Response to the Evidence Review Group Report commissioned by the NHS R&D HTA programme on behalf of NICE for Lapatinib for HER2 over-expressing breast cancer

GlaxoSmithKline 28 July 2008

GSK welcomes the opportunity to respond to the ERG's comments. It is hoped that the responses given below to the key comments add some clarity to the issues raised and reduce some of uncertainties in the submission.

This document should be read in the context of GSK's response to the ACD which is appended.

The headings below correspond to the format in ERG report.

Background

2.2.1. Table 9.4 in the MS Appendix 9.4 suggests that there were 93 patients in the study, of whom 12% received trastuzumab monotherapy. In the paper by Gelmon and colleagues, it appears that 11 of the 103 (10.7%) patients received trastuzumab monotherapy. It is not clear why the MS uses figures which are slightly different to those in the cited reference.

This was an inadvertent error on GSK's behalf. In the Gelmon study, 11 of 103 patients received trastuzumab monotherapy beyond progression (equating to 10.7%), not 11 of 93 patients as calculated by GSK (11.8%).

Clinical Effectiveness Review

3.1.2.1. Only one relevant RCT which met the inclusion criteria and this provides the main evidence base for the MS.

This was correct at the time of the original submission. Since the previous submission new randomised data comparing trastuzumab plus capecitabine with capecitabine alone - study GBG 26 / BIG 3-05 (von Minckwitz 2007) allows a more robust indirect comparison with trastuzumab plus capecitabine to be made.

3.1.2.1. There is currently no peer reviewed publication of the 3rd April 2006 dataset.

The independently-assessed data for the 03 April 2006 cut-off which forms the basis for this review has now been published online in the peer-reviewed journal Breast Cancer Research & Treatment as follows:

> Cameron D, Casey M, Press M, et al. A phase III randomised comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. Breast Cancer Res Treat 2008; 11 Jan. Epub ahead of print publication.

3.1.5. Data in the MS are from the 3rd April cut off data set, describing that "data collection from the study is still ongoing for further analysis". This appears to indicate that the 266 disease progression events had not occurred by the time of the 3rd April cut off, in which the analysis of TTP may not be sufficiently statistically powered.

At the 3rd April cut off a total of 266 progressive events were only required if an interim analysis of TTP did not lead to early termination of the study, and the study

was required to continue. In the event, the interim analysis found a statistically significant advantage in TTP for the combination versus capecitabine alone and the IDMC recommended termination of the study. The significant improvement in TTP demonstrated in this interim analysis (conducted with a 15 November 2005 cut-off date) indicates that with the planned 133 events planned at this point the study had sufficient power to detect a difference.

Further background is provided below:

The sample size calculation for the primary endpoint (independently-assessed TTP) was based on the fact that two analyses were planned occurring at equally spaced numbers of progression events.

(i) An interim analysis was planned after 133 independently-assessed events (adjusted to account for possible differences between investigator and independent review, allowing 146 investigator-reported events).

(ii) If this first analysis of TTP did not lead to early termination of the study for futility, then the study would continue to a second analysis of TTP at 266 events.

This calculation was based on achieving a statistical power of 90% to detect a 50% increase in median TTP (from an estimated 3 months in the group receiving capecitabine alone to 4.5 months in the group receiving lapatinib plus capecitabine).

An Independent Data Monitoring Committee (IDMC) was convened to review accumulating efficacy and safety data from the trial and to provide an opportunity to terminate the study after the interim analysis if:

(i) There were concerns regarding safety

(ii) There was strong evidence of superior efficacy of lapatinib plus capecitabine versus capecitabine alone

(iii) There was strong evidence that lapatinib plus capecitabine failed to show superiority if the study was allowed to run to its planned completion.

The interim analysis (conducted with a 15 November 2005 cut-off date) yielded a highly statistically significant increase in TTP for the group receiving lapatinib plus capecitabine compared to those receiving capecitabine alone (36.9 weeks vs. 19.7 weeks; HR 0.51 (95% CI: 0.35, 0.74; p=0.00032). At this time point, 146 investigator-reported disease progression events had been reported in 324 patients. This equated to 114 independently-assessed documented progression events (45 in the lapatinib + capecitabine group and 69 in the capecitabine monotherapy group).

