Lapatinib for women with previously treated advanced or metastatic breast cancer

Response to NICE questions 22 September 2009

1. Specify the cell changes made to the cost effectiveness model to implement the results from the Cox regression model for OS i.e. the modified model. Provide both details of how the Cox model was used and the derivation (i.e. scale and shape parameters) of the Weibull distribution and to which the Cox HR was applied to obtain the inputs for the other distribution.

No changes were made to the model calculations to implement the results from the Cox regression model. However, because lapatinib plus capecitabine (L+C) was defined as the reference treatment for OS in scenarios R4-R7, whereas the model was designed with capecitabine monotherapy (C-only) as the reference treatment, the PH Weibull model parameters for C-only (gamma_PH_CapStgOS and lambda_PH_CapStgOS [cells F139 and F140 on the analyze sheet, respectively]) must be derived from the estimated Weibull model parameters for L+C and the HR for L+C vs. C-only. Specifically, gamma for C-only is equal to the gamma from the L+C Weibull. Lambda for C-only is set equal to $\lambda \times (1/HR)^{(1/\gamma)}$, where λ=lambda for L+C Weibull, γ=gamma for L+C Weibull, and HR=the HR for L+C vs. C-only. For convenience, these calculations are provided in the model (see cells N285 and N286 of the Analyze sheet). Lambdas and gammas for the OS Weibull model for L+C are entered into the "Stratified Weibull" input cells (gamma_Strat_LapStgOS and lambda_Strat_LapStgOS [cells F285 and F286, respectively]) and the HR for L+C vs. C-only is entered into the L+C PH Weibull HR input cell (HR_LapStgOS [cell F283]). The lambdas and gammas for the PH Weibull for C-only (gamma_PH_CapStgOS and lambda_PH_CapStgOS [cells F139 and F140 respectively]) are then calculated based on these values in cells N285 and N286. The derived values in these cells can then be copied into or linked to the gamma_PH_CapStgOS and lambda_PH_CapStgOS cells.

Appendix 1 shows the values of all the survival function parameters for PFS and OS that were used to generate results for all scenarios presented in the reconciliation table (including the final base case model). These include the lambda and gamma parameters of the Weibull survival functions along with the HRs for L+C vs. C-only. The table includes for each parameter the variable name and the cell reference in the Analyze sheet.

2. Outline precisely i.e. with enough detail to allow results to be checked, how the results of the Cox regression for OS were turned into input parameters to the cost effectiveness model.

See response to Q1 above for the methods for entering the Weibull model parameters and HRs into the model.

3. Was PFS also adjusted for crossover using the same Cox regression approach with the same covariates as for OS?

Following release of the Independent Data Monitoring Committee recommendation on 3 April 2006 the study investigators were made aware of the results from the interim analysis, enrolment to EGF100151 was halted, and subjects on capecitabine monotherapy were offered crossover therapy. Due to the open label nature of study EGF100151, knowledge of these preliminary results by the investigator had the potential to introduce bias in an analysis of PFS beyond 3 April 2006. Therefore updated analyses beyond 3 April 2006 on PFS have not been performed. As crossover did not occur in data through to 3 April 2006, adjusting for crossover was not necessary.

4. Clarify the exact approach used to estimate PFS for both arms, and the derivation of the parameter inputs relating to PFS used in the cost effectiveness model.

PFS for C-only was estimated by fitting a Weibull survival function to failure time data from EGF100151 using accelerated failure time regression (SAS Proc LIFEREG). Parameter estimates from the AFT regression were then transformed to lambdas (λ) and gammas (γ) as shown below in Table 1.

