LAPATINIB FOR BREAST CANCER (FOR USE IN WOMEN WITH PREVIOUSLY TREATED ADVANCED OR METASTATIC BREAST CANCER): POST APPEAL

REPORT BY THE DECISION SUPPORT UNIT

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TABLES

1. INTRODUCTION

The aim of this report is to consider the evidence submitted by GlaxoSmithKline (GSK) for the appraisal of lapatinib (Tyverb, GSK Pharmaceuticals) for the treatment of women with previously treated advanced or metastatic breast cancer, following the directions of the NICE Appeal Panel.

Specifically, the manufacturer and other consultees and commentators were asked to submit evidence of whether and how lapatinib falls within the supplementary advice relating to end of life medicines.

The purpose of this report is to provide a review of the evidence submitted by GSK only. It does not consider any evidence submitted by other parties.

Specifically, we review the evidence submitted by GSK in three areas:

1. Updated estimates of overall survival (OS) based on
    a. Data from the pivotal trial EGF100151 with a cut off date of 1st Oct 2008 compared to 28 Sept 2007 in the previous submission.
    b. Various adjustments made to attempt to control for the crossover of patients in the capecitabine monotherapy arm of the trial to the lapatinib and capecitabine combination arm.
2. Estimates of overall survival based on post hoc subgroups of patients
3. Updated estimates of cost effectiveness that incorporate the revised estimates of OS and progression free survival (PFS), as well as amendments to some other parameters relating to adverse events and costs. Some of the estimates relating to subgroups were also translated into estimates of cost effectiveness.

2. UPDATED SURVIVAL ESTIMATES

Of the alternative approaches to estimating overall survival presented by GSK, their preferred approach is a Cox regression using crossover as a time varying covariate and a number of other covariates which reflect baseline prognostic factors.

There are several issues worthy of comment in relation to this survival modelling and the GSK preference for the Cox regression approach.

i) Inclusion of baseline covariates

No rationale is provided for how the covariates included in the Cox regression model (ECOG status, number of metastatic sites and presence of liver metastases) were selected for inclusion in the preferred model. There are several other potential covariates which are likely to be important since there is evidence of an imbalance between those patients on capecitabine who do versus those who do not crossover. These covariates include; time from last dose of trastuzumab, time since diagnosis of metastases and time from diagnosis [see Table 3.1]

ii) Methods for dealing with crossover

Whilst the use of a time-dependent covariate to capture treatment crossover has been used in the medical literature, the methods against which this approach is compared in the GSK submission are relatively simple. It is worth noting that all give estimates of treatment effect smaller than that obtained using a time-dependent covariate with additional adjustment. An important question is how might these estimates compare to more sophisticated methods, especially rank-based and likelihood-based modelling approaches (Branson & Whitehead, 2002;Robins & Tsiatis, 1991).

In our experience, based on an as yet unpublished simulation study funded by NICE, in the case when there is crossover from the control arm only (and assuming an underlying Weibull distribution) commonly adopted approaches of censoring patients at their switching time or considering treatment as a time-dependent covariate can be found to be particularly inappropriate, giving very biased estimates of the true treatment effect in situations where patients' switching patterns are strongly related to their underlying prognosis. Excluding switching patients from the analysis altogether

gave relatively small biases in situations with a low proportion of switchers but selection bias increased as switching probabilities were increased. Both the methods of Robins and Tsiatis (1991) and the Branson and Whitehead (2002) gave estimates close to the true treatment effect, though the method of Branson & Whitehead gave the smallest biases of all methods in situations where the potential for selection bias was high. This method performed particularly well when the difference in lifetime between 'good' and 'poor' prognosis patients was high, which meant patients who switched had worse underlying survival than those who did not, and was particularly robust in settings when a high proportion patients switched.

iii) Modelling the data not affected by crossover

Crossover is not considered to be an issue in the lapatinib and capecitabine arm of the trial. Thus the GSK report states that a Weibull model was fitted to these data and to which the inverse of the hazard ratio (HR) estimate is applied to obtain the corresponding shape and scale parameters for the capecitabine arm. However, there appears to be no information on the fit of the Weibull distribution to the lapatinib and capecitabine arm of the trial.