After review of these data, on 20 March 2006 the IDMC recommended, based on the superior efficacy results seen, that study enrolment should be halted and women receiving capecitabine alone offered the opportunity to receive lapatinib in addition to capecitabine. GSK formally terminated the study on 03 April 2006 at which point 399 patients had been enrolled. An updated analysis of TTP and other endpoints was then conducted with this cut-off date.

3.4 The manufacturer has attempted to quantify use of trastuzumab beyond progression. This is based on data from a commercial database, supplemented by data from poor quality international trials (which may not be relevant to UK practice). This does not appear to give a particularly reliable evidence base for the use of trastuzumab beyond progression.

Quantifying the extent to which existing therapies are used within the relevant patient population continues to be problematic due to the non-availability on local or national NHS audit data. GSK has therefore employed the approach outlined below.

A review of patient treatment records submitted to the IMS Oncology Analyzer MBC Enhanced Tumour Study database by UK breast oncologists. As described in GSK's Manufacturer Submission to NICE (Appendix 9.4), the IMS Oncology Analyzer database is the largest, most comprehensive commercially available oncology patient-record database. In the absence of national audits of NHS patient treatment, the IMS Oncology Analyzer is arguably the most reliable source available for studying treatment pathways in metastatic breast cancer (MBC).

GSK's submission to NICE in April 2007 used the most current IMS Oncology Analyser dataset available at that time (January 2004 to September 2006) at which time the database reported case histories from 1,410 UK patients that had metastatic disease. Over the last two years IMS has expanded the Oncology Analyzer database by developing the Metastatic Breast Cancer Oncology Analyzer Enhanced Tumour Study (MBC-OA-ETS), with the objective to better enable the study of treatment pathways in the MBC setting. In this study additional cases relating to patients receiving therapy for the treatment of MBC were collected and incorporated with data collected as part of the standard IMS Oncology Analyzer. As with the IMS Oncology Analyzer, all patient records are completed by physicians treating breast cancer. The names of clients subscribing to the database are not disclosed to the respondents, and as such the case history reporting should be seen as unbiased.

Since the original market research studies were performed in 2004-2006 there are more data available in the IMS Oncology Analyzer database on which to base conclusions regarding clinical practice. Further details can be found in the ACD response.

Regarding the quality of the efficacy data for trastuzumab regimens, we acknowledge that although the studies identified in the pooled analysis may not be the most rigorous in design this pooled analysis was simply a pragmatic step to utilise the available trastuzumab beyond progression data and enable cost effectiveness analysis to be conducted. Indeed the ERG stated that this was the only approach available (section 3.1.5.1 ERG report).

Since the previous submission new randomised data comparing trastuzumab plus capecitabine with capecitabine alone - study GBG 26 / BIG 3-05 (von Minckwitz 2007) allows a more robust indirect comparison to be made.

3.4. The indirect comparison conducted by the manufacturer uses data from rather poor quality studies, none of which included a capecitabine monotherapy arm.

We agree with point above, the indirect pooled analysis was used simply because this was the only pragmatic method of comparison available. We recognise the limitations in using unadjusted, non randomised comparator studies. As mentioned above, since the previous submission new randomised data comparing trastuzumab plus capecitabine with capecitabine alone - study GBG 26 / BIG 3-05 (von Minckwitz 2007) allows a more robust indirect comparison to be made.

Economic Evaluation

4.3.1. Comparators used

Within the "Critical Appraisal checklist of economic evaluation" table the ERG questions whether comparators in the MS match those in NICE scope that states:

"Standard comparators; capecitabine vinorelbine, taxane regimens and other appropriate chemotherapy regimens in standard practice in England and Wales.

Comparators stated by the MS included capecitabine monotherapy, vinorelbine monotherapy, trastuzumab either in combination with capecitabine or vinorelbine or as monotherapy".

"Note regimens including trastuzumab in this setting have not been licensed or proven. Lacking an alternative treatment, trastuzumab as "rechallenge therapy" has been shown to be currently used in this setting".

GSK agrees with the ERG's clinical advisors who confirm that trastuzumab is continued beyond progression in conjunction with either capecitabine or vinorelbine, whereas trastuzumab monotherapy is rarely used beyond disease progression (Section 2.3.3, ERG report), and concluded that the selected comparators in GSK's evaluation were appropriate (Section 3.1.2, ERG report).

