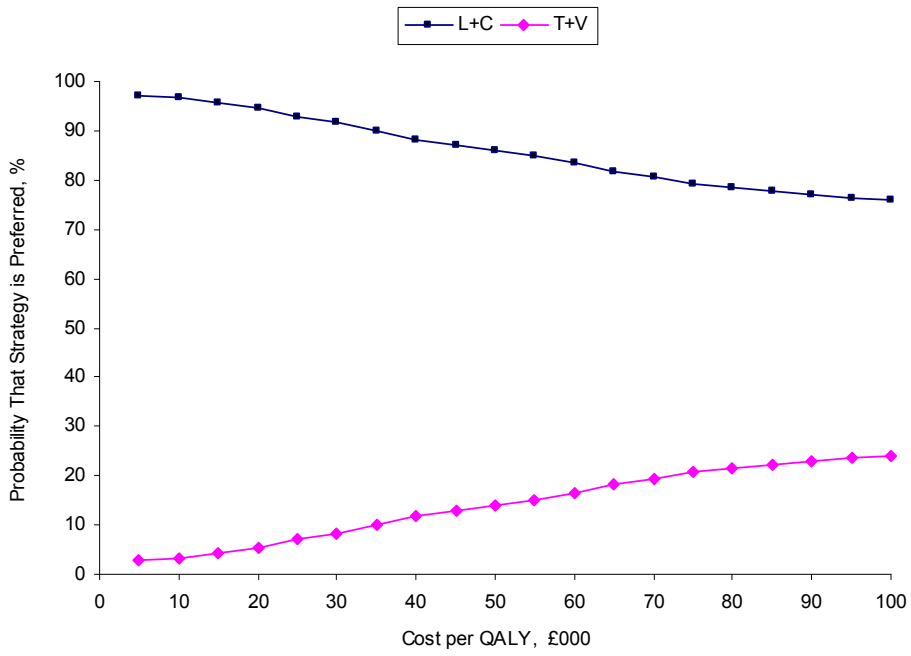


Figure 6. Cost-effectiveness acceptability curves for lapatinib plus capecitabine versus trastuzumab plus vinorelbine



Lapatinib plus capecitabine versus trastuzumab plus capecitabine

Figure 7 Cost-effectiveness plane for lapatinib plus capecitabine versus trastuzumab plus capecitabine

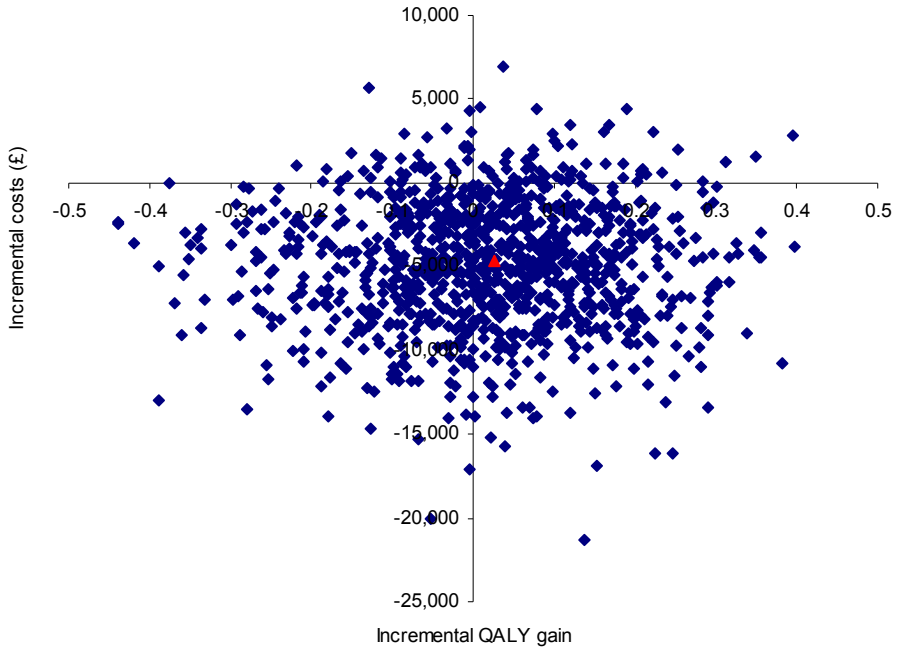
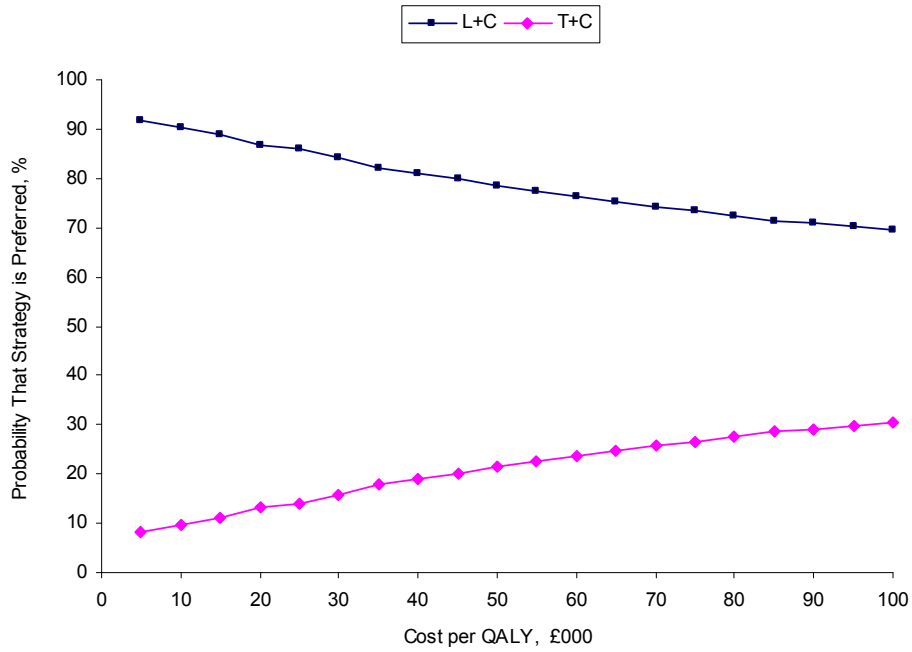