3. REVISED COST-EFFECTIVENESS MODEL

GSK provided a breakdown of the cost-effectiveness results of their model as they make stepwise changes to the estimation of overall survival, revision of costs, and inclusion of adverse events. These results are provided below in Table 2. The DSU looked to replicate these stepwise changes by taking the original basecase model "R1" and implementing each change as noted in their executive summary document. The DSU compared the results of this process with the final revised model submitted by GSK to ensure consistency.

3.1 Adverse Events

The DSU revised the R1 (basecase) version of the model to include adverse event (AE) costs, and revised the incidents and costs of each AE. In the original basecase, no adverse events were included but instead were examined in a sensitivity analysis. Compared to that sensitivity analysis, in the revised model Grade 1 and 2 AE's have been removed by GSK but a higher cost and incidence of Grade 3 and 4 AE's have been included as they have been uplifted from 2006 to 2008 values. These changes are shown below in Table 1.

Table 1 - Adverse Events

	Original Model (sensitivity analysis only)			**Revised Model**		
	Incidence		**Cost £**	**Incidence**		**Cost £**
	C+L arm	**C-only arm**		**C+L arm**	**C-only arm**	
Diarrhoea G1	108.6%	73.8%	115.5			
Diarrhoea G2	39.4%	30.4%	279.1			
Diarrhoea G3	15.2%	11.0%	3,662.0	15.2%	11.0%	3,866.0
Diarrhoea G4	1.5%	0.0%	3,662.0	1.5%	0.0%	3,866.0
Nausea G1	79.8%	70.2%	116.1			
Nausea G2	22.7%	28.8%	279.7			
Nausea G3	4.0%	4.2%	2,448.3	4.0%	4.2%	2,710.5
Nausea G4	0.0%	0.0%	2,471.9	0.0%	0.0%	2,710.5
Fatigue G1	33.8%	30.4%	111.0			
Fatigue G2	18.7%	18.3%	111.0			
Fatigue G3	3.5%	5.2%	533.8	3.5%	5.2%	536.1
Fatigue G4	0.5%	0.5%	533.8	0.5%	0.5%	536.1
PPE G1	65.7%	73.3%	111.0			

PPE G2	52.5%	50.3%	111.0			
PPE G3	14.6%	15.2%	111.0	14.6%	15.2%	86.0
PPE G4	0.0%	0.0%	2,311.0	0.0%	0.0%	2,460.4
Non-PPE rash G1	37.4%	15.2%	128.5			
Non-PPE rash G2	9.6%	4.7%	128.5			
Non-PPE rash G3	1.5%	1.0%	135.5	1.5%	1.0%	104.6
Non-PPE rash G4	0.0%	0.0%	135.5	0.0%	0.0%	104.6
LVEF event G1	1.0%	0.0%	455.0			
LVEF event G2	2.0%	1.0%	455.9			
LVEF event G3	0.5%	0.0%	455.9	0.5%	0.0%	516.3
LVEF event G4	0.0%	0.0%	2,149.9	0.0%	0.0%	3,133.9

The overall effect of this in the GSK model is to increase the expected costs of both the L+C strategy and the C-only strategy, whilst QALYs remain the same. The result is a slight increase in the estimated ICER from £94k to £95k. The DSU was unable to match exactly the ICER given for R1 by GSK but the difference was negligible.

Table 2 – Summary of GSK changes to economic model

	Overall Survival				Base-year costs	Cost AEs incl?	L+C		C-only		L+C vs C-only			DSU confirmed?
	Adjusted for BL	Adjusted for XO	Estimation PFS and OS	OS dataset			Costs £	QALYs	Costs £	QALYs	Costs £	QALYs	Cost per QALY £	
R1	No	Censored	PH Weibull	Sep-07	2006	No	26,939	0.897	12,924	0.748	14,015	0.149	93,825	Yes
R2	No	Censored	PH Weibull	Sep-07	2006	Yes	27,690	0.897	13,478	0.748	14,212	0.149	95,145	No (ICER 95,222)
R3	No	Censored	PH Weibull	Sep-07	2008	Yes	28,864	0.897	14,424	0.748	14,440	0.149	96,672	Yes
R4	No	Censored	PH Weibull	Oct-08	2008	Yes	29,599	0.935	14,727	0.763	14,872	0.171	86,736	Yes
R5	No	Censored	Modified model	Oct-08	2008	Yes	29,037	0.927	15,000	0.778	14,037	0.150	93,877	
R6	No	XO as TDV	Modified model	Oct-08	2008	Yes	29,037	0.927	14,776	0.766	14,261	0.161	88,594	
R7	Yes	XO as TDV	Modified model	Oct-08	2008	Yes	29,037	0.927	14,206	0.737	14,832	0.190	77,996	