4.4.1.2.3 (p57) Utility Reduction. The ERG comments that the post progression utility estimate used in the cost-effectiveness model was derived using the statistical model reported by Lloyd and colleagues. These values may over state the utility reduction due to disease progression since Llloyd and colleagues demonstrated a significant sex by progression compared with women. Recalculating the utility reduction, taking account of the sex-by progression interaction gives a lower utility reduction for women than a mixed sex cohort.

We estimated the disutility from disease progression to be 32% relative to the utility with no progression. This estimate can be obtained directly from the Lloyd paper by using the formula presented on p 57 of the ERG report and assuming a mean age of 53 years consistent with that in the EGF100151 study.

We believe that it is most appropriate to use the utility values for the overall population, not just females, because we are interested in community-based preferences, not just preferences for females.

In applying the same logic an alternative would be to use the disutility for all ages, not that specific to patients with MBC. Using the mean age in the population rather than the mean age for the EGF100151 trial, the disutility from progression increases from 32% to 38%. Our estimate of the community-based disutility from progression is therefore likely to be conservative and consequently would have the effect of improving the cost effectiveness estimates of lapatinib plus capecitabine.

4.4.1.2.4. Resource use

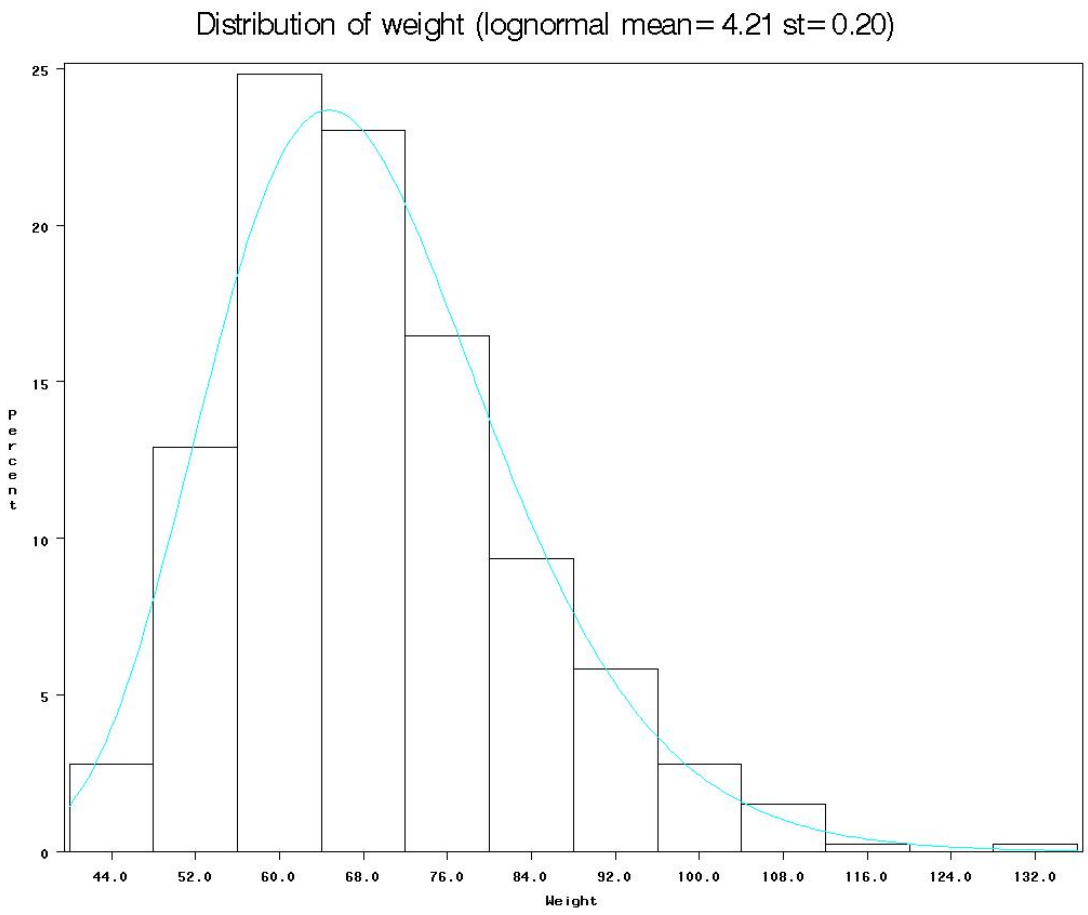
It is not clear why the weight and BSA distributions from the EGF100151 trial were not used directly, rather than inferring distributions based on the trial mean and standard deviation. Alternatively, a simpler calculation could have been adopted using mean BSA and mean weight for the base case and assessing the effect of variation in these parameters in the sensitivity analysis.