Figure 8 Cost-effectiveness acceptability curves for lapatinib plus capecitabine versus trastuzumab plus capecitabine



Lapatinib plus capecitabine versus trastuzumab monotherapy

Figure 9. Cost-effectiveness plane for lapatinib plus capecitabine versus trastuzumab monotherapy

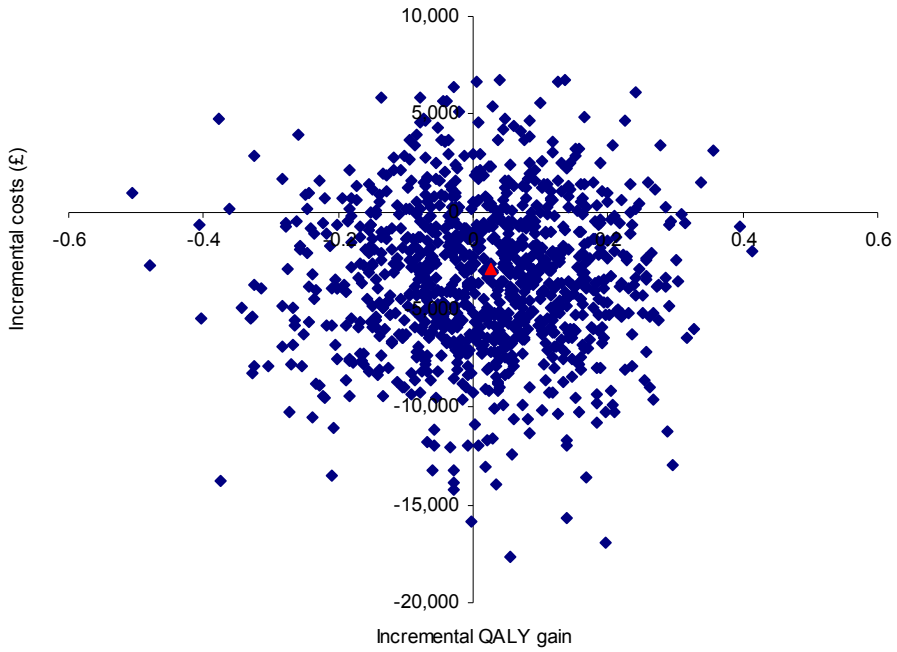
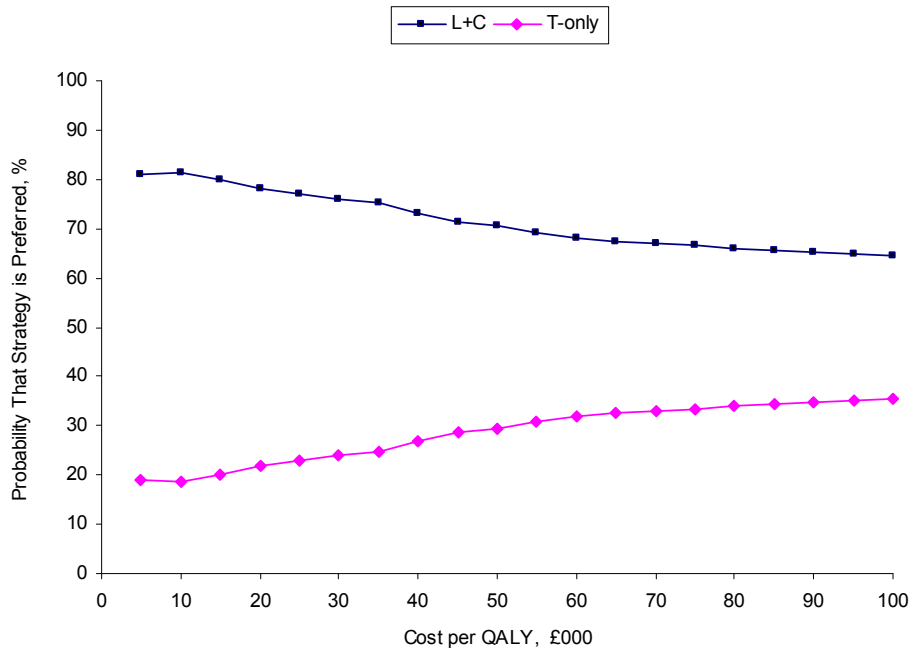


Figure 10. Cost-effectiveness acceptability curves for lapatinib plus capecitabine versus trastuzumab monotherapy



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Appendix 4
Changes to model parameters concerning health outcomes for capecitabine monotherapy, lapatinib plus capecitabine, and trastuzumab-containing regimens

1.1. Model parameters

1.1.1. Modelling health outcomes for capecitabine monotherapy and lapatinib plus capecitabine

The methodology for modelling health outcomes for capecitabine monotherapy and lapatinib plus capecitabine using the September 08 overall survival results is identical to that used in our original submission.

Table 1 shows the resulting parameters for the Weibull models of overall survival and progression-free survival. The data used in the current health economic analysis relate to the September 2007 cut-off for study EGF100151, using independently assessed time-to-event outcomes.