Table 1. IRC PFS (April 06) stratified model parameters for lapatinib plus capecitabine

	Estimate	SE
AFT model output (from SAS)		
Intercept	5.146	0.0721
Scale	0.7456	0.0534
Survival function parameters		
λ	0.005823	0.000420
γ	1.341202	0.096057
λ =exp(-Intercept). $SE_\lambda = SE_{intercept} \times \lambda$. γ =1/scale. SEγ=SEγ / γ^2		

In the model PFS at time t for C-only is then estimated as $PFS_{C\text{-}only}[t]=\exp(-(\lambda t)^{\gamma})$. PFS at time t for L+C is then calculated as $PFS_{L+C}[t]=\exp(-(\lambda [HR \wedge 1/\gamma] \times t)^{\gamma})$ where $HR=HR_{L+C \text{ vs. } C\text{-}only}$. Note that this is equivalent to the more traditional Weibull formulation of $PFS_{L+C}[t]= \exp(-(\lambda \times t)^{\gamma})^{HR}$

5. How were the covariates (ECOG status, number of metastatic sites and presence of liver metastases) selected for inclusion in the Cox regression? and why were time from last dose of trastuzumab, time since diagnosis of metastases and time from diagnosis not included as covariates?

Eleven baseline and disease history factors were investigated. These factors are well documented, are historically correlated with survival and, as such, are prognostic for the management of metastatic breast cancer (Henderson 1998). These factors are: ECOG performance status (0/ =1); number of metastatic sites (<3/=3); site of disease (visceral/non-visceral); liver metastases (Y/N); stage of disease (IIIB or IIIC/IV); hormone receptor status (ER- and PR-/ ER+ or PR+); time since last dose of prior trastuzumab (=8 weeks/>8 weeks); number of prior chemotherapy regimens (<3/= 3); age; time from diagnosis to randomisation; and time from metastatic diagnosis to randomisation.

Each factor was considered univariately with treatment in the model. Factors found to be significant at a = 0.05 where then considered in a stepwise regression model to evaluate the effects of the significant baseline disease history and prognostic factors from the univariate models. Treatment was retained in the model, while the prognostic factors were evaluated using stringent criteria for inclusion using entry/exit criteria of a = 0.05. The Cox regression model based on this stepwise procedure identified the following three prognostic factors (number of metastatic sites; ECOG performance status; presence/absence of liver metastases) as having a significant impact on OS in the presence of treatment (EMEA, Tyverb EPAR 2008). The time-dependent covariate for crossover was then added to the model.

Time from last dose of trastuzumab, time since diagnosis of metastases and time from diagnosis were considered as covariates. However these were not found to be statistically significant in the presence of treatment and therefore were not retained in the model.

6. How were subgroups selected?

Details on how the subgroups were selected are provided in Appendix 3.1 to our submission of 25 August 2009. It should be noted that the subgroup data provided for study EGF100151 are only intended as supportive of the results provided in the ITT population.

It is widely documented in the literature that, with the addition of successive treatments, the response and duration of response to a cancer treatment is decreased (Dufresne 2008) and therefore treatment decisions are frequently guided by previous treatments received.

Study EGF100151 demonstrates the clinical benefit of lapatinib plus capecitabine when administered to patients receiving multiple prior treatment regimens, including multiple regimens of trastuzumab. A clinically relevant question is therefore whether the clinical benefit is maintained or improved when the combination is administered to patients with fewer prior regimens.

The following subgroup analyses were therefore completed:

i. One or two versus three or more prior regimens: This analysis grouped patients who had one or two versus three or more prior regimens, with the regimen defined as any regimen in any setting.

ii. One versus more than one prior metastatic trastuzumab regimens: This analysis grouped patients who had one prior versus those with more than one prior trastuzumab-based regimen in the metastatic setting.

iii. Post first-line metastatic trastuzumab: This analysis was more specific and examined patients who had received trastuzumab for first-line metastatic breast cancer and then received lapatinib plus capecitabine or capecitabine alone as second-line therapy.

These analyses were not pre-defined and were therefore exploratory analyses conducted to provide further data to support marketing. The split between one or two versus three or more prior regimens in subgroup analysis (i) and the two other subgroup analyses (ii) and (iii) that specifically relate the intervention to trastuzumab prior therapy, were based on GSK's target positioning for the lapatinib plus capecitabine combination within its licensed indication.

7. Were estimates of OS and/or PFS for subgroups also adjusted for crossover using the Cox regression with the same covariates as the base case?