3.2 Costs

The manufacturer also updated specific cost parameters in the model. The parameter changes made in the model are highlighted in bold in Table 4 below. The DSU implemented these parameter changes, and after running the model the resulting ICER (£96,692) matched the estimate given by GSK. This suggests that a change made at this stage may have been made at the earlier point by GSK, which explains why the ICER didn't exactly match after including the adverse event changes.

The slight increase in the ICER is a result of increases to the total costs of both strategies, whilst the QALYs understandably remain the same.

3.3 Changes to survival

As well as making changes to the costs of both strategies, GSK has adjusted the methods to estimate survival in the model. With respect to OS, the estimates are based on the Cox regression model discussed above. These changes have been made to the model by altering the parameter values for the Weibull model as well as adjusting the model to allow the use of hazard ratio estimates.

Table 3 below shows the revised gamma and lambda parameters used in the model (new values in bold). These values were taken from the revised GSK model. The total effect of making these changes to the survival estimates in the original model is to increase the incremental cost between L+C vs C-only, as well as an increase in the incremental QALYs. The result of these changes is a fall in the ICER from £93,825 (original model) and £96,672 (after revisions to costs) to £77,996. The DSU is therefore satisfied that the results presented by GSK can be replicated, provided that the same input parameters are used.

According to the narrative description of how the revised survival analysis estimates were incorporated into the economic model, it appears that two different approaches are used for OS and PFS in the two treatment arms. For OS a Weibull distribution is fitted to the lapatinib and capecitabine arm of the trial (which has no crossovers), and to which the inverse of the HR estimate is applied to obtain the corresponding shape

and scale parameters for the capecitabine arm. Note in fact that the shape parameter will remain unchanged using this approach due to the nature of the hazard function for the Weibull distribution. For PFS a Weibull distribution is fitted to the capecitabine arm and the corresponding HR (for PFS) applied in order to obtain the shape and scale parameters for the lapatinib and capecitabine arm [page 27, GSK submission]. However, a substantial proportion of switchers (26 of 36 patients) crossed over prior to disease progression [page 9 GSK submission]. It is not clear whether the fitting of the Weibull distribution to this arm adequately took account of treatment switching, and if so how.

For the actual Weibull parameters entered into the cost effectiveness model it would appear that both OS and PFS are calculated in the same way, with the lapatinib and capecitabine arm being derived from the capecitabine arm. This appears contrary to the narrative description of the methods and raises questions about how the parameter values were actually derived. In addition, the method for calculating the scale parameter based on the hazard ratio is not consistent between the original and revised models. It may be the case that a different parameterisation of the Weibull distribution has been used but without clarification from GSK, the DSU is unable to verify that the revised cost effectiveness model is correct.

Table 3 - Revised Survival Parameters

Parameter	Original Model		New Model	
	C arm	C+L arm	C arm	C+L arm
PH or Stratified - OS	PH	PH	PH	PH
PH or Stratified - PFS	PH	PH	PH	PH
PFS Gamma – PH PFS Lambda - PH	1.3920 0.0058	Hazard Ratio = 0.6085	**1.3412** 0.0058	**Hazard Ratio =** **0.5500**
PFS – Gamma – Strat PFS – Lambda – Strat	1.3412 0.0058	1.4676 0.0036	1.3412 0.0058	1.4676 0.0036
OS Gamma – PH OS Lambda - PH	1.3822 0.0017	Hazard Ratio = 0.8703	**1.3591** 0.0018	**Hazard Ratio =** **0.7500**
OS – Gamma – Strat OS – Lambda – Strat	1.3203 0.0017	1.4529 0.0015	1.3203 0.0017	**1.3591** **0.0014**