Table 1. Weibull curve parameters statistical analysis of study EGF100151 – September 07 cut-off

Parameter	Mean	Standard deviation	Distribution
Overall survival model Apr'06			
Weibull scale parameter, lambda (l)	0.0019	0.0002	Bootstrap estimates
Weibull shape parameter, gamma (γ)	1.4846	0.1072	Bootstrap estimates
Overall survival model Sep'07			
Weibull scale parameter, lambda (l)	0.0017	0.0001	Bootstrap estimates
Weibull shape parameter, gamma (γ)	1.3822	0.0676	Bootstrap estimates
Progression-free survival model			
Weibull scale parameter, lambda (l)	0.0058	0.0004	Bootstrap estimates
Weibull shape parameter, gamma (γ)	1.3920	0.0632	Bootstrap estimates

γ =1/scale. λ =exp(-Intercept - Estimate $_{L+C\ vs\ C\text{-}only}$).

Figure 1 (a and b) show a comparisons of the observed Kaplan-Meier estimates of overall survival for capecitabine monotherapy and lapatinib plus capecitabine, using a. the April 06 data cut-off, and b. the latest overall survival data (Sept 07). The figures suggest that the Weibull regression models provide a good fit against the empirical data.

Figure 1a. Observed and fitted Weibull model of overall survival for capecitabine monotherapy and lapatinib plus capecitabine (April 06 cut-off)

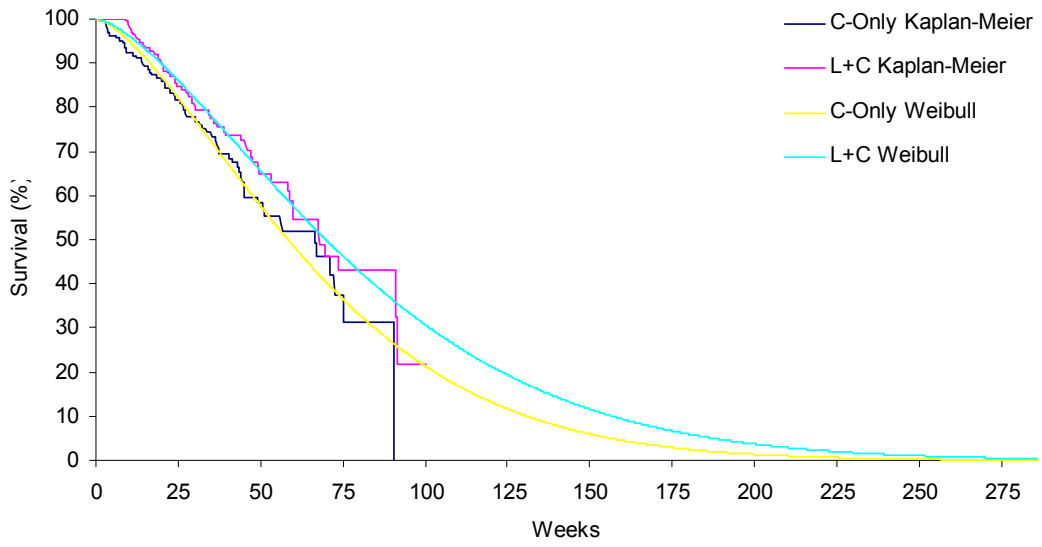
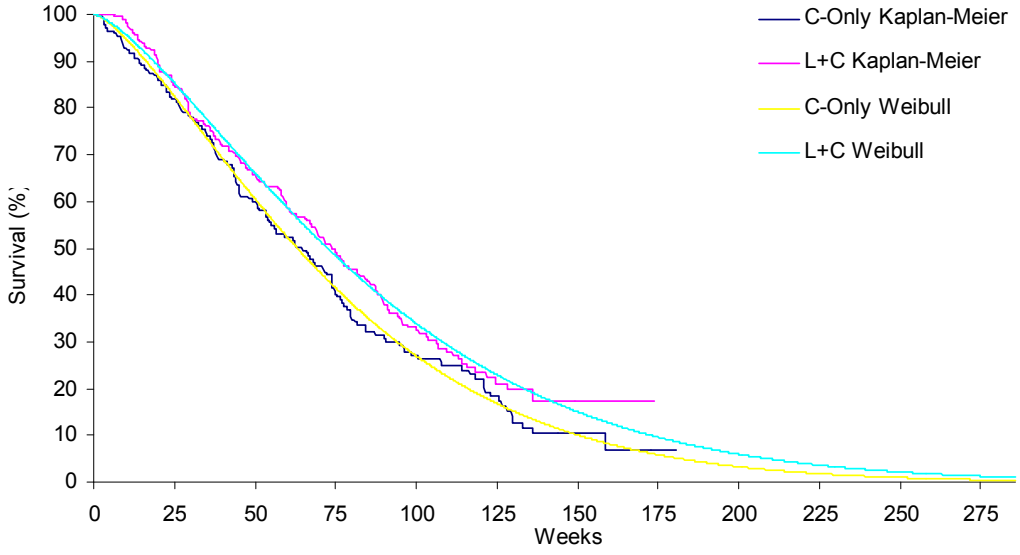


Figure 1b. Observed and fitted Weibull model of overall survival for capecitabine monotherapy and lapatinib plus capecitabine (September 07 cut-off)



The resulting hazard ratios describing the relative benefit of lapatinib plus capecitabine versus capecitabine monotherapy are shown in Table 2.