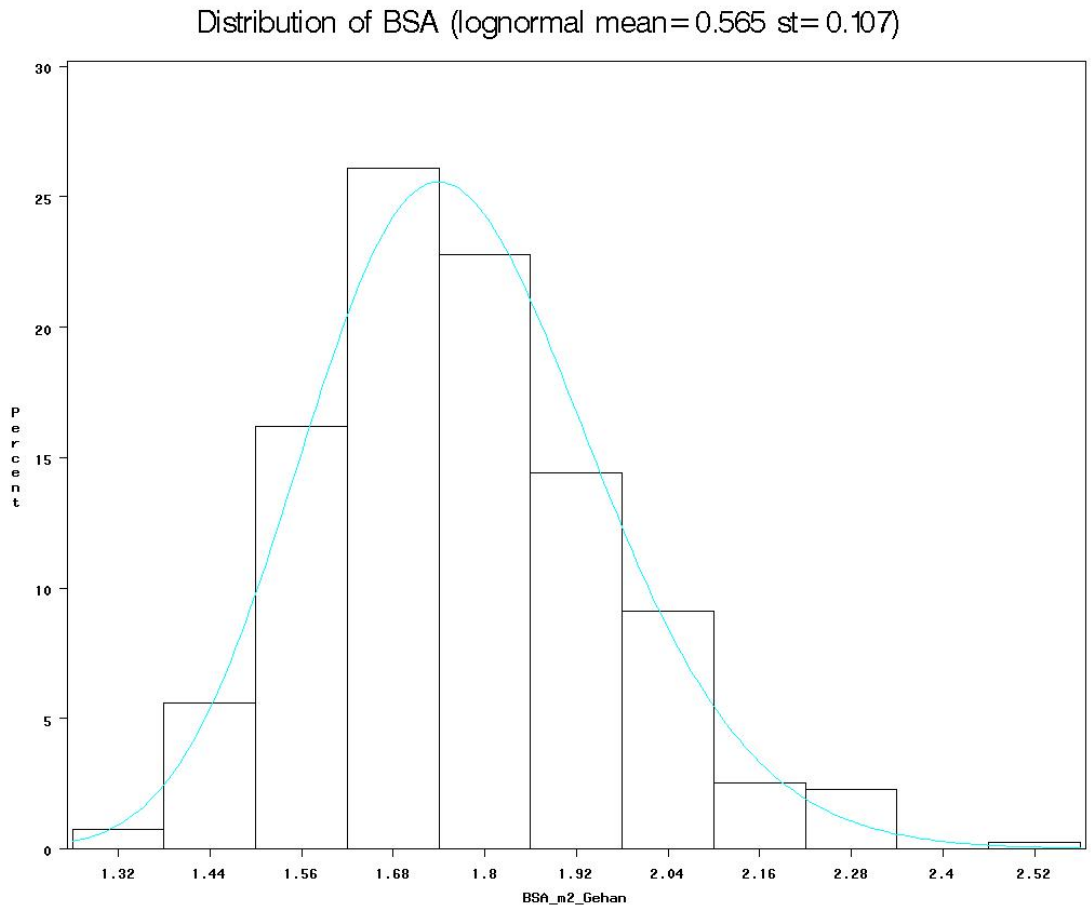
While the approach by the ERG is simpler, it may generate spurious estimates of wastage. For example, if the mean weight of patients is 75 kg, the estimate of wastage of trastuzumab using the approach employed by the ERG is zero regardless of the estimated dispersion of weight around the mean (while this is not the case in the base-case analysis, it would affect results in deterministic and probabilistic sensitivity analyses). Given that the lognormal distribution has been shown to closely approximate the actual weight and BSA distribution of patients in the EGF100151 trial, we believe that use of the approach employed in the original submission is appropriate

The model estimates the number of vials of trastuzumab and vinorelbine used based on the estimated weight and BSA distribution of patients with HER2+ MBC, assuming that physicians administer the medication precisely as indicated (i.e., there is no dose rounding) and that unused vials are discarded. The comments below deal with the methods used to estimate vials used based on these assumptions.