Table 4 - Revised Costs

Cost/resource parameter	Original model				New model			
	Progression-free – mean cost (se)	Post-progression – mean cost (se)	Distribution	Source	Progression-free – mean cost (se)	Post-progression – mean cost (se)	Distribution	Source
Unit cost lapatinib (per tablet)	£11.49	n/a	n/a	Final list price	£11.49	n/a	n/a	BNF 57 (2009)
Unit cost capecitabine (per tablet)	£2.46	n/a	n/a	BNF 52 (2006)	£2.46	n/a	n/a	BNF 57 (2009)
Pharmacy costs lapatinib (per day of use)	£0.571 (n/a)	n/a	n/a	Derived from Tappenden (2006a)	**£0.61 (n/a)**	n/a	n/a	Derived from Tappenden (2006a)
Pharmacy costs capecitabine (per day of use)	£0.857 (n/a)	n/a	n/a	Derived from Tappenden (2006a)	**£0.92 (n/a)**	n/a	n/a	Derived from Tappenden (2006a)
Monitoring costs for lapatinib (per month)	£55.33 (£7.06)	n/a	Lognormal	Ward (2006)	**£70.66 (£9.01)**	n/a	Lognormal	NHS reference cost (2007-2008)
Other medications to manage adverse events (per month)	£56.95 (£7.26)	£66.23 (£8.45)	Lognormal	Remak (2004)	**£61.81 (£7.88)**	**£71.88 (£9.17)**	Lognormal	Remak and Brazil (2004)
Clinical consultation/visits (per month)	£87.29 (£11.13)	£268.72 (£34.28)	Lognormal	Remak (2004)	**£94.74 (£12.08)**	**£291.64 (£37.20)**	Lognormal	Remak and Brazil (2004)

Hospitalisation (per month)	£59.23 (£7.55)	£165.74 (£21.14)	Lognormal	Remak (2004)	**£64.28 (£8.20)**	**£179.88 (£22.94)**	Lognormal	Remak and Brazil (2004)
Diagnostics (per month)	£239.69 (£30.57)	£81.89 (£10.45)	Lognormal	Remak (2004)	**£260.13 (£33.18)**	**£88.88 (£11.34)**	Lognormal	Remak and Brazil (2004)
Radiotherapy (per month)	£20.83 (£2.66)	£18.74 (£2.39)	Lognormal	Remak (2004)	**£22.60 (£2.88)**	**£20.34 (£2.59)**	Lognormal	Remak and Brazil (2004)
Other special interventions (per month)	£30.80 (£3.93)	£107.04 (£13.65)	Lognormal	Remak (2004)	**£33.43 (£4.26)**	**£116.18 (£14.82)**	Lognormal	Remak and Brazil (2004)

4. SUBGROUP ANALYSIS

GSK provide cost-effectiveness results for two of the three subgroup analyses that was conducted. Firstly they estimate the results for patients treated with one or two prior regimens, with an estimated gain in median OS of 7.4 months (HR 0.51, p=0.009). Secondly they estimate the results for patients treated with 1 prior trastuzumab-based regimen in the metastatic setting, with an estimated gain in median OS of 3.4 months (HR 0.79, p=0.077).

As well as the inherent dangers with post-hoc subgroup analyses, it is unclear in this case how the precise definitions of the subgroups were arrived at. For example, whilst it appears clinically plausible that higher levels of prior treatment may affect subsequent therapy, what is the rationale for the subgroups chosen? Regardless of the rationale it is also not clear whether the analyses presented for the subgroups take account for treatment switching, and from Table 3.1 [page 12, GSK submission] it appears that there is some imbalance in terms of the number of prior regimens and time since these between those patients who crossover and those who do not.

The revised basecase model (R7 in Table 2) estimates mean incremental life years gained as 0.292yrs (3.5months) and is assumed to be based on a hazard ratio of 0.75 (p=0.013). The first subgroup analysis is based on a hazard ratio of 0.51 and generates a mean incremental gain in life years of 0.693 years (8.32 months). This leads to an improvement in the ICER from £77,996 to £54,575 (See Table 5). The second subgroup population has a slightly larger hazard ratio than the base case (0.79 versus 0.75), suggesting that there is less benefit in terms of overall survival for this subgroup of patients. However, the mean incremental gain in life years from the model is reported as 0.378 yrs (4.54 months), an increase compared to the base case. The ICER also improves compared to the basecase, falling to £70,474.