For the economic evaluation of the subgroups, the HRs for OS were calculated with crossover as a time-dependent variable and included the same covariates as in the analysis of the overall population. As noted in response to question 3, PFS was not adjusted for crossover due to the fact that analyses have not been performed on data beyond 3 April 2006. However, because the examination of results within subgroups breaks randomization, the HRs for PFS used in the economic evaluation of the subgroups were estimated using Cox proportional hazards regression with the same covariates as those employed in the Cox regression analyses of overall survival (i.e., in order to control for any potential imbalances across groups in these factors within the subgroups). Hazard ratios for OS and PFS from the Cox regression analysis for the subgroups are reported in Table 2.

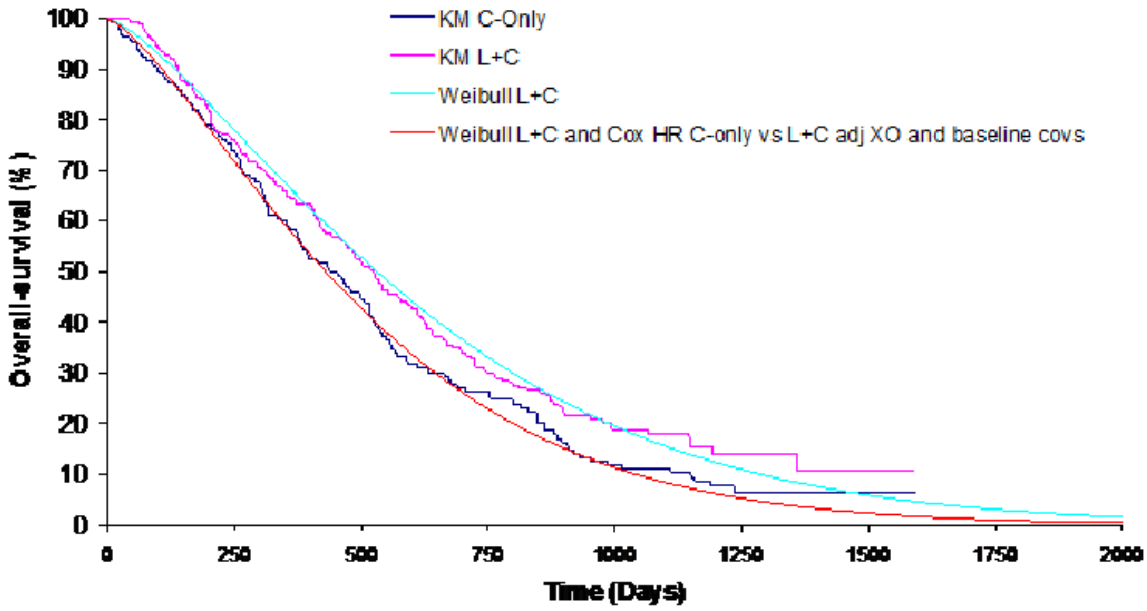
Table 2, HRs for OS and PFS from the Cox regression analysis for the subgroups

	One or two prior regimens				1 prior Trastuzumab			
		PFS IRC		OS		PFS IRC		OS
Covariate	HR	Pr>ChiSq	HR	Pr>ChiSq	HR	Pr>ChiSq	HR	Pr>ChiSq
L+C vs. C-only	0.318	0.0066	0.527	0.0226	0.467	<.0001	0.683	0.0083
ECOG at Baseline	0.586	0.1505	0.497	0.0145	0.725	0.0929	0.667	0.0042
Liver Metastases at Baseline	0.69	0.3259	0.901	0.7018	0.628	0.0167	0.47	<.0001
No of Metastatic Sites at Baseline	0.62	0.2113	0.787	0.3984	1.028	0.8873	0.623	0.0008
Cross Over			3.941	0.0195			0.715	0.2356

8. Why was a Weibull distribution chosen for the lapatinib OS arm estimate? Please provide evidence of goodness of fit e.g. Kaplan Meier curve with the fitted distribution and alternatives

The goodness of fit of the Weibull models for PFS and OS were assessed in the original submission and were not formally assessed in the re-analysis. However, as shown in the figures below, visual inspection of the survival functions suggest that the Weibull model provides a good fit to the Kaplan Meier estimated OS for the L+C group.

