ADDENDUM TO MTA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Lapatinib and trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone receptor positive breast cancer which over-expresses HER2

This project was commissioned by the NIHR HTA Programme as project number 09/101/01

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DOES NOT CONTAIN IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Lapatinib and trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone receptor positive breast cancer which over-expresses HER2

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In the past, Anne Armstrong has received consultancy fees, reimbursement for attending a conference and hospitality at a conference, from Roche. The North West Medicines Information Centre, where Helen Davis is the Assistant Director, has received a consultancy fee from GlaxoSmithKline in the past for participation in a group discussing various mechanisms for managing NHS medicines budgets

Rider on responsibility for report:

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors:

Nigel Fleeman	Project lead, involved in all aspects of the clinical review and report writing.
Adrian Bagust	Critical appraisal of manufacturers' economic models, development of de novo model and report writing.
Angela Boland	Involved in all aspects of the economics review and report writing.
Rumona Dickson	Support of review process and commented on draft versions of the final report.
Yenal Dundar	Conducted literature searches and contributed to the screening and selection process.
May Moonan	Prepared background section, contributed to analysis and interpretation of data and commented on draft versions of the final report.
James Oyee	Contributed to analysis and interpretation of data, prepared sections of the report relating to statistical issues and commented on draft versions of the final report.
Michaela Blundell	Additional statistical support.
Helen Davis	Contributed to background section and commented on draft versions of the final report.
Anne Armstrong	Contributed to analysis and interpretation of data and commented on draft versions of the final report.
Nicky Thorp	Contributed to background section, analysis and interpretation of data and commented on draft versions of the final report.

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1 INTRODUCTION

Prior to the Appraisal Committee (AC) meeting of February 16th 2011, the report and decision models provided by the Assessment Group (AG) were made available to consultees from whom comments were requested. As part of this process the two manufacturer's provided responded formally by means of the Factual Error Check procedure identifying perceived errors identified in the AG's models. The AG was able to review these comments prior to the AC meeting, and provided a response to each point raised. In some cases these errors could be confirmed, and the effect of such amendments were estimated and reported in summary to the committee on February 16th. The Addendum provides a summary of the changes made to the models as a consequence of this scrutiny, and the resulting amended cost-effectiveness results.

2 AMENDMENTS TO TRASTUZUMAB MODEL

2.1 Problems identified and AG responses

The manufacturer of trastuzumab identified problems with the AG model under 2 headings:

1) **Adjustment for patients who died in PFS on the calculation of post-progression survival** This involved a single parameter entry involved in estimating the proportion of patients surviving alive to enter post-progression survival in the intervention arm of the analysis. The manufacturer indicated that this had been underestimated by the AG, and when checked it was confirmed that the parameter should be corrected and that the manufacturer's revised ICER estimate was appropriate.

2) **Calculation of Progression-Free Survival and the associated trastuzumab costs** The manufacturer questioned to use of projective modelling rather than Kaplan-Meier estimates of progression-free survival which they considered more appropriate, leading to a lower estimated incremental cost-effectiveness ratio (ICER). The AG explained that the particular characteristics of the trial data set did not suggest that one methodology was obviously superior on theoretical grounds, and that the AG judged that the use of projective modelling more reliably reflected the uncertainty in the trial data than other methods. Therefore, the AG did not accept the manufacturer's approach on this matter.

2.2 Revised model results

Revised outcome and cost-effectiveness estimates are presented in Tables 1 and 2 after correction of the model parameter described above, resulting in a reduced ICER of £69,514 per QALY gained compared to that shown in the AG report (£73,135 per QALY gained)

Table 1: Estimated undiscounted survival outcomes after 20 years with error correction

Treatment	Days			Life-years		
	PFS	PPS	OS	PFS	PPS	OS
ANA	194.0	671.7	865.7	0.53	1.84	2.37
TRA+ANA	509.8	611.8	1121.5	1.40	1.67	3.07
Increment	+315.8	-59.9	+255.9	+0.86	-0.16	+0.70

Table 2: Estimated discounted cost-effectiveness results after 20 years with error correction