The DSU did not have the GSK models with these subgroup analyses included, and so we looked to replicate the results ourselves by adjusting the hazard ratio in the revised base case model. The resulting ICERs that were produced by just changing the hazard ratios to the ones reported did not match those reported by GSK. The GSK report does not detail how this subgroup analysis has been incorporated into their new cost-

effectiveness results. Therefore the DSU remains unable to confirm their validity without further clarification from the manufacturer.

Table 5 - GSK subgroup cost-effectiveness results

Revised basecase results												
	Basecase			**Basecase with TPAP**			**EOL case**			**EOL case with TPAP**		
	L+C	C-only	Incr.	L+C	C-only	Incr.	L+C	C-only	Incr.	L+C	C-only	Incr.
QALYs	0.927	0.737	0.190	0.927	0.737	0.190	1.404	1.156	0.248	1.404	1.156	0.248
Total Cost	£29,037	£14,206	£14,832	£25,509	£14,206	£11,303	£29,037	£14,206	£14,832	£25,509	£14,206	£11,303
Cost per QALY gained	£77,996			£59,441			£59,734			£45,524		
Subgroup analysis for patients treated with one or two prior regimens												
	Basecase			**Basecase with TPAP**			**EOL case**			**EOL case with TPAP**		
	L+C	C-only	Incr.	L+C	C-only	Incr.	L+C	C-only	Incr.	L+C	C-only	Incr.
QALYs	1.050	0.636	0.414	1.050	0.636	0.414	1.660	1.071	0.589	1.660	1.071	0.589
Total Cost	£35,741	£13,153	£22,588	£32,262	£13,153	£19,109	£35,741	£22,588	£14,832	£32,262	£13,153	£19,109
Cost per QALY gained	£54,575			£49,169			£38,347			£32,440		
Subgroup analysis for patients treated with one prior trastuzumab-based regimen in the metastatic setting												
	Basecase			**Basecase with TPAP**			**EOL case**			**EOL case with TPAP**		
	L+C	C-only	Incr.	L+C	C-only	Incr.	L+C	C-only	Incr.	L+C	C-only	Incr.
QALYs	0.946	0.691	0.255	0.946	0.691	0.255	1.389	1.068	0.321	1.389	1.068	0.321
Total Cost	£31,078	£13,134	£17,943	£27,496	£13,134	£14,362	£31,078	£13,134	£17,943	£27,496	£13,134	£14,362
Cost per QALY gained	£70,474			£56,406			£55,833			£44,688		

5. CONCLUSIONS

It is difficult to verify from the information supplied by GSK why the estimates of the Cox regression model preferred by GSK should be considered superior to those generated by the other methods presented, or whether alternative covariates should have been included in the statistical model. The DSU would recommend other methods for dealing with crossover should also be considered.

There are also several other areas that lack clarity in the GSK report which are important inputs to the cost effectiveness estimates. It is unclear whether the Weibull model claimed to be fitted to the lapatinib and capecitabine data for overall survival is an appropriate distribution. It is also unclear whether adjustments were made to account for crossover in the PFS data.

The DSU is satisfied that adjustments made to the cost effectiveness model in relation to costs and adverse events have been implemented appropriately. The DSU is also satisfied that no other changes have been made to the model other than changes relating to OS and PFS. We are unclear however, how the input parameters for OS and PFS have been derived. There appears to be inconsistency between the described methods and those found in the spreadsheet model. This issue requires clarification in order to be verified.

We recommend the subgroup analyses are treated with extreme caution. In addition to standard concerns about such analyses, there is little rationale provided for the precise subgroup analyses performed. In addition, we were unable to replicate the cost effectiveness results based on these figures.

References

Robins JM and Tsiatis AA. Correcting for non-compliance in randomized trials using rank preserving structural failure time models, *Communications in Statistics: Theory and Methods*, 1991; 20: 2609-2631

Branson M, Whitehead J. Estimating a treatment effect in survival studies in which patients switch treatment. Stat Med. 2002 Sep 15;21(17):2449-63.