

Lapatinib and trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone receptor-positive breast cancer which over-expresses human epidermal growth factor 2 (HER2): a systematic review and economic analysis

N Fleeman, A Bagust, A Boland, R Dickson, Y Dundar, M Moonan, J Oyee, M Blundell, H Davis, A Armstrong and N Thorp



December 2011
10.3310/hta15420

Health Technology Assessment
NIHR HTA programme
www.hta.ac.uk





How to obtain copies of this and other HTA programme reports

An electronic version of this title, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (www.hta.ac.uk). A fully searchable DVD is also available (see below).

Printed copies of HTA journal series issues cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our despatch agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per issue and for the rest of the world £3 per issue.

How to order:

- fax (with **credit card details**)
- post (with **credit card details** or **cheque**)
- phone during office hours (**credit card** only).

Additionally the HTA website allows you to either print out your order or download a blank order form.

Contact details are as follows:

Synergie UK (HTA Department)
Digital House, The Loddon Centre
Wade Road
Basingstoke
Hants RG24 8QW

Email: orders@hta.ac.uk

Tel: 0845 812 4000 – ask for 'HTA Payment Services'
(out-of-hours answer-phone service)

Fax: 0845 812 4001 – put 'HTA Order' on the fax header

Payment methods

Paying by cheque

If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *University of Southampton* and drawn on a bank with a UK address.

Paying by credit card

You can order using your credit card by phone, fax or post.

Subscriptions

NHS libraries can subscribe free of charge. Public libraries can subscribe at a reduced cost of £100 for each volume (normally comprising 40–50 titles). The commercial subscription rate is £400 per volume (addresses within the UK) and £600 per volume (addresses outside the UK). Please see our website for details. Subscriptions can be purchased only for the current or forthcoming volume.

How do I get a copy of HTA on DVD?

Please use the form on the HTA website (www.hta.ac.uk/htacd/index.shtml). *HTA on DVD* is currently free of charge worldwide.

The website also provides information about the HTA programme and lists the membership of the various committees.

Lapatinib and trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone receptor-positive breast cancer which over-expresses human epidermal growth factor 2 (HER2): a systematic review and economic analysis

N Fleeman,¹ A Bagust,¹ A Boland,¹ R Dickson,^{1*}
Y Dundar,¹ M Moonan,² J Oyee,¹ M Blundell,¹ H Davis,³
A Armstrong⁴ and N Thorp⁵

¹Liverpool Reviews and Implementation Group (LRiG), University of Liverpool, Liverpool, UK

²Department of Public Health Medicine, University of Liverpool, Liverpool, UK

³North West Medicines Information Centre, Liverpool, UK

⁴The Christie NHS Foundation Trust, Manchester, UK

⁵Clatterbridge Centre for Oncology NHS Foundation Trust, Wirral, UK

*Corresponding author

Declared competing interests of the authors: 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.

Published December 2011

DOI: 10.3310/hta15420

This report should be referenced as follows:

Fleeman N, Bagust A, Boland A, Dickson R, Dundar R, Moonan M, *et al.* Lapatinib and trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone receptor-positive breast cancer which over-expresses human epidermal growth factor 2 (HER2): a systematic review and economic analysis. *Health Technol Assess* 2011;**15**(42).

Health Technology Assessment is indexed and abstracted in *Index Medicus/MEDLINE*, *Excerpta Medica/EMBASE*, *Science Citation Index Expanded (SciSearch®)* and *Current Contents®/Clinical Medicine*.

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series *Health Technology Assessment*.

Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned and funded by the HTA programme on behalf of NICE as project number 09/101/01. The protocol was agreed in February 2010. The assessment report began editorial review in September 2010 and was accepted for publication in January 2011. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

Editor-in-Chief: Professor Tom Walley CBE
 Series Editors: Dr Martin Ashton-Key, Professor Aileen Clarke, Dr Tom Marshall, Professor John Powell, Dr Rob Riemsma and Professor Ken Stein
 Associate Editor: Dr Peter Davidson
 Editorial Contact: edit@southampton.ac.uk

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

ISSN 2046-4932 (DVD)

© Queen's Printer and Controller of HMSO 2011. This work was produced by Fleeman *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (<http://www.publicationethics.org/>).

This journal may be freely reproduced for the purposes of private research and study and may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NETSCC, Health Technology Assessment, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.

Printed on acid-free paper in the UK by the Charlesworth Group.