	ANA	TRA+ANA	Incremental
Cost per patient			
Drugs	£ 549	£ 36,251	+£ 35,702
Monitoring	£ 602	£ 1,898	+£ 1,297
Adverse event	£ 0	£ 92	+£ 92
BSC	£ 11,194	£ 11,953	+£ 759
Terminal care	£ 1,647	£ 1,696	+£ 49
All costs	**£ 13,992**	**£ 51,891**	**+£ 37,899**
Outcomes per patient			
Life-years	2.22	2.89	+0.67
QALYs	**1.24**	**1.79**	**+0.55**
ICER			**£69,514 / QALY**

Results of probabilistic sensitivity analysis (PSA) after error correction yielded a probabilistic ICER of £65,284 per QALY gained, with a 6.3% probability of an ICER less than £50,000 per QALY, and no measurable probability of an ICER less than £40,000 per QALY. These results are illustrated in Figures 1 and 2.

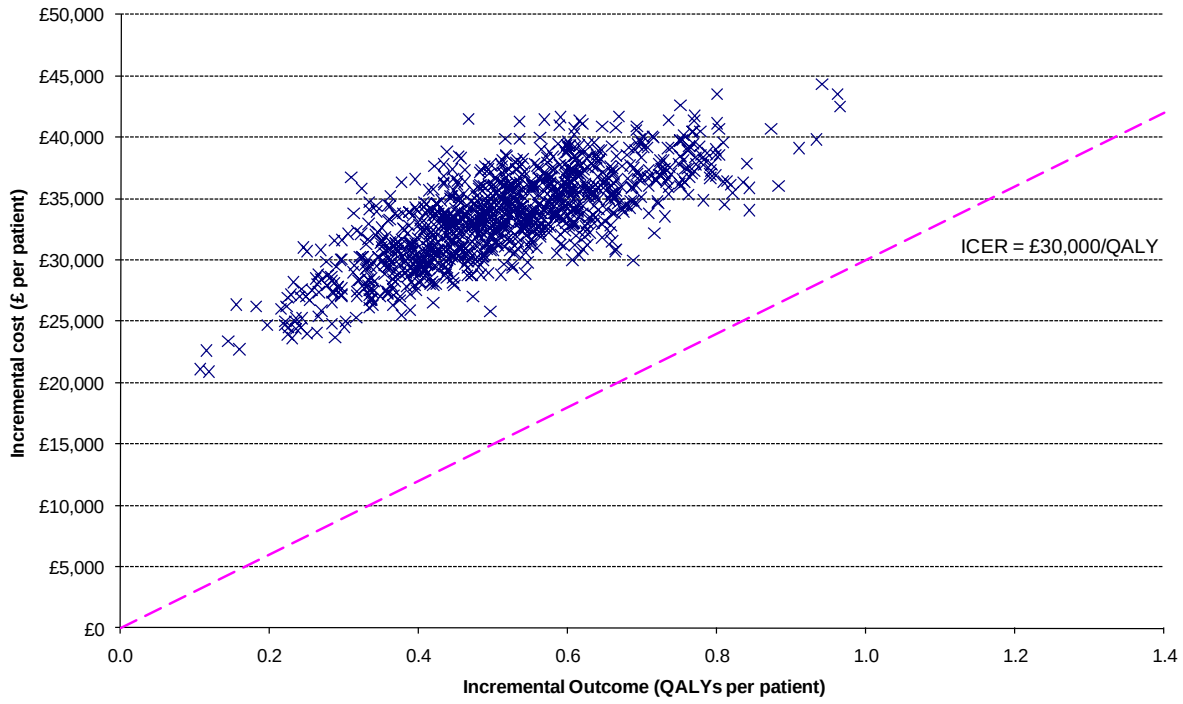

Figure 1 Revised PSA of TRA+ANA vs ANA only: scatterplot of 1000 probabilistic iterations