Figure 1. Kaplan Meier and Weibull OS for HER2+ patients from the EGF100151 trial (ITT population)



Kaplan-Meier and Weibull curves for the OS subgroup data are given in figures 2 and 3.

Figure 2. Kaplan Meier and Weibull OS for HER2+ patients from the EGF100151 trial treated with one or two prior regimens

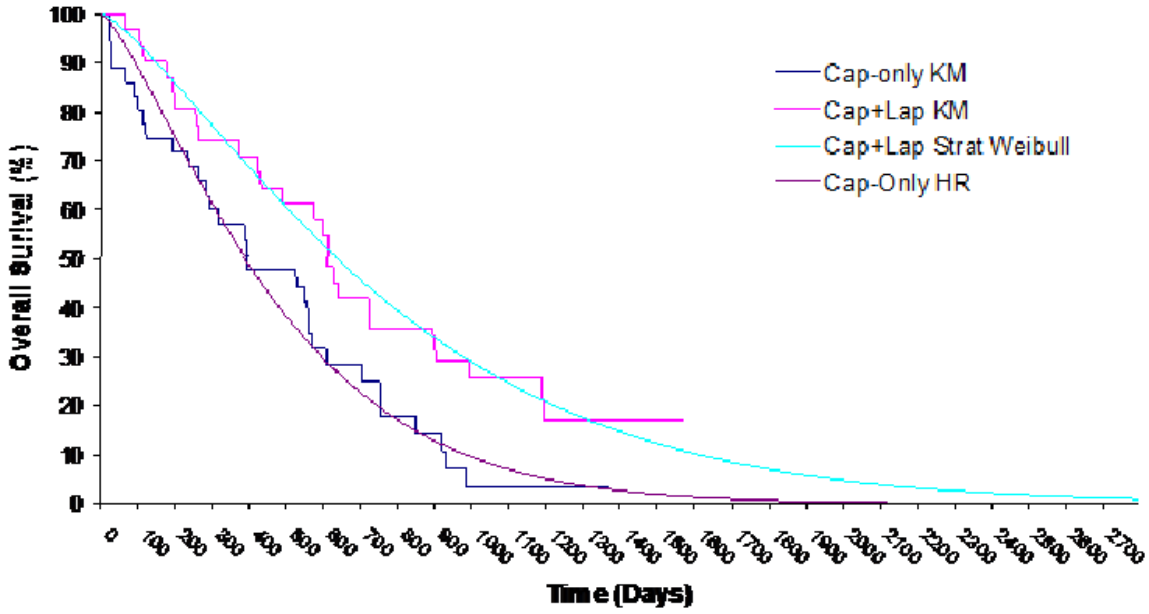
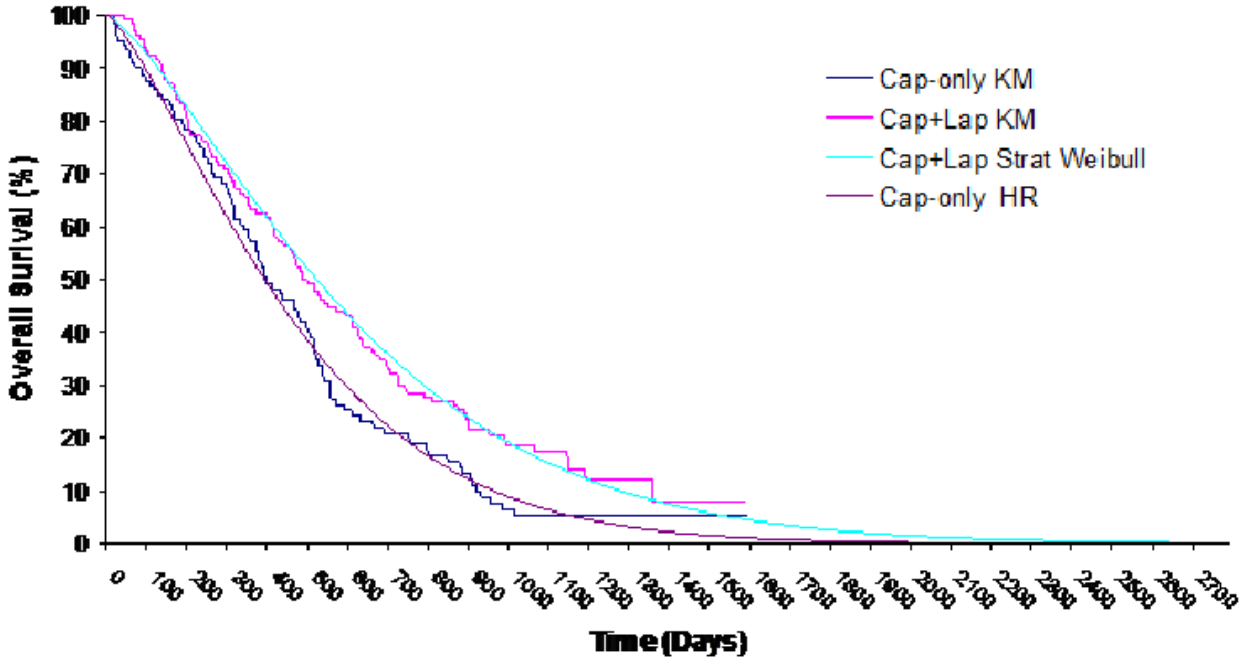