Abstract

Lapatinib and trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone receptor-positive breast cancer which over-expresses human epidermal growth factor 2 (HER2): a systematic review and economic analysis

N Fleeman,¹ A Bagust,¹ A Boland,¹ R Dickson,^{1*} Y Dundar,¹ M Moonan,² J Oyee,¹ M Blundell,¹ H Davis,³ A Armstrong⁴ and N Thorp⁵

¹Liverpool Reviews and Implementation Group (LRiG), University of Liverpool, Liverpool, UK

²Department of Public Health Medicine, University of Liverpool, Liverpool, UK

³North West Medicines Information Centre, Liverpool, UK

⁴The Christie NHS Foundation Trust, Manchester, UK

⁵Clatterbridge Centre for Oncology NHS Foundation Trust, Wirral, UK

*Corresponding author

Background: Breast cancer is the uncontrolled, abnormal growth of malignant breast tissue affecting predominantly women. Metastatic breast cancer (mBC) is an advanced stage of the disease when the disease has spread beyond the original organ. Hormone receptor status and human epidermal growth factor 2 (HER2) status are two predictive factors that are taken into consideration when estimating the prognosis of patients with breast cancer.

Objectives: To review the clinical effectiveness and cost-effectiveness evidence base for lapatinib (LAP) in combination with an aromatase inhibitor (AI) and trastuzumab (TRA) in combination with an AI for the first-line treatment of patients who have hormone receptor-positive (HR+)/human epidermal growth factor 2-positive (HER2+) mBC.

Data sources: Relevant electronic databases and websites, including MEDLINE, EMBASE and the Cochrane Library, were searched until May 2010. Further data were derived from the manufacturers' submissions for LAP+AI and TRA+AI.

Review methods: A systematic review of the clinical effectiveness and cost-effectiveness of LAP+AI and TRA+AI was undertaken. As it was deemed inappropriate to compare LAP+AI with TRA+AI, two separate assessments of cost-effectiveness versus AIs alone were undertaken.

Results: Three trials were included in the systematic review [the patient populations of the efficacy and safety of lapatinib combined with letrozole (EGF30008) trial, the efficacy and safety of trastuzumab combined with anastrozole (TAnDEM) trial and the efficacy and safety of letrozole combined with trastuzumab (eLEcTRA) trial]. As a result of differences in the exclusion criteria and because one trial was halted prematurely, comparisons across trials were believed to be inappropriate and meta-analysis was not possible. Individually, however, the findings from the trials all suggest that LAP+AI or TRA+AI results in improved progression-free survival and/or time to progression when compared with AIs alone. The trials do not show a statistically significant benefit in terms of overall survival. Two separate economic analyses were conducted based on the completed trials; neither LAP+AI nor

TRA + AI was found to be cost-effective when compared with AI monotherapy.

Limitations: Because of differences in the EGF30008 and the TAnDEM trials, the Assessment Group believes the indirect comparisons analyses conducted by the manufacturers are inappropriate and, for the same reason, chooses not to compare LAP + AI with TRA + AI in an economic evaluation.

Conclusions: LAP + AI and TRA + AI appear to be clinically more effective than AI monotherapy, but neither is cost-effective compared with AIs alone. It was not possible to compare LAP + AI with TRA + AI. Future research should include research into treating mBC in the HR+/HER2+ population who are not TRA (or LAP) naive and into comparing the clinical effectiveness of AIs as monotherapy in patients with HER2+ and human epidermal growth factor 2-negative breast cancer.

Funding: The National Institute for Health Research Technology Assessment programme.

Contents

Glossary	vii
List of abbreviations	ix
Executive summary	xi
1. Background	1
Description of health problem	1
Description of technologies under assessment	3
Current service provision	5
2. Definition of the decision problem	7
Decision problem	7
Overall aims and objectives of assessment	8
3. Assessment of clinical effectiveness	9
Methods for reviewing effectiveness	9
Results	10
Summary	27
4. Assessment of cost-effectiveness	31
Systematic review of existing cost-effectiveness evidence	31
Overview and critique of GlaxoSmithKline economic evaluation	32
Overview and critique of Roche economic evaluation	38
Independent economic assessment	45
Summary of cost-effectiveness evidence	57
5. Discussion	61
6. Conclusions and research recommendations	63
Recommendations for further research	63
Acknowledgements	65
References	67
Appendix 1 Literature search strategies	75
Appendix 2 Tables of excluded studies with rationale	77
Appendix 3 Final protocol	79
Health Technology Assessment programme	95

Glossary

Biological therapy Treatments that use natural substances from the body, or drugs made from these substances, to fight cancer or to lessen the side effects that may be caused by some cancer treatments, e.g. trastuzumab.