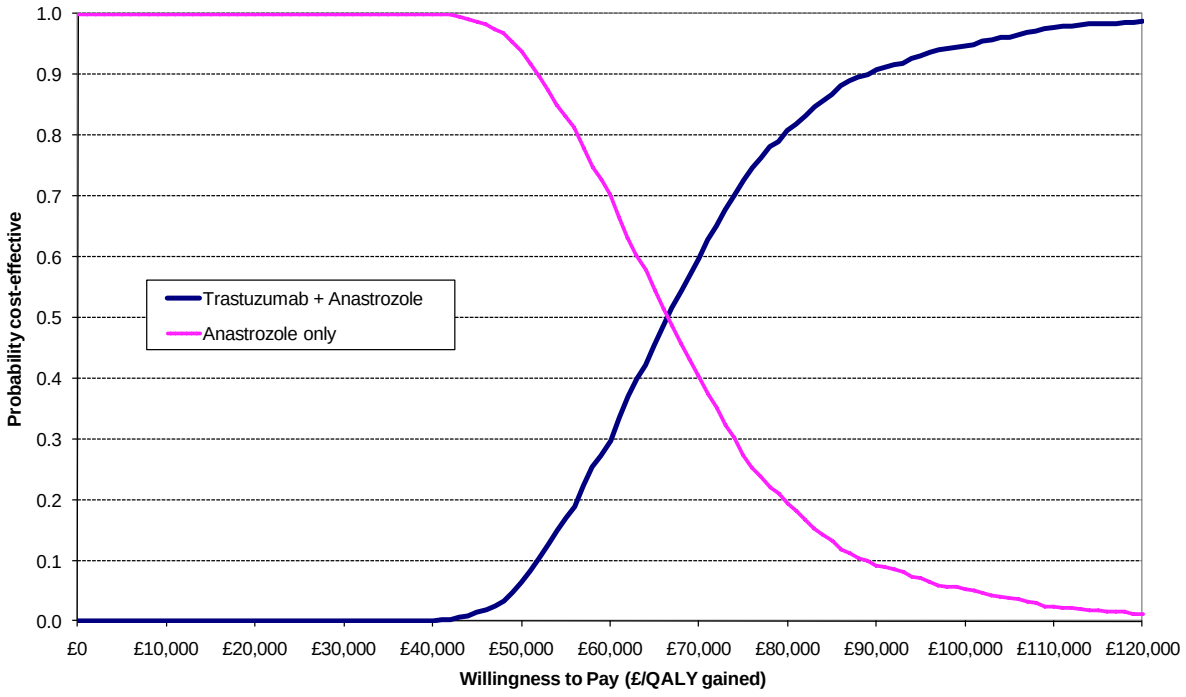

Figure 2 Revised PSA of TRA+ANA vs ANA only: cost-effectiveness acceptability curve

3 AMENDMENTS TO LAPATINIB MODEL

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3.1 Problems identified and AG responses

The manufacturer of lapatinib identified problems with the AG model under 5 headings:

1) **Calculation error on the Calcs_Let sheet of the AG executable model** This concerns the use of PPS estimates relating the intervention arm rather than the comparator arm in model calculations. The AG have confirmed that a coding error was made as described by the manufacturer, leading to a slight increase in the deterministic ICER for use of lapatinib.

2) **Error in Sampling the Decrement in Utility with Diarrhoea/Vomiting (D/V) for the Lapatinib treatment in the AG executable model** The AG can confirm the problem indicated which concerns the calculation of uncertainty relating to one model parameter, and is influential in probabilistic sensitivity analysis, but not in the calculation of the deterministic ICER. This was caused by the omission of one term in a control parameter formula in the 'Parameters' worksheet. In addition the AG has identified that the standard error for the D/V utility decrement was over-estimated. Both problems have been corrected, and leading to a revised probabilistic ICER of £276,478 per QALY gained.

3) **Error in Inputs Used for Sampling the Proportion of Patients Progressing with LET in the AG executable model** This concerns the parameters required in the estimation of uncertainty in calculations of the time spent in PPS for patients in the comparator arm of the analysis. The AG has confirmed that this arose from a transcription error. When corrected this further reduces the probabilistic ICER, but has no influence on the deterministic ICER.