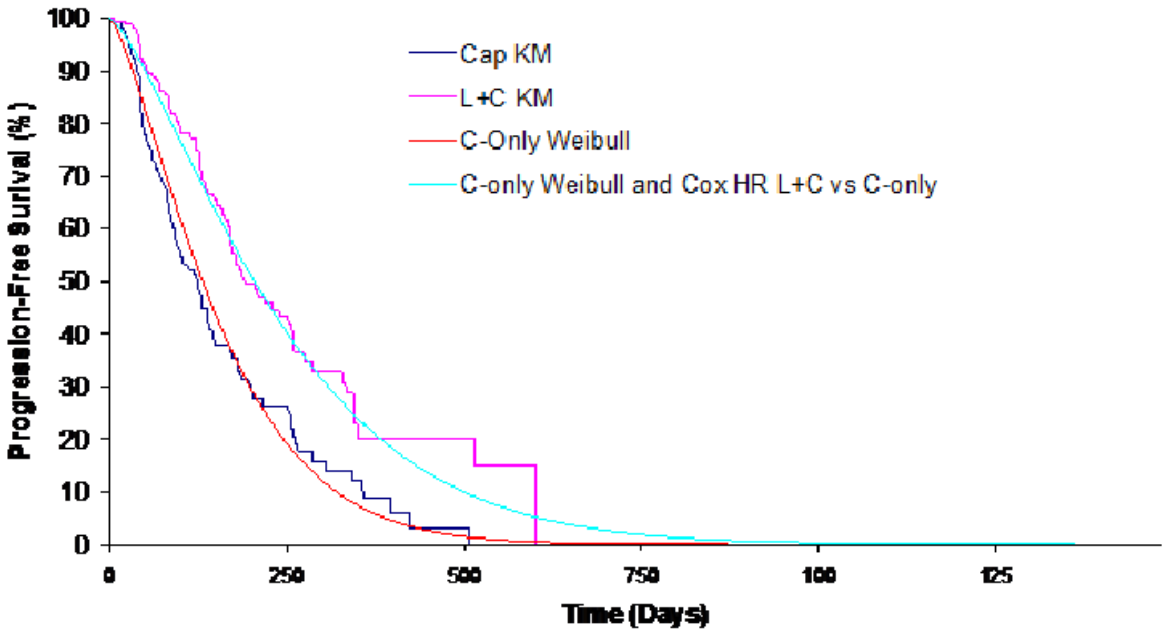
Figure 3. Kaplan Meier and Weibull OS for HER2+ patients from the EGF100151 trial treated with one prior trastuzumab-based regimen in the metastatic setting



9. As 8 but for PFS (if this is relevant)

As noted in the response to question 8, the goodness of fit of the Weibull models for PFS and OS were assessed in the original submission and were not formally assessed in the re-analysis. However, as shown in the figures below, visual inspection of survival functions suggests that the Weibull model provided a good fit to the Kaplan Meier estimated PFS for the C-only group.