Chemotherapy Treatment with drugs that kill cancer cells.

Endocrine therapy Treatment that adds, blocks or removes hormones. Also commonly known as hormonal or antioestrogen therapy.

Human epidermal growth factor receptor 2 positive (HER2+) Over-expression of the HER2 receptor (HER2 receptors present in cancer cells).

Human epidermal growth factor receptor 2 negative (HER2-) HER2 receptors are not present in cancer cells.

Heterogeneity In statistics this means that there is between-study variation. If heterogeneity exists, the pooled effect size in a meta-analysis has no meaning as the presence of heterogeneity indicates that there is more than one true effect size in the studies being combined.

Hormone receptor A receptor that binds a hormone.

Hormone receptor positive (HR+) A tumour consisting of cells that express receptors for certain hormones, usually the oestrogen receptor (ER), i.e. oestrogen receptor positive (ER+), or the progesterone receptor (PgR), i.e. progesterone receptor positive (PgR+).

Meta-analysis A quantitative method for combining the results of many studies into one set of conclusions.

Oestrogen A general term for female steroid sex hormones that are secreted by the ovaries and responsible for typical female sexual characteristics.

Oestrogen receptor (ER) Proteins that bind oestrogens.

Oestrogen receptor positive (ER+) Cells that contain a receptor (protein) to which oestrogens can bind (attach).

Oestrogen receptor negative (ER-) Cells that do not have a receptor to which oestrogens will bind.

Quality-adjusted life-year (QALY) An index of survival that is weighted or adjusted by a patient's quality of life during the survival period. QALYs are calculated by multiplying the number of life-years by an appropriate utility or preference score.

Receptor A protein molecule embedded in a membrane to which a signal molecule (ligand), such as a pharmaceutical drug, may attach itself and which usually initiates a cellular response (although some ligands merely block receptors without inducing any response).

List of abbreviations

AE	adverse event
AG	Assessment Group
AI	aromatase inhibitor
ANA	anastrozole
ASCO	American Society of Clinical Oncology
AUC	area under the curve
CBR	clinical benefit rate
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CR	complete response
CRD	Centre for Reviews and Dissemination
CSR	clinical study report
ECOG	the European Cooperative Oncology Group
EGF30008	efficacy and safety of lapatinib combined with letrozole trial
eLEcTRA	efficacy and safety of letrozole combined with trastuzumab trial
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions
ER	oestrogen receptor
ER+	oestrogen receptor positive
EXE	exemestane
FACT	Functional Assessment of Cancer Therapy
FDA	the US Food and Drug Administration
FISH	fluorescence in situ hybridisation
HER2	human epidermal growth factor receptor 2
HER2+	human epidermal growth factor receptor 2 positive
HER2-	human epidermal growth factor receptor 2 negative
HR	hazard ratio
HR+	hormone receptor positive
HR-	hormone receptor negative
ICER	incremental cost-effectiveness ratio
IHC	immunohistochemistry
IPCW	inverse probability censoring weight
ITT	intention to treat
i.v.	intravenous
LAP	lapatinib
LET	letrozole
LVEF	left ventricular ejection fraction
LYG	life-year gained
mBC	metastatic breast cancer
MS	manufacturer's submission/manufacturers' submissions
NICE	National Institute for Health and Clinical Excellence
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFLY	progression-free life-year
PFS	progression-free survival
PgR	progesterone receptor
PgR+	progesterone receptor positive

PP	per protocol
PPLY	post-progression life-years
PPS	post-progression survival
PR	partial response
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RPSFT	rank-preserving structural failure time
SAE	serious adverse event
SE	standard error
TAM	tamoxifen
TAnDEM	efficacy and safety of trastuzumab combined with anastrozole trial
TRA	trastuzumab
TTP	time to progression

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

Breast cancer is the uncontrolled, abnormal growth of malignant breast tissue affecting predominantly women. Metastatic breast cancer (mBC) is an advanced stage of the disease when the disease has spread beyond the original organ.

Hormone receptor status and human epidermal growth factor 2 (HER2) status are two predictive factors that are taken into consideration when estimating the prognosis of patients with breast cancer. Tumours that express either oestrogen receptor-positive (ER+) or progesterone receptor-positive (PgR+) are commonly referred to as being hormone receptor positive (HR+), and patients with HR+ breast cancer generally have an improved prognosis compared with those who are hormone receptor negative (HR-). More recently, it has been discovered that over-expression of ErbB2 protein (also known as HER2), which is a member of the epidermal growth factor receptor family, and/or amplification of the *HER2* gene results in an abnormally high number of *HER2* genes per cancer cell, which results in cancer cells growing and dividing more quickly. Thus, human epidermal growth factor 2-positive (HER2+) breast cancer is considered to be an aggressive disease and there is growing evidence that the prognosis of HER2+ patients is generally poor, whether or not they are HR+ or HR-.