Table 2 Relative hazard ratios for lapatinib plus capecitabine versus capecitabine monotherapy

Parameter	*Value*	*Standard deviation*	*Distribution*
Progression-free survival hazard ratio	0.6085	0.06885	Bootstrap estimates
Overall survival hazard ratio (April 06)	0.83440	0.10455	Bootstrap estimates
Overall survival hazard ratio (September 07)	0.8703	0.07459	Bootstrap estimates

$HR=\exp(-Estimate_{L+C \text{ vs. } C\text{-only}})$

Table 3 compares the PFS and OS data derived from the Kaplan-Meier curves of EGF100151 against the modelled data, for both the April 06 and September 07 cut-offs).

Table 3 PFS and OS data derived from the Kaplan-Meier curves of EGF100151

	Outcome measure	Data type	Lapatinib plus capecitabine	Capecitabine-only	Difference
April 06 cut-off	Median PFS (days)	EGF100151 data (Kaplan-Meier)	189	122	67
		Modelled data (Proportional hazards regression)	217	132	85
	Mean PFS (days)	EGF100151 data (Kaplan-Meier) *	259	160	99
		Modelled data (Proportional hazards regression)*	250	157	93
	Median OS (days)	EGF100151 data (Kaplan-Meier)	473	465	8
		Modelled data To end of FU (last failure time) (Proportional hazards regression)	488	407	81
	Mean OS (days)	EGF100151 data (Kaplan-Meier) **	459	404	55
		Modelled data To end of FU (last failure time) (Proportional hazards regression) **	440	400	40
Sept 07 cut-off	Median OS (days)	EGF100151 data (Kaplan-Meier)	517	452	65
		Modelled data To end of FU (last failure time) (Proportional hazards regression)	507	441	66
	Mean OS (days)	EGF100151 data (Kaplan-Meier)***	577	506	71
		Modelled data To end of FU (last failure time) (Proportional hazards regression)***	570	509	62

* Last failure time in both arms was progression (i.e., PFS[t_{max}]=0. Mean PFS therefore calculated to maximum follow up of either L+C or C-only (L+C, 600 days)

**Last failure time in L+C arm was censored (OS[t_{max}]>0); in C-only arm, death (OS[t_{max}]=0). Mean OS therefore calculated to maximum FU of either L+C or C-only (L+C, 701 days)

***Last failure time in both arms was censored (OS[t_{max}]>0). Mean OS therefore calculated to the earliest maximum FU of either L+C or C-only (L+C, 1215 days)

1.1.2. Modelling the relative effectiveness of trastuzumab with or without chemotherapy

In GSK's original submission the cost-effectiveness of lapatinib plus capecitabine (L+C) versus capecitabine monotherapy (C-only) was estimated based on effectiveness data from the pivotal lapatinib trial (EGF100151). To obtain estimates of effectiveness for L+C and C-only, PH Weibull survival functions were fit to patient-level failure-time data on PFS and OS from the EGF100151 trial.

An indirect comparison of the cost-effectiveness of L+C versus TZ as monotherapy (TZ-only), or in combination with capecitabine (TZ+C) or vinorebline (TZ+V) was also conducted. Lacking data from head-to-head studies, we estimated the clinical effectiveness of TZ-based therapies based on a pooled estimate of median TTP / PFS with continued TZ in prospective and retrospective cohort studies of this treatment strategy (TTP and PFS were assumed to be similar in this population). While the use of effectiveness data from non-comparative studies may be necessary in the absence of head-to-head trials, results of the GBG 26/BIG 3-05 trial, a head-to-head comparison of TZ+C versus C-only in HER2+ trastuzumab-refractory patients, have recently become available[1,2] (please see GSK's response to the Appraisal Consultation Document for lapatinib for details). Accordingly, an analysis was performed to estimate hazard ratios for TZ+C versus C-only for PFS/TTP and OS using data from the GBG 26/BIG 3-05 trial and methods similar to those employed to estimate the PFS and OS for L+C versus C-only from the EGF100151 data (i.e., PH Weibull survival models) for use in this updated evaluation of the cost-effectiveness of lapatinib.

The GBG 26/BIG 3-05 study

The GBG 26/BIG 3-05 study was a randomized controlled trial of TZ+C vs. C-only in women with HER2+ MBC who had received at least one prior course of TZ and no more than one prior course of palliative chemotherapy (CT). In both groups, capecitabine (C) was administered 2500 mg/m² on days 1-14, every 21 days. Patients randomized to TZ+C received TZ 6 mg/kg every three weeks in addition to C. The study was planned to recruit 241 pts per arm to show an improvement from 4 to 5.1 months (hazard ratio 0.8) from continuing TZ. However, the trial was closed end of May 2007 on advice of the Independent Data Monitoring Committee after having recruited only 156 patients because of slow accrual. Preliminary results of the GBG 26/BIG 3-05 study based on a median of 11.8 months of follow-up were presented at the 2007 San Antonio Breast Cancer Symposium (SABCS)[1]. Results based on 15.6 months of follow-up were subsequently presented at the 2008 American Society of Clinical Oncology (ASCO) Annual Meeting[2]. Results for PFS, TTP, and OS reported at SABCS 2007 and ASCO 2008 are summarized in Table 4 below.

Table 4. Summary of results from GBG 36 / BIG 3-05

		SABCS 2007				ASCO 2008			
Outcome	**Treatment**	**Median**	**P**	**HR[1]**	**p**	**Median**	**P**	**HR[1]**	**P**
PFS	T+C	8.5	Nr	0.71	nr	nr	Nr	nr	Nr
	C-only	5.6				nr			
TTP	T+C	nr	Nr	nr	nr	8.2	0.0338	0.69	0.034
	C-only	nr				5.6			
OS	T+C	20.3	Nr	0.79	nr	25.5	0.257	0.76	0.26
	C-only	19.9				20.4			

nr=not reported

[1]From Cox proportional hazard regression model (presumed). It should be noted that the HR obtained from the PH Weibull AFT regression model does not necessarily equal that obtained from Cox PH regression model

It should be noted that PFS and OS were reported at SABCS 2007 whereas TTP and OS were reported at ASCO 2008. No statistical testing was reported for results in the SABCS 2007 poster.