Figure 4. Kaplan Meier and Weibull PFS for HER2+ patients from the EGF100151 trial (ITT population)



Kaplan-Meier and Weibull curves for the PFS subgroup data are given in figures 5 and 6.

Figure 5. Kaplan-Meier and Weibull IRC-assessed PFS for HER2+ patients from the EGF100151 trial treated with one or two prior regimens

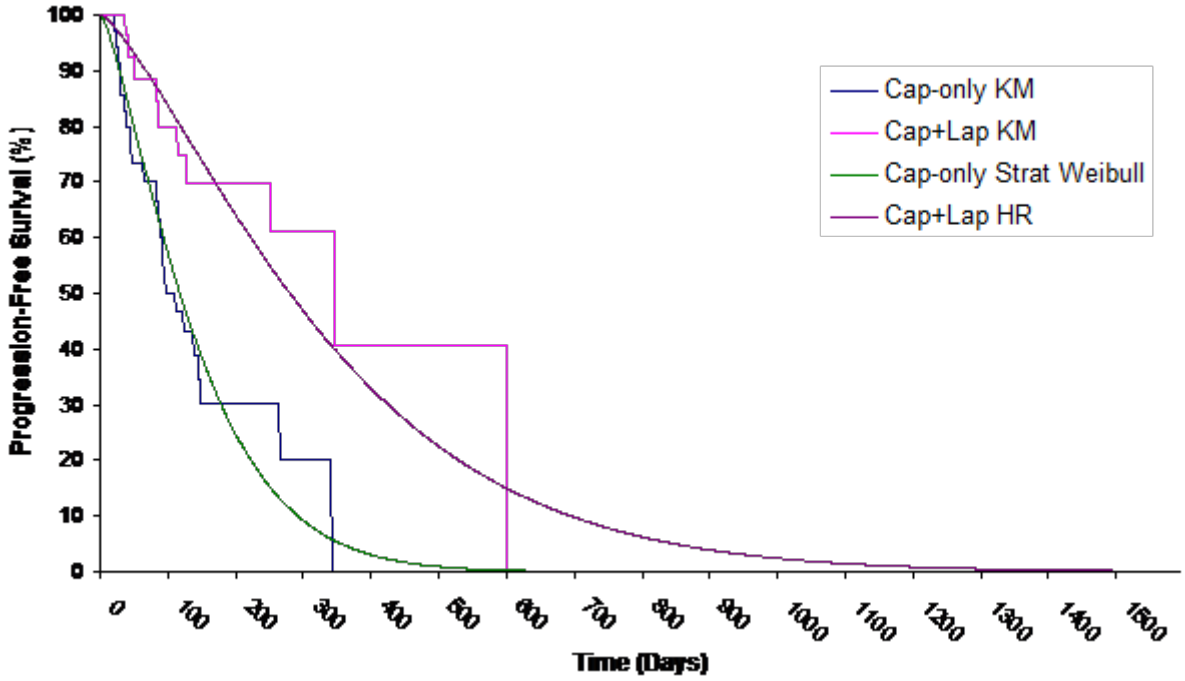
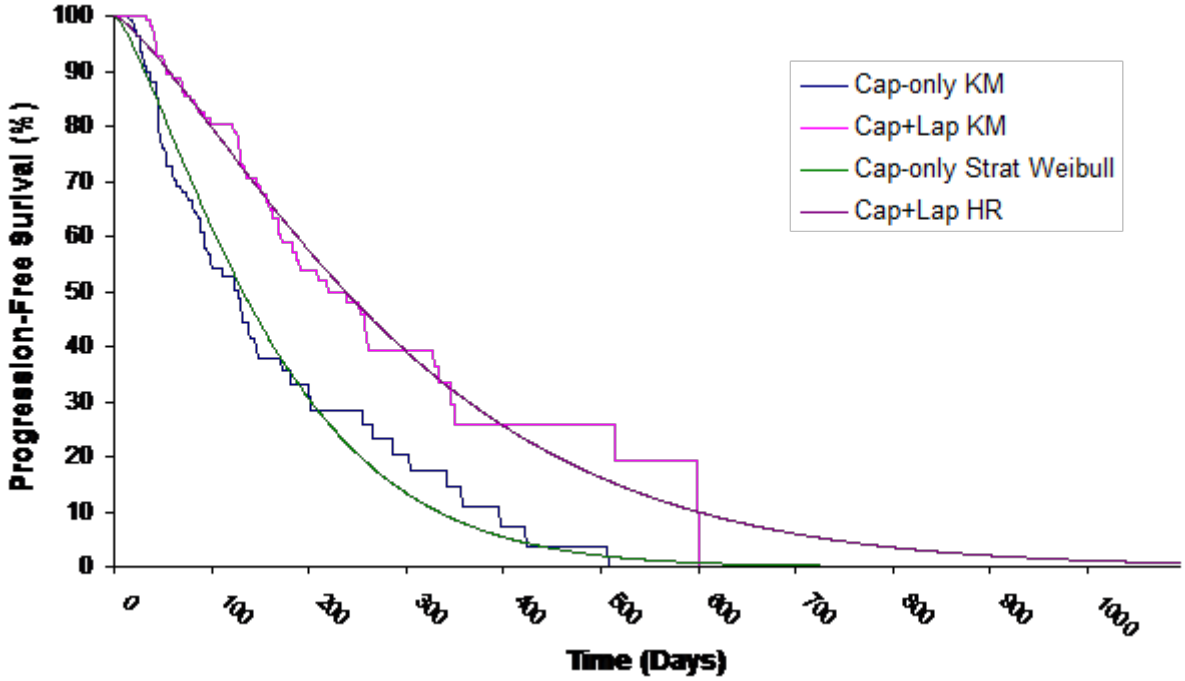