The aim of current treatments for mBC is to palliate symptoms, prolong survival and maintain a good quality of life with minimal adverse events (AEs). Trastuzumab (TRA) (Herceptin[®], Roche) is commonly given in combination with chemotherapy [paclitaxel or docetaxel (Taxotere[®], Sanofi-Aventis)] for patients with HR+/HER2+ mBC. Data on the number of women with HR+/HER2+ mBC are not routinely collected, but the number of patients estimated to be suitable for treatment with either lapatinib (LAP) (Tyverb[®], GlaxoSmithKline) or TRA in combination with an aromatase inhibitor (AI) has been estimated to be relatively small (under 200 patients per year).

Objectives

The remit of this appraisal is to review the clinical effectiveness and cost-effectiveness evidence base for LAP in combination with an AI (LAP + AI) and TRA in combination with an AI (TRA + AI) within their licensed indications for the first-line treatment of patients who have HR+/HER2+ mBC.

Methods

Evidence for clinical effectiveness of LAP + AI and TRA + AI for the first-line treatment of HR+/HER2+ mBC was assessed by conducting a systematic review of published research evidence. The review was undertaken following the general principles published by the Centre for Reviews and Dissemination's (CRD's) guidance for undertaking reviews in health care.

Randomised controlled trials (RCTs) were identified by searching major electronic medical databases including MEDLINE, EMBASE and the Cochrane Library. Two reviewers

independently screened all titles and abstracts. Data were extracted by one reviewer using a standardised data extraction form and checked independently by a second reviewer. The quality of the individual clinical effectiveness studies was assessed independently by two reviewers according to criteria based on the CRD's guidance for undertaking reviews in health care.

It was intended by the Assessment Group (AG) that meta-analyses would be conducted in which direct evidence would be pooled using a standard meta-analysis and, where a direct comparison between LAP + AI and TRA + AI was not possible, by indirect comparisons. However, the AG considered it inappropriate to conduct either of the analyses, as discussed further below.

Results

Assessment of clinical effectiveness

Quantity and quality of research available

A total of 2069 references were identified, of which two trials [the efficacy and safety of lapatinib combined with letrozole (EGF30008) trial and the efficacy and safety of trastuzumab combined with anastrozole (TAnDEM) trial] met the inclusion criteria. A further trial [efficacy and safety of letrozole combined with trastuzumab (eLEcTRA) trial], which was halted prematurely and reported only as a conference abstract, was also included following information passed on to the AG by Roche at the National Institute for Health and Clinical Excellence (NICE) consultation meeting in February 2010.

Overall, the risk of bias assessment conducted by the AG found the EGF30008 and the TAnDEM to be of a good standard. The eLEcTRA was deemed to be of poorer quality, which may be a reflection of poor-quality reporting rather than trial design as this trial was published as an abstract.

A much greater proportion of patients in the EGF30008 trial received second-line chemotherapy than in the TAnDEM trial. The EGF30008 trial also explicitly excluded patients with extensive symptomatic visceral disease and patients in which the disease was considered by the investigator to be rapidly progressing or life-threatening; this was not an explicit exclusion criteria of the other two trials.

Assessment of effectiveness

All of the three main trials examining the efficacy of LAP + letrozole (LET) (Femara[®], Novartis) (EGF30008 trial), TRA + anastrozole (ANA) (Arimidex[®], AstraZeneca) (TAnDEM trial) and TRA + LET (eLEcTRA trial) suggest that LAP + AI or TRA + AI result in improved outcomes when compared with AIs alone (LET, ANA and LET, respectively). Although these differences were not significant for overall survival (OS), significantly different outcomes were reported for progression-free survival (PFS)/time-to-treatment progression (TTP) in the EGF30008 and the TAnDEM trials. Large differences were also reported in the eLEcTRA trial. Both overall response rate and clinical benefit rate appeared to be improved for patients taking LAP + AI or TRA + AI in all three trials. An interesting finding from EGF30008 and eLEcTRA was that AIs alone appeared to be less effective in the HR+/HER2+ population than in the HR+/HER2- population.