Methods

The three parameters of PH Weibull models were estimated for T+C and C-only for TTP (λ^{TTP}, γ^{TTP}, $HR^{TTP}_{T+C\ vs\ C\text{-}only}$) and OS ($\lambda^{OS}$, γ^{OS}, $HR^{OS}_{T+C\ vs\ C\text{-}only}$) in GBG 26 / BIG 3-05 using Accelerated Failure Time (AFT) regression (SAS PROC LIFEREG) and product-limit survival estimates for TTP and OS reported at ASCO 2008.[1] Data from the ASCO 2008 poster were used because these data were based on complete follow-up (median 15.6 months). Although the ASCO 2008 poster reported only TTP and not PFS, it was reasonable to approximate PFS with TTP, because in patients with MBC, deaths from causes other than breast cancer are rare. Also, as shown in Table 4 above, the effect of T+C versus C-only on TTP reported at ASCO 2008 (HR=0.69) was similar to that reported for PFS at SABC 2007 (HR=0.71). Product limit survival estimates for TTP and OS in GBG 36/BIG 3-05, reproduced from Figures 5 and 6 of the ASCO 2008 poster, are shown in Figures 2 and 3 below.

Figure 2. TTP in GBG 26/ BIG 3-05 trial: Figure 5 in ASCO 2008 poster

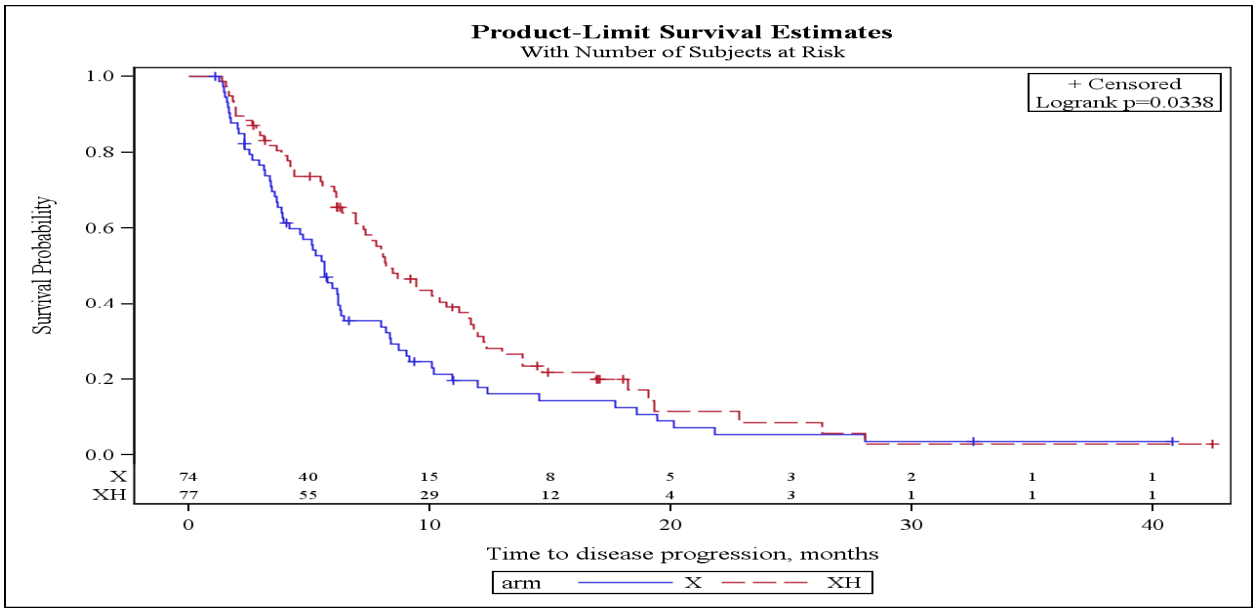
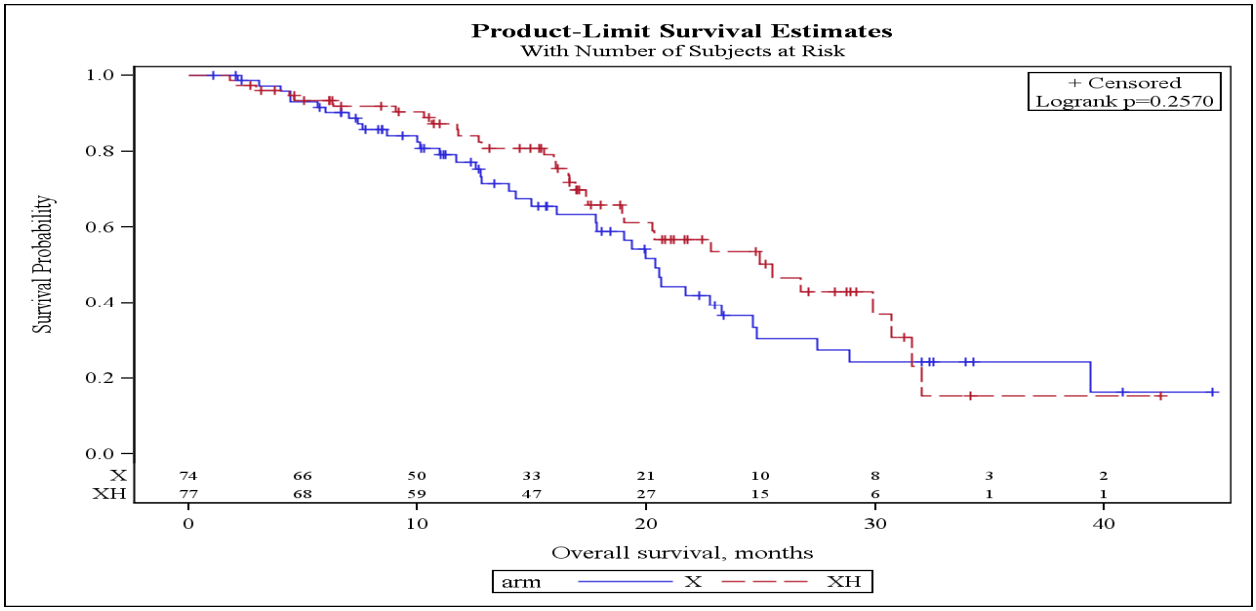