We estimated the weight and BSA distribution of the population using data on weight and BSA at baseline for all patients in the EGF100151. The model was programmed to allow users to either calculate amount of medication used (1) assuming no wastage and calculating number of grams used based on the mean weight or BSA or (2) assuming wastage and calculating vials used based on the distribution of weight and BSA and g/kg and g/m^2. To facilitate switching between these two analyses, and to facilitate the use of alternative estimates of mean weight and BSA, we parameterized the distributions of weight and BSA assuming that the two would be log normally distributed. We then estimated the proportion of patients within various equally spaced categories of weight and BSA based on these distributions with categories ranging from "0 to (Mean – 2 x SD)" to "(Mean+2 x SD) to the 99.99%tile", with the width of each category equal to 0.2 x SD (it should be noted that the minimum weight was not assumed to be 2 SDs below the mean; rather this was the upper end of the lowest weight category).

The assumption that weight and BSA would be distributed as lognormal variables was based on inspection of the two distributions showing them to be truncated at zero and skewed to the right. The parameterized lognormal distributions fit the actual distributions remarkably well as shown below.





The table below shows the estimated distribution of patients by number of vials of trastuzumab required assuming weekly dosing and 3 weekly dosing respectively and using the parameterized lognormal distribution of weight and the actual distribution of weight respectively. These analyses confirm that the use of the parameterized lognormal distributions rather than the actual weight distributions is reasonable and does not materially affect the estimated number of vials or mg of trastuzumab used.

Number of Vials/mg	2 mg/kg/d q1w		6 mg/kg/d q3w	
	Lognormal Distribution	Actual Distribution	Lognormal Distribution	Actual Distribution
1/150	69.8%	71.1%	0%	0%
2/300	31.2%	28.9%	5.9%	4.3%
3/450	0%	0%	6.3%	66.8%
4/600	0%	0%	28.5%	25.3%
5/750	0%	0%	0%	0%
6/900	0%	0%	2.6%	3.5%
Avg. vials	1.31	1.29	3.31	3.32
Avg. mgs	196.76	193.29	495.86	497.47

These analyses confirm that the use of the parameterized lognormal distributions rather than the actual weight distributions is reasonable and does not materially effect then estimated number of vials or mg of trastuzumab used.

A comparison of the estimated mean dose for trastuzumab and vinorelbine assuming no wastage, assuming wastage based on the lognormal distribution, and assuming wastage based on the mean (ERG approach) in Table 2.1 suggests that the approach employed by the ERG generates an estimate of vinorelbine use that is similar to that generated by the original model, therefore the two methodologies have little differential effect on the results. On the other hand, for trastuzumab the approach employed by the ERG generates estimates of use per dose that are greater than those obtained assuming no wastage, but less than those generated using the lognormal distribution.

Table 2.1. Comparison of estimated doses assuming no wastage, and wastage based on the lognormal distribution and ERG methodology

	Trastuzumab		
	2 mg/kg weekly	**6 mg/kg 3-weekly**	**Vinorelbine 25 mg/m2 weekly**
Prescribed dose (adjusted for RDI)	1.98 mg/kg	5.94 mg/kg	22.25 mg/m^2
Expected medication used per dose (mg)			
No waste	136.422	409.26	39.38
With waste			
Using lognormal distribution	196.76	495.86	51.03
Using mean (ERG)	150.00	450.00	50.00

We acknowledge that attempts are made to batch-produce trastuzumab infusions and minimise drug wastage, but since the trastuzumab SmPC specifies that vials are for single use it would seem highly unlikely that wastage can be avoided altogether. Therefore to understand the extent of trastuzumab wastage we commissioned 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 are presented in Appendix 1). Results indicated that 46% of respondents have a policy relating to the repeat use of IV vials and consider all to be single use. Thirty three percent have a policy and consider some IV vials for multiple use (where possible). The remainder have no policy relating to repeat use of IV vials. Participants were asked to estimate the proportion of total trastuzumab that is discarded, i.e. wasted, in the treatment of metastatic breast cancer patients. On average respondents estimated that 15% of trastuzumab used for the treatment of metastatic breast cancer is wasted (range 5%-60%).

We believe that to exclude wastage would be extreme, and that the estimate of 15% trastuzumab wastage is most likely to reflect true clinical practice.