Although both AEs and SAEs were more common in the LAP + LET and TRA + AI groups than in those treated with AIs alone, no new safety concerns were identified from the trials. For LAP + LET, the most significant AE was diarrhoea, experienced by around two-thirds of all patients. The majority of cases of AEs (including diarrhoea) were of grade 1 or 2 severity. For TRA + ANA patients, the most frequently reported AEs were fatigue, diarrhoea and vomiting,

experienced by around one-fifth of all patients, of which the majority were grade 1 or 2 severity. Fatigue was also a problem for around one-quarter of patients who received TRA + LET, but infections, gastrointestinal disorders and musculoskeletal and connective tissue disorders were even more common.

As direct comparison across trials would be too crude and simplistic, both manufacturers conducted adjusted indirect comparisons. However, the AG believed indirect comparisons were not appropriate because the patient populations were not sufficiently similar in the EGF30008 and the TAnDEM trials. The AG reached this conclusion when examining median OS in the AI arms, which was reported to be ≤ 23.9 months (unadjusted intention-to-treat population) or 28.6 months (centrally confirmed hormone receptor status) in the TAnDEM trial compared with 32.3 months in the EGF30008 trial. If it is assumed that LET and ANA are equally effective (as NICE guidance on early breast cancer suggests), then a similar median OS would be expected in the LET and ANA arms if the populations were sufficiently similar. Thus, it was felt that any comparisons made across trials would not be reliable and, hence, the AG focused on within-trial comparisons.

Assessment of cost-effectiveness

Cost-effectiveness review

The AG did not identify any relevant papers for inclusion in the cost-effectiveness review. A poster presented at the American Society of Clinical Oncology 2010 conference, comparing LAP + LET versus TRA + ANA based on an indirect comparisons analysis, was identified by Roche. Aside from the concerns with conducting indirect comparisons highlighted by the AG above, it is difficult to comment on the reliability of the cost-effectiveness results presented in this poster without access to more detailed information on costs.

Submitted economic evaluations by manufacturers

The two economic evaluations submitted by the manufacturers appear to meet the NICE reference case criteria. However, the AG is critical of the projective modelling approaches used by the manufacturers in this group of patients, which it believes can lead to substantial bias in OS estimates. In addition, the AG also identified several costing inaccuracies and inconsistencies in both of the economic evaluations submitted.

For the direct comparisons, GlaxoSmithKline demonstrated that LAP + LET is not cost-effective compared with LET and Roche demonstrated that TRA + ANA is not cost-effective compared with ANA.

Both of the manufacturers undertook indirect comparisons analyses in order to be able to compare LAP + LET versus TRA + ANA. For reasons outlined above, the AG believes that the indirect comparisons analyses conducted by the manufacturers are unreliable.

Roche makes the case for TRA + ANA to be considered as an end-of-life treatment for women with HR+/HER2+ mBC. The AG does not have sufficient information to verify whether or not all three NICE criteria for consideration of end-of-life treatments are met.

Assessment Group's cost-effectiveness results and sensitivity analysis

The AG reports the results of two separate de novo cost-effectiveness analyses using a common framework and common parameter values, but employing effectiveness data drawn only from a single RCT (either the EGF30008 or the TAnDEM trial). The AG model has employed outcome data derived from the relevant clinical trial in the form of Kaplan–Meier estimated survival

values augmented by projected survival estimates calibrated against the observed data. The AG used PFS and post-progression survival estimates directly as the basis for calculating expected OS in each group of the RCT.

As the AG is of the opinion that the evidence base is too unstable to allow meaningful comparison of LAP + LET versus TRA + ANA, the only questions that may be addressed legitimately are:

- Can LAP + LET be considered a cost-effective treatment compared with LET alone?
- Can TRA + ANA be considered a cost-effective treatment compared with ANA alone?

Base-case result: lapatinib in combination with letrozole versus letrozole alone

The AG concludes that in HR+/HER2+ women with mBC, LAP + LET compared with LET is not cost-effective. Using a time horizon of 20 years, the AG estimates an incremental cost-effectiveness ratio (ICER) that exceeds £225,000 per quality-adjusted life-year (QALY) gained for the comparison of LAP + LET versus LET; the incremental total costs and QALYs per patient treated are estimated as £26,150 and 0.116, respectively.

Base-case result: trastuzumab in combination with anastrozole versus anastrozole alone

The AG concludes that in HR+/HER2+ women with mBC, TRA + ANA compared with ANA is not cost-effective. Using a time horizon of 20 years, the AG estimates an ICER that exceeds £69,000 per QALY gained for the comparison of TRA + ANA versus ANA; the incremental total costs and QALYs per patient treated are estimated as £37,899 and 0.545, respectively.