Figure 6. Kaplan-Meier and Weibull IRC-assessed PFS for HER2+ patients from EGF100151 trial treated with one prior trastuzumab-based regimen in the metastatic setting



10. Provide the cost effectiveness models which generate the ICER estimates for the subgroups reported in the document.

The subgroup models are provided as separate files.

References (for questions 5 and 6)

Dufresne A, Pivot X, Tournigand C, et al. Impact of chemotherapy beyond first line in patients with metastatic breast cancer. Breast Cancer Res Treat 2008; 107: 275-279.

Euopean Medicines Agency. Assessment Report for Tyverb. EMEA/H/C/795. EMEA/302222/2008.

Henderson IC, Patek AJ. The relationship between prognostic and predictive factors in the management of breast cancer. Breast Cancer Res Treat 1998; 52: 261-288.

Appendix 1							
Values of survival function parameters used in each reconciliation scenario							
Variable	**Variable Name**	**Cell Reference Analyse Sheet**	**R1 - R3**	**R4**	**R5**	**R6**	**R7**
PFS							
Data-set			April-06	April-06	April-06	April-06	April-06
Method			$PFS_{L+C}[t]$ and $PFS_{C\text{-}only}[t]$ from PH Weibull Model	$PFS_{L+C}[t]$ and $PFS_{C\text{-}only}[t]$ from PH Weibull Model	$PFS_{C\text{-}only}[t]$ from Weibull model; $PFS_{L+C}[t] = PFS_{C\text{-}only}[t]^{HRL+CvC\text{-}only}$ HR from log rank	$PFS_{C\text{-}only}[t]$ from Weibull model; $PFS_{L+C}[t] = PFS_{C\text{-}only}[t]^{HRL+Cv}_{C\text{-}only}$ HR from log rank	$PFS_{C\text{-}only}[t]$ from Weibull model; $PFS_{L+C}[t] = PFS_{C\text{-}only}[t]^{HRL+CvC\text{-}only}$ HR from log rank
OS							
Data-set			Sep-07	Oct-08	Oct-08	Oct-08	Oct-08
Method			$OS_{L+C}[t]$ and $OS_{C\text{-}only}[t]$ from PH Weibull Model	$OS_{L+C}[t]$ and $OS_{C\text{-}only}[t]$ from PH Weibull Model	$OS_{L+C}[t]$ from Weibull model; $OS_{C\text{-}only}[t] = OS_{L+C}[t]^{HR}_{C\text{-}only\ vs\ L+C}$ HR from log rank	$OS_{L+C}[t]$ from Weibull model; $OS_{C\text{-}only}[t] = OS_{L+C}[t]^{HR}_{C\text{-}only\ vs\ L+C}$ HR from Cox model	$OS_{L+C}[t]$ from Weibull model; $OS_{C\text{-}only}[t] = OS_{L+C}[t]^{HRC\text{-}only\ vs\ L+C}$ HR from Cox model
Adj for XO			Censor	Censor	Censor	Time-Dependent Variable	Time-Dependent Variable
Adj for BL			No	No	No	No	Yes
Variable							
C-Only strategy							
Overall survival							
PH Weibull model							
Weibull shape parameter, gamma	gamma_PH_CapStgOS	F139	1.38217	1.31372	1.35906	1.35906	1.35906
Weibull scale parameter, lambda	lambda_PH_CapStgOS	F140	0.00174	0.00170	0.00166	0.00169	0.00177
Stratified Weibull Model							
Weibull shape parameter, gamma	gamma_Strat_CapStgOS	F142	1.32031	1.32031	1.32031	1.32031	1.32031
Weibull scale parameter, lambda	lambda_Strat_CapStgOS	F143	0.00174	0.00174	0.00174	0.00174	0.00174
Progression-free survival							
PH Weibull model							
Weibull shape parameter, gamma	gamma_PH_CapStgPF	F146	1.391982	1.391982	1.341202	1.341202	1.341202