4.4.1.2.4. Resource costs. The MS reports average monthly costs per patient from Remak and Brazil (2004) separately identifying and costing resource use in the pre and post progression period. The generalisability of the Remak and Brazil survey was not addressed in the MS.

We consider the Remak and Brazil study is applicable to the submission for the following reasons. Firstly it filled an evidence gap confirmed by the National Cancer Intelligence Centre at the National Statistics Office that no reliable, centrally held

information on the separate incidence of each stage of breast cancer in the UK was available.

The Remak and Brazil study uses the incidence approach to estimate the lifetime cost of cases first diagnosed in a given year. This differs from the prevalence approach where estimates of the total cost of disease in a given year are forecast. The incidence approach is more useful for the evaluation of healthcare options as it provides a baseline against which new interventions can be assessed (Drummond 1992).

The approach adopted in this paper analysed and included UK breast cancer data from 1994 to 2001 from four English cancer registries (Northern and Yorkshire, East Anglia, Thames (London region), and West Midlands) as well as the Scottish cancer registry. Consequently we view the survey as geographically representative and generalisable to the UK setting.

4.4.1.2.5. Costs

The ERG commented on the use of unit costs for hospital administration of trastuzumab. The ERG checked this source and found a different unit cost for trastuzumab administration (of £117 compared to the £207.22 adopted for the base case for the submission.

Trastuzumab administration costs in GSK's original submission (£245.22) were taken from NHS Reference Costs 2006, the most current available at the time. The cost includes the cost of an outpatient chemotherapy consultation £207.22 (interquartile range £171 to £277) (Ref Department of Health Reference Costs 2006). In addition the handling cost of a complex IV infusion (£38) was added (Tappenden and Hind 2006). The cost suggested by the ERG (£117) is referenced to a medical oncology outpatient consultation of £109 (Netten and Dennett 1999) uplifted to 2006 prices (£117). This cost was referenced in the HTA review guidance No. 33 in 2002. As the reference cost is the most recent and accurate data source here we believe this it is the more up to date cost that provides the most accurate assessment of the current impact on the NHS; we believe that the use of costs from almost ten years ago is questionable.

4.4.1.4.2. Scenario analysis. Clinical advice to the ERG indicated that it is more typical in UK practice to administer trastuzumab once every three weeks. Since the dose is tripled when changing from weekly to three weekly administrations (from 2mg/m^2 to 6mg/m^2) changing frequency of dosing has minimal effect on drug costs, but has a large impact on administration costs.

The ERG scenario analyses 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 we do recognise the use of three weekly dosing of trastuzumab by some oncologists. In order to gain further insight on this issue market research was undertaken with oncology pharmacists. Respondents fed back that 11.6% of trastuzumab in metatstatic breast cancer is given weekly. Therefore we believe that this figure should be used in any scenario analyses.

4.4.1.4.3 (p70/71). Probabilistic sensitivity analysis

Survival model parameters (lambda and gamma for PFS and OS models for capecitabine and the hazard ratio for PFS and OS for lapatinib plus capecitabine) were estimated outside the model, using non parametric bootstrap techniques and stored in a hidden worksheet. No further detail is given as to how these bootstrap samples were generated so no judgement can be made on the appropriateness of the techniques used.

Bootstrapping was conducted using the method of Efron (1993) and also described by Pasta et al (1999). Briefly, bootstrap sample estimates of the parameters of the Weibull distribution and the RDI were obtained by sampling with replacement from the EGF100151 dataset to obtain 10000 bootstrap sample replicates. For each of these bootstrap sample replicates, we conducted AFT regressions for PFS and OS to obtain the parameters of the Weibull distributions and calculated RDIs for each treatment.

4.4.1.4.3 (p71). Use of Hazard Ratios

It appears that the hazard ratio for overall survival with trastuzumab is not sampled in the PSA, but is kept at the base case value (0.8344). This departs from the base case assumption that overall survival with trastuzumab containing regimens is the same as lapatinib plus capecitabine.

In the base-case, expected post progression survival with trastuzumab-based strategies was assumed to be equal to that for lapatinib and capecitabine. This linkage is maintained in the PSA, with post progression survival for trastuzumab varying as progression free survival, overall survival, and therefore post progression survival with lapatinib and capecitabine changes; therefore the overall survival has been sampled in the PSA.

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