Lapatinib in combination with aromatase inhibitor versus trastuzumab in combination with aromatase inhibitor

The AG emphasises, again, that the currently available clinical evidence base is too unstable to allow meaningful comparison of LAP + AI versus TRA + AI.

Sensitivity analyses undertaken by the Assessment Group

For the comparison of LAP + LET versus LET, the univariate sensitivity analysis shows that the ICER is most sensitive to the choice of health-state utility parameter values, the cost of LAP and is insensitive to most of the other variables. In all cases, the ICER remains > £148,000 per QALY gained. The probabilistic sensitivity analysis (PSA) shows that the probability of LAP + LET being cost-effective is 0.1% at a willingness-to-pay threshold of £50,000 per QALY gained; to achieve a 50% probability of LAP + LET being cost-effective, the willingness-to-pay threshold needs to increase to around £231,000 per QALY gained.

For the comparison of TRA + ANA versus ANA, the univariate sensitivity analysis shows that the ICER is most sensitive to the choice of health-state utility parameter values, the cost of TRA and discounting rates only. In all cases, the ICER exceeds £58,000 per QALY gained. The PSA shows that there is no measurable probability of TRA + ANA being cost-effective compared with ANA at a willingness-to-pay threshold of £40,000.

Discussion

Strengths and limitations of the analyses and uncertainties

Only three RCTs have been identified, which present head-to-head comparisons of the interventions of interest to this appraisal. It was not possible to compare the data across the trials

because of differences in the patient populations. However, each individual trial suggests a benefit in terms of PFS/TTP for LAP + LET, TRA + ANA and TRA + LET compared with LET, ANA and LET alone, respectively. Furthermore, the EGF30008 and the eLEcTRA trials suggest that LET alone is less effective in the HR+/HER2+ population than in the HR+/HER2- population.

From a health economics perspective, the AG agrees with both manufacturers that LAP + LET and TRA + ANA are not cost-effective compared with AIs alone for women with HR+/HER2+mBC. The ICERs estimated by the AG for LAP + LET versus LET and TRA + ANA versus ANA are higher than those estimated by the manufacturers. The AG did not address the cost-effectiveness of LAP + LET versus TRA + ANA as there were insufficient comparative clinical data available to allow estimation of meaningful ICERs.

Generalisability of the findings

None of the patients in the EGF30008 or the TAnDEM trial received prior treatment with TRA. This is not surprising as, at the time the trials were recruiting, the use of TRA for patients with early or advanced breast cancer was relatively rare. This contrasts greatly with what is increasingly happening in clinical practice today for a patient diagnosed with early HER2+ breast cancer, where TRA is the standard treatment of choice. Thus, in reality, typically only de novo patients with HR+/HER2+ mBC will be eligible for TRA + AI, as per the wording of the recently awarded European Medicines Agency licence. Patients who have been treated with TRA previously are eligible for treatment with LAP + AI; however, it is uncertain whether or not the clinical effectiveness of LAP + AI is the same for patients who are and who are not TRA naive.

Conclusions and research recommendations

Clinical effectiveness evidence demonstrates that LAP + LET, TRA + ANA or TRA + LET improves median PFS/TTP compared with AI monotherapy in patients with HR+/HER2+ mBC; LET also appears to be less effective in patients with HR+/HER2+ mBC than in those with HR+/HER2- mBC. To date, the trials do not show a statistically significant benefit in terms of OS for patients taking LAP + LET versus AI monotherapy or TRA + ANA versus AI monotherapy. However, the OS data in the HR+/HER2+ population of the EGF30008 trial had yet to reach maturity and no OS data were presented for eLEcTRA, presumably because this trial was halted prematurely. The results of the economic evaluations conducted by the manufacturers, and confirmed by the AG, demonstrate that LAP + LET is not cost-effective compared with AI monotherapy, nor is TRA + ANA cost-effective compared with AI monotherapy.

As a result of differences in the patient populations of the EGF30008 and the TAnDEM trials, the AG believes the indirect comparisons analyses conducted by the manufacturers are inappropriate and for the same reason chooses not to compare LAP + LET with TRA + ANA in an economic evaluation.

Given the uncertainties in the evidence base, the AG suggests that the following research priorities should be addressed (in order of priority).

1. Given that most patients who present for HR+/HER2+ mBC are now likely to have been previously treated with TRA for early breast cancer, further research may be required into treating mBC in the HR+/HER2+ population who are not TRA (or LAP) naive. It is noted by the AG that such a study (EGF114299) is planned by GlaxoSmithKline.
2. As trials are increasingly allowing patients to cross over following disease progression, attempts should be made to consider how to adjust for crossover at the trial design stage.