Figure 3. OS in GBG 26/BIG 3-05 trial: Figure 6 in ASCO 2008 poster



Patient-level failure time data for TTP and OS were obtained by first digitizing the survival proportions and censoring times for TTP and OS reported in Figures 5 and 6 of the GBG 26/BIG 3-05 2008 ASCO poster using digitising software (XY extract). These data were then combined with information on numbers of subjects at risk at five month intervals of follow-up (as reported in each figure) to approximate the analytical data sets that were used to generate the figures (i.e., for each patient in the trial, a failure time and censoring variable were created). Ambiguity in censoring times was resolved using the Microsoft Excel Solver assuming that censoring events would be distributed uniformly across five month time intervals. Product-limit estimated TTP and OS obtained from these replicate datasets are shown in Figures

4 and 5 below. These figures closely match those reported in the 2008 ASCO poster (Figures 2 and 3 above [original Figures 5 and 6 in the poster]).

Figure 4. Product limit estimated TTP generated from replicated GBG 26/BIG 3-05 dataset

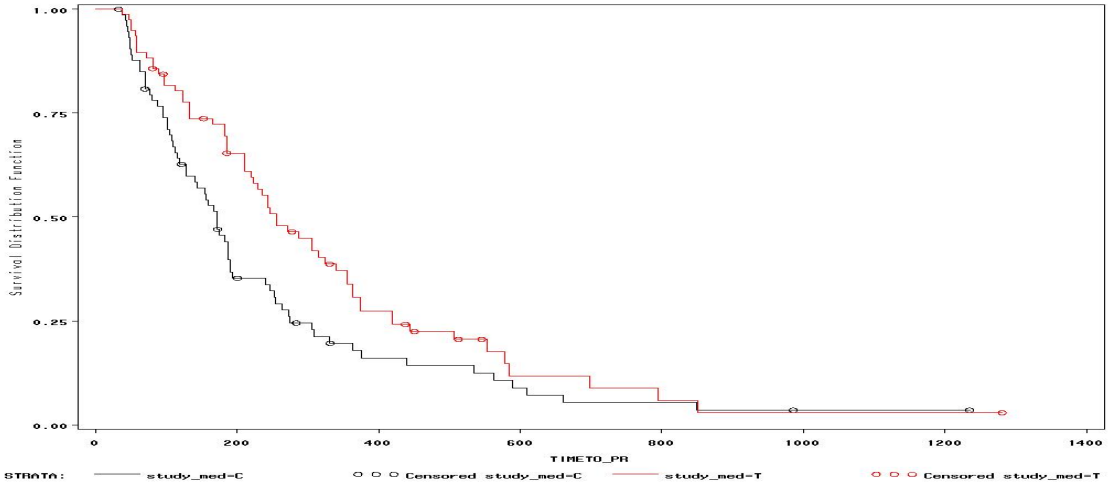
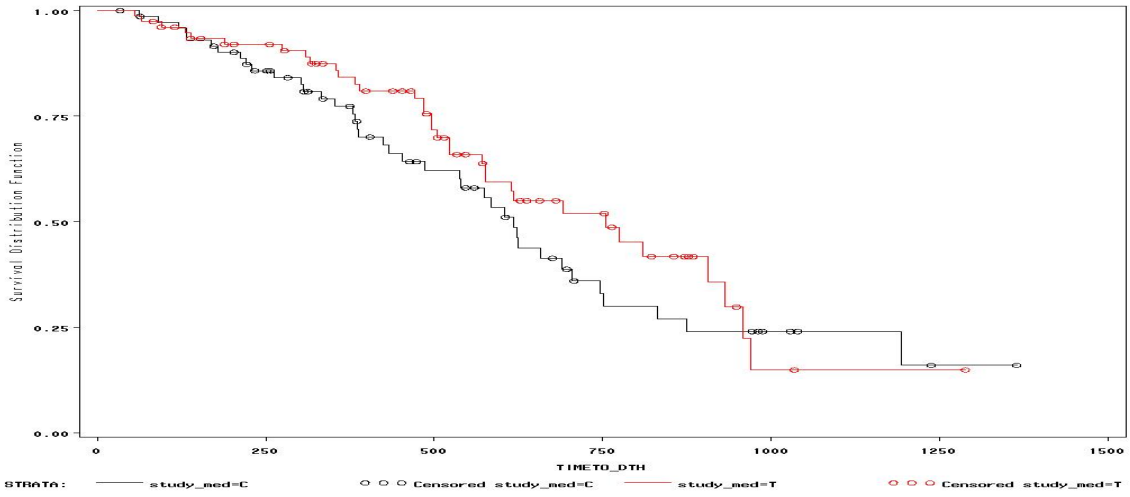


Figure 5. Product-limit estimated OS generated from replicated GBG 26/BIG 3-05 dataset



These replicate datasets were then analyzed using AFT regression (SAS PROC LIFEREG) to obtain parameters of the Weibull distributions for TTP and OS. These parameters are shown in Table 5 below.