4) **Potential Bias in the Sampling of PFS in the AG executable model** A third issue was identified affecting probabilistic sensitivity analysis, and concerns the method used to represent uncertainty in estimates of PFS over time. The manufacturer expressed concern that the AG's approach may have a differential effect which favours the comparator arm over the intervention arm. The Assessment Group agrees that the discrepancy referred to will occur during PSA. Other approaches were explored but were not considered satisfactory.

However, as similar uncertainty values are used in both arms, and the time during which such differential estimation can occur is small, it was considered that the net impact of the discrepancy arising from the current method is minor and unlikely to have a significant impact on the probabilistic ICER (it has no effect on the deterministic ICER). Therefore the AG does not consider any amendment is necessary relating to this issue.

5) **Lack of transparency which limits the testing of the robustness and reliability of the AG executable model** The manufacturer of lapatinib raised 6 concerns about aspects of the model where they felt more information would have allowed further scrutiny of some aspects of the AG's model. In each case the AG has responded, providing additional information relevant to the points identified. None of these issues required any amendments to be made to the AG's model.

3.2 Revised model results

Revised outcome and cost-effectiveness estimates are presented in Tables 3 and 4 after correction of the model parameter described above, resulting in an increased deterministic ICER of £225,131 per QALY gained compared to that shown in the AG report (£220,626 per QALY gained)

Table 3: Estimated undiscounted survival outcomes after 20 years with error correction

Treatment	Days			Life-years		
	PFS	PPS	OS	PFS	PPS	OS
LET	254.5	742.4	996.9	0.70	2.03	2.73
LAP+LET	343.4	717.2	1060.6	0.94	1.96	2.90
Increment	+88.9	-25.2	+63.7	+0.24	-0.07	+0.17

Table 2: Estimated discounted cost-effectiveness results after 20 years with error correction

	LET	LAP+LET	Incremental
Cost per patient			
Drugs	£ 686	£ 26,025	+£ 25,366
Monitoring	£ 702	£ 1,446	+£ 744
Adverse event	£ 0	£ 98	+£ 98
BSC	£ 12,620	£ 12,574	-£ 46
Terminal care	£ 1,653	£ 1,641	-£ 12
All costs	**£ 15,661**	**£ 41,811**	**+£ 26,150**
Outcomes per patient			
Life-years	2.56	2.73	+0.17
QALYs	**1.25**	**1.36**	**+0.12**
ICER			**£225,131 / QALY**

Results of probabilistic sensitivity analysis (PSA) after error correction yielded a probabilistic ICER of £228,913 per QALY gained, with a 0.1% probability of an ICER less than £50,000 per QALY, and no measurable probability of an ICER less than £40,000 per QALY. These results are illustrated in Figures 3 and 4.