Weibull scale parameter, lambda	lambda_PH_CapStgPF	F147	0.005820	0.005820	0.005823	0.005823	0.005823
Stratified Weibull Model							
Weibull shape parameter, gamma	gamma_Strat_CapStgPF	F149	1.34120	1.34120	1.34120	1.34120	1.34120
Weibull scale parameter, lambda	lambda_Strat_CapStgPF	F150	0.00582	0.00582	0.00582	0.00582	0.00582
C+L strategy							
Overall survival							
PH Weibull model							
Hazard ratio	HR_LapStgOS	F283	0.87032	0.84291	0.82000	0.80000	0.75000
Stratified Weibull Model							
Weibull shape parameter, gamma	gamma_Strat_LapStgOS	F285	1.45285	1.45285	1.35906	1.35906	1.35906
Weibull scale parameter, lambda	lambda_Strat_LapStgOS	F286	0.00152	0.00152	0.00144	0.00144	0.00144
Progression-free survival							
PH Weibull model							
Hazard ratio	HR_LapStgPF	F289	0.60847	0.60847	0.55000	0.55000	0.55000
Stratified Weibull Model							
Weibull shape parameter, gamma	gamma_Strat_LapStgPF	F291	1.467567	1.467567	1.467567	1.467567	1.467567
Weibull scale parameter, lambda	lambda_Strat_LapStgPF	F292	0.003583	0.003583	0.003583	0.003583	0.003583

Note: R1-R3 differed only in terms of inclusion of AEs and base-year of costs. The stratified Weibull model parameters are not used directly in any scenario (i.e., proportionality is assumed). However, for OS, because L+C is the reference treatment in scenarios R4-R7, whereas the model was initially designed with C-only as the reference treatment, the lambdas and gammas for the C-only OS PH Weibull (cells F139 and F140) are derived from the lambdas and gammas from the L+C OS stratified Weibull model and the L+C vs C-only OS HR. Accordingly, the lambdas and gammas for L+C for OS are entered into the L+C OS Stratified Weibull model cells (F285 and F286). The HR for L+C vs C-only is entered into the HR_LapStgPF cell. The calculation of the lambdas and gammas for C-only based on the lambdas and gammas for L+C and the HR for L+C vs C-only is "hard wired" in the N285 and N286 cells, where gamma_PH_CapStgOS=gamma_Strat_LapStgOS and lambda_PH_CapStgOS=lambda_strat_LapStgOS x (1/HR_LapStgPF)^(1/gamma_Strat_LapStgOS). The values in these cells can then be copied into or the cells linked to the appropriate gamma and lambda cells for the C-only.