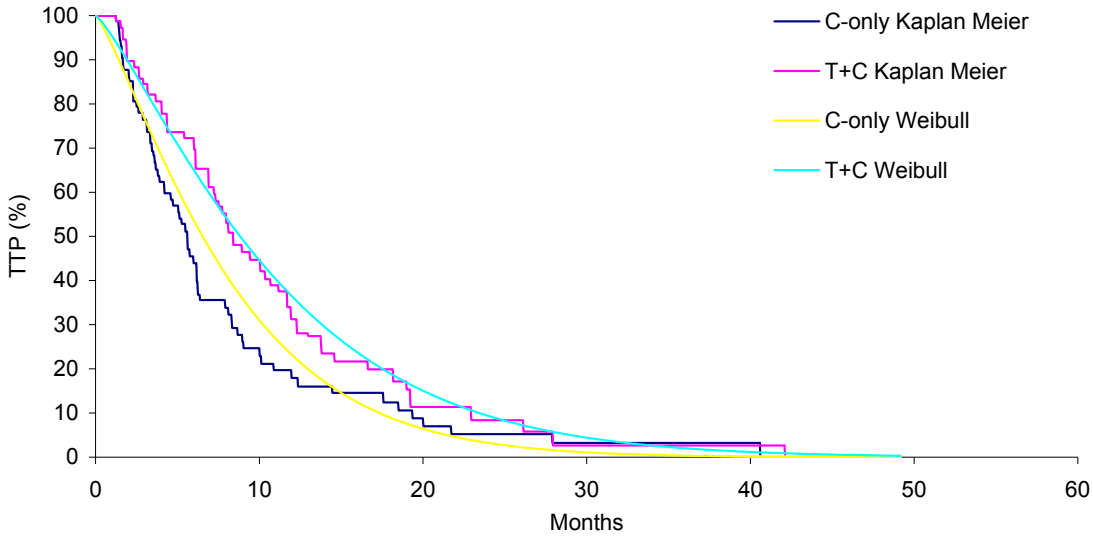
Table 5. Parameters of Weibull Model from Von Minckwitz et al, 2008

	TTP		OS	
	Estimate	**SE**	**Estimate**	**SE**
AFT model output (from SAS)				
Intercept	5.8913	0.1043	6.8014	0.1027
Estimate $_{L+C\ vs.\ C\text{-}only}$	0.3015	0.1457	0.1397	0.1368
Scale	0.8131	0.0536	0.5788	0.0539
Survival function parameters				
Λ	0.003736	0.000390	0.001279	0.000131
γ	1.229861	0.081073	1.727713	0.160891
HR $_{L+C\ vs\ C\text{-}only}$	0.739708	0.107775	0.869619	0.118964
γ =1/scale. λ =exp(Intercept + Estimate $_{L+C\ vs\ C\text{-}only}$). HR=exp(Estimate$_{L+C\ vs.\ C\text{-}only}$)				

Comparisons of the PH Weibull and Kaplan-Meier (Product Limit) estimated TTP and OS from GBG 26/BIG 3-05 are shown in Figures 6 and 7 below.

Figure 6 – please ignore figure number on embedded figure

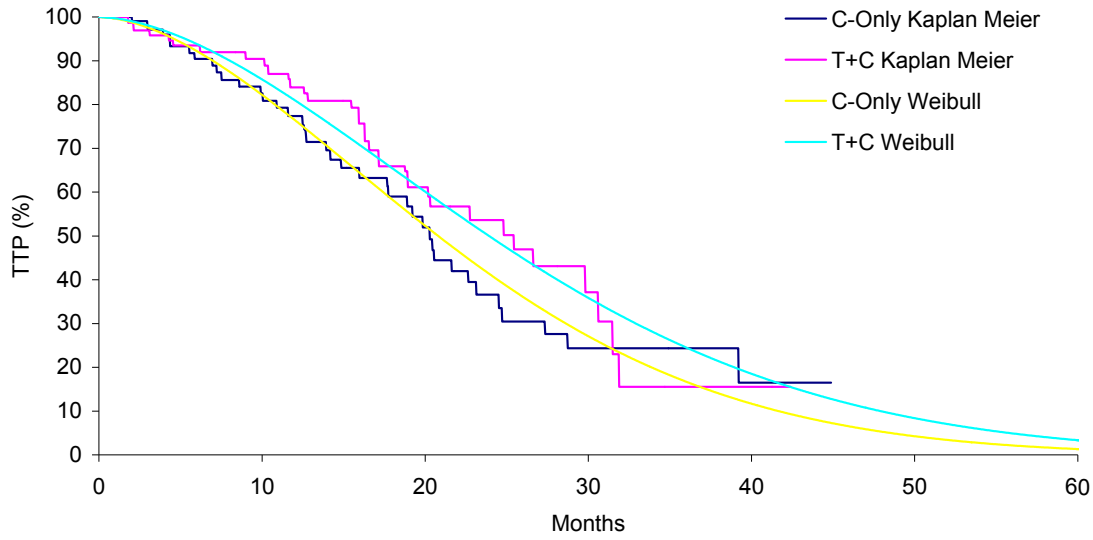
Figure 5. Kaplan-Meier and PH Weibull estimated TTP from GBG 26 /BIG 3-05