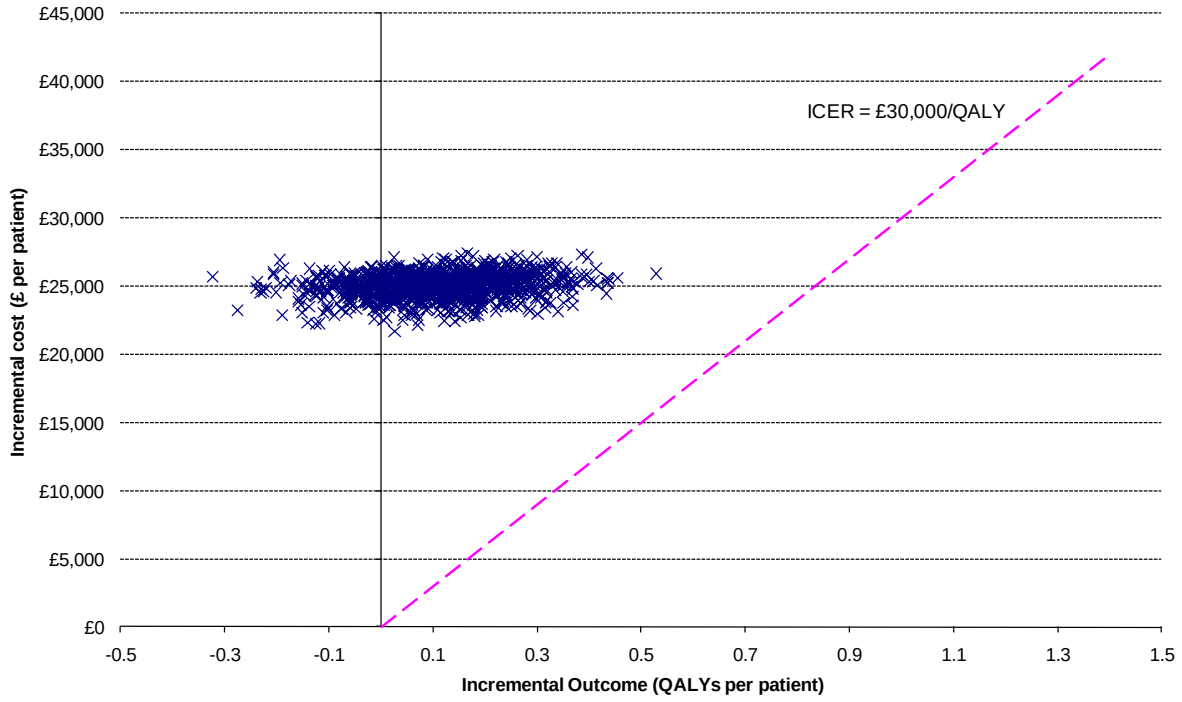

Figure 3 Revised PSA of LAP+LET vs LET only: scatterplot of 1000 probabilistic iterations

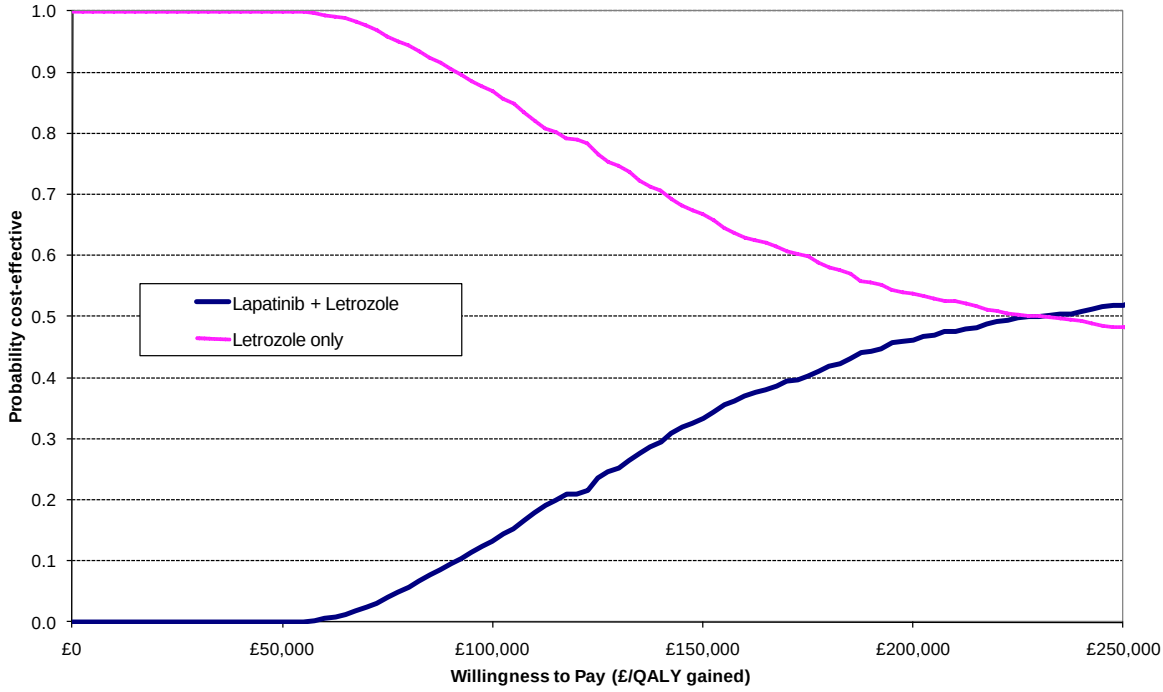

Figure 4 Revised PSA of LAP+LET vs LET only: cost-effectiveness acceptability curve