3. As the EGF30008 reports, there were large differences in PFS for HER2+ and HER2- patients receiving both LAP + LET and, in particular, LET. Further research may be warranted comparing the clinical effectiveness of AIs as monotherapy in patients with HER2+ and HER2- breast cancer.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1

Background

Description of health problem

Breast cancer is the uncontrolled, abnormal growth of malignant breast tissue affecting predominantly women. Though frequently referred to as a homogeneous disease, breast cancer has been recognised as a biologically heterogeneous disease¹ with several subgroups, including those with different stages and types of the disease. Metastatic breast cancer (mBC) is an advanced stage of the disease when the disease has spread beyond the original organ. Common sites of metastasis include bone, the liver, lung and brain.

Aetiology

After gender, the strongest risk factor for breast cancer is age. The incidence of breast cancer increases with age, doubling every 10 years until menopause, after which the rate of increase slows. Breast cancer is rare under the age of 20 years.

Genetic and hormonal risk factors have also been identified in the aetiology of breast cancer,^{2,3} and women with a family history of breast cancer have an increased risk of developing the disease.⁴ Mutations in some genes can increase the risk of developing breast cancer. Mutations of the breast cancer 1 (*BRAC1*) gene, which belongs to a class of genes known as tumour suppressor genes, account for 2% of breast cancers, where the risk is as high as 85% by the age of 35 years.⁵ Breast cancer 2 (*BRCA2*) mutations account for up to 1% of breast cancers, with a 60% chance of breast cancer. Other gene mutations contributing less frequently to familial breast cancer include mutations in tumour protein 53 (*p53*), MutS Homolog1 (*MSH1*), MutS Homolog2 (*MSH2*) and phosphatase tensin homologue (*PTEN*).

Higher concentrations of some endogenous hormones appear to increase breast cancer risk.⁶ Early age at menarche, late natural menopause, later age at first full-term pregnancy and never breastfeeding are all associated with an increased risk of breast cancer,⁶ whereas childbearing and higher numbers of full-term pregnancies increase protection.⁶ Use of exogenous hormones such as oral contraception, oestrogen replacement therapy and combined endocrine therapy increase the risk of breast cancer, as do other factors such as breast density (a risk factor independent of endogenous hormones), a body mass index of 25+ in post-menopausal women, moderate-to-heavy alcohol intake and a sedentary lifestyle.⁶

Pathology and prognosis

There are several prognostic factors that are taken into account by clinicians when deciding on treatment options and making a clinical prognosis.⁷ These include age, tumour size, histological type, nuclear grade, histological grade, number of metastatic axillary lymph nodes and clinical stage. Patients with stage IV disease are classified as having mBC according to the tumour/nodes/metastasis staging system developed and maintained by the American Joint Committee on Cancer⁸ and the Union for International Cancer Control.⁹

Hormone receptor status and human epidermal growth factor 2 (HER2) status are two other predictive factors that are taken into consideration in estimating the prognosis of patients with

breast cancer. As noted above, many breast cancer tumours are stimulated to grow and change by ERs and PgRs. Tumours that express either oestrogen receptor-positive (ER+) or progesterone receptor-positive (PgR+) are commonly referred to as being hormone receptor positive (HR+), and patients with HR+ breast cancer generally have an improved prognosis compared with those who are hormone receptor negative (HR-). Overviews of hormonal therapy, at least in the adjuvant therapy of early breast cancer,^{10,11} suggest that, where such evidence is sufficiently well defined, it is the ER rather than the PgR activity that is the most useful prognostic factor. More recently it has been discovered that over-expression of ErbB2 protein (also known as HER2), which is a member of the epidermal growth factor receptor family, and/or amplification of the *HER2* gene results in an abnormally high number of *HER2* genes per cancer cell, which results in cancer cells growing and dividing more quickly. Thus, human epidermal growth factor 2-positive (HER2+) breast cancer is considered to be an aggressive disease and there is growing evidence that the prognosis of HER2+ patients is generally poor, whether or not they are HR- or HR+. It should be emphasised that prior to this understanding of the role of HER2, trials did not routinely present data on this subgroup of patients.

Both HR+ tumours and HER2+ tumours are determined by immunohistochemistry (IHC).⁵ Fluorescence in situ hybridisation (FISH) can also be used to measure HER2 expression by measuring the number of gene copies present. An IHC score of ≥ 3 or a FISH amplification of > 2.1 confirms a HER2+ status. An IHC of > 2 is usually confirmed by FISH.⁵ Biological markers such as HER2 are also used as a predictor of prognosis and as a guide to therapy.

In England and Wales, 80%, 72% and 64% of people diagnosed with breast cancer live for at least 5 years, 10 years and 20 years after diagnosis, respectively.¹² Although therapeutic innovations have provided modest improvements in survival rates over the past two decades, mBC remains an incurable disease and the aim of treatment is to prolong survival and palliation.¹³ Following a diagnosis of mBC, the average length of survival has been reported to be 12 months for those receiving no treatment,¹⁴ compared with 18–24 months for those receiving chemotherapy, a figure reduced by up to 50% for patients who are HER2+.¹⁵

Epidemiology

Breast cancer is the most common cancer in the UK with 48,034 new cases diagnosed in 2008, 99% (47,693) being in women.¹⁶ Accounting for almost one-third (31%) of all new cases of cancer in women in the UK, the lifetime risk of breast cancer for a woman is one in nine.¹⁶

There is little regional variation in breast cancer rates in the UK,¹⁷ although there appears to be geographical variation within Europe. Breast cancer is one of the few cancers to show a clear trend of increasing rates from the most to least deprived groups,¹⁶ with rates in the most deprived groups around 20% lower than in the most affluent.¹⁶ The European age-standardised incidence rate (EASR) for women has increased by 5% from 114 per 100,000 in 1998 to 120 per 100,000 in 2007, with the number of cases rising from 40,377 to 45,695, an increase of 13%. The EASR has been projected to increase from 119 per 100,000 in 2000–4 to 124 per 100,000 in 2020–4, with the average number of new cases per year rising from 41,900 to 55,700 over the same time period. Analysis of breast cancer survival by level of deprivation has, however, consistently shown higher survival for more affluent women.¹⁸

UK data on breast cancer by stage of disease are not routinely collected and so neither the incidence nor the prevalence of mBC in the UK is known. However, assuming that 25% of all women diagnosed with breast cancer have mBC, of whom 6% are HR+/HER2+ [based on 2008 and 2009 data obtained from the Clatterbridge Centre for Oncology NHS Foundation Trust (Nicky Thorp, Clatterbridge Centre for Oncology NHS Foundation Trust, June 2010, personal communication)], approximately 700 patients each year may be diagnosed with HR+/HER2+

mBC in the UK. An independent estimate from 2008 data derived from the IMS Oncology Analyzer™ (IMS Health®, Plymouth Meeting, PA, USA) obtained by GlaxoSmithKline¹⁹ has estimated there may be around 450 new cases of HR+/HER2+ mBC each year in the UK, whereas Roche²⁰ has estimated the number to be nearer to 1000 based on data from Dybdal *et al.*²¹ and their own market research.

Impact of health problem

The impact of a diagnosis of mBC breast cancer on a patient is both physiological and psychological,²² affecting not only the patients but also their families and wider social network. Physical ill-health can stem from both the disease and disease treatment. The National Institute for Health and Clinical Excellence (NICE) Clinical Guideline No. 81 (CG81)²³ gives guidance for the management of complications such as lymphoedema, fatigue and metastases. Adequate rehabilitation is vital as women may be less productive after treatment for the disease.²⁴ The psychological impact on the patient can be debilitating, including depression and fear of loss of autonomy,²⁵ sexuality and body image.²⁶

Description of technologies under assessment

Lapatinib

Lapatinib (LAP) (Tyverb®/Tykerb®, GlaxoSmithKline) inhibits the tyrosine kinase components of the epidermal growth factor receptors (ErbB1 and ErbB2), implicated in the growth of various tumours.²⁷ LAP belongs to a group of medicines called protein kinase inhibitors that work by blocking enzymes known as protein kinases. Protein kinases can be found in some receptors on the surface of cancer cells including HER2. HER2, a receptor for epidermal growth factor, is involved in stimulating the cells to divide uncontrollably. By blocking these receptors, LAP helps to control cell division.

The most common side effects of LAP are loss of appetite, diarrhoea, nausea, vomiting, rash and fatigue. Monitoring of left ventricular function and for pulmonary toxicity should be carried out regularly. Monitoring of liver function should be performed before treatment and at monthly intervals.²⁸ The manufacturer has advised caution in the use of LAP in patients with moderate-to-severe hepatic impairment and severe renal impairment. Pregnancy should be avoided and breastfeeding discontinued during treatment with LAP.

Lapatinib is an orally active drug given once per day and is available as 250-mg tablets