No. at Risk						
T+C	74	15	5	2	1	0
C-only	77	29	4	1	1	0

Figure 7 – please ignore figure number on embedded figure

Figure 6. Kaplan-Meier and PH Weibull estimated OS from GBG 26 /BIG 3-05



No. at Risk						
T+C	74	50	21	8	2	0
C-only	77	59	27	6	1	0

As the objective was to estimate HRs for T+C versus C-only using methods similar to those employed to estimate HRs for L+C versus C-only, alternative survival distributions (e.g., gamma) were not explored. However, based on visual inspection, the fitted models match the empirical survival distributions well. Also, measured in terms of the "area under the curve", expected TTP and OS are similar based on the Kaplan-Meier survival curves and the fitted curves. Expected TTP is 47.3 weeks for TZ+C and 35.6 weeks for C-only based on the Kaplan-Meier estimates (difference=11.7 weeks). Based on the PH Weibull model, expected TTP is 48.4 weeks for TZ+C and 35.8 weeks for C-only (difference=12.6 weeks). Measured out to 42.3 months (maximum follow-up in GBG 26/BIG 3-05) expected OS is 106 weeks for TZ+C and 97 weeks for C-only based on the Kaplan-Meier estimates (difference=9 weeks). Based on the Weibull model, expected OS is 107 weeks for TZ+C and 96 weeks for C-only (difference=11 weeks).

Discussion

Using data from GBG26 /BIG 3-05 and AFT regression, we estimated the PH Weibull HR for T+C versus C-only for TTP to be 0.73971; the corresponding figure for OS was 0.86962. This compares with estimates 0.60847 for PFS and 0.87032 for OS for L+C versus C-only using similar methods and data from EGF100151 (PFS from April 2006 PFS data-cut and OS from September 2007 OS data-cut) .

In the hierarchy of research designs, the results of randomized, controlled trials are considered to be evidence of the highest grade[3]. According to NICE, data from head-to-head trials should be presented in the reference-case analysis, if available.[4] Glenny and colleagues describe an approach recommended by NICE for conducting indirect comparisons which involves approximating a direct comparison by comparing HRs with a respect to common control group (5). The use of data from GBG 26/BIG 3-05 are consistent with this approach as this trial compared T+C to a control arm similar to that with which L+C was compared in EGF100151 (i.e., C-only).

However, the use of HRs for T+C versus C-only estimated from GBG 26/BIG 3-05 in an indirect comparison with L+C is not without limitations. Specifically, patients in the

EGF100151 study were more advanced/refractory than those in the GBG 26/BIG 3-05 study as evidenced by the fact that 98% of patients in the GBG 26/BIG 3-05 study were receiving 2nd line CT whereas 50% of those in the EGF100151 trial had received ≥4 prior lines of CT. This difference in patient populations is reflected in the study outcomes. In the EGF 100151 trial, median PFS with C-only was 17.6 weeks (4.1 months) whereas in the GBG 26 / BIG 3-05 trial, median PFS with C-only was 24.3 weeks (5.6 months). Similarly, median OS for C-only in the EGF100151 trial (Sep2007 data) was 64.7 weeks (14.9 months) whereas median OS in the GBG 26/BIG 3-05 trial was 88.6 weeks (20.4 months).

Whist it is clear, therefore, that the population in the EGF100151 study was more heavily pre-treated than that in the GBG 26/BIG 3-05 trial, and that an indirect comparison of survival times for PFS or OS with L+C from EGF100151 with that for TZ+C from GBG 26/BIG 3-05 may be biased, only the HRs for TZ+C vs. C-only for TTP and OS from the GBG 26/BIG 3-05 trial were used in the economic comparison. This is consistent with the approach recommended by Glenny and colleagues.[5] So the key question is whether the effect of ErbB2-targeted treatment, expressed in terms of a relative hazard (i.e., HR) for progression or death compared with C-only, is affected by the "refractoriness" of disease. While the possibility of such an interaction must be recognised, GSK knows of no data to support such a hypothesis for either TZ or lapatinib.

Another issue concerning the GBG 26/BIG 3-05 data relates to the fact that since the enrollment was terminated early, there are some differences across treatment groups in the baseline characteristics of the enrolled subjects. In particular, age was a mean of 59 years in those receiving C-only and a mean of 52.5 years in those receiving TZ+C. Although no p-value was provided, assuming a SD of age of 10 years, similar to that in EGF100151 and consistent with the age-range reported for GBG 26/BIG 3-05, the difference of 6.5 years in mean age is likely to be statistically significant (mean age was 2.1 years greater with L+C vs. C-only in EGF100151; this difference was not statistically significant). Whilst there is a possibility of bias due to differences in age between treatment groups in the GBG 26/BIG 3-05 study, GSK knows of no data to support the hypothesis of worsening outcomes by age among women with ErbB2+ MBC. In the Cox proportional hazards regression models on TTP and OS conducted for EGF100151, age was not a significant predictor of either TTP or OS.

Finally, it should be noted that TTP data were used from GBG 26/BIG 3-05, and the HR for T+C versus C-only for TTP was used to approximate the HR for T+C vs. C-only for PFS. This was necessary because data on PFS were not reported in the final analysis of data from the GBG 26/BIG 3-05 study. GSK believes this is reasonable, as the effect of T+C versus C-only on TTP based on final analysis of 15.6 months follow-up (HR=0.69) was similar to that reported for PFS based on preliminary analysis of 11.8 months follow-up (HR=0.71). In EGF100151 the HR for L+C versus C-only for independently-assessed TTP (HR=0.57) was similar to that for independently assessed PFS (HR=0.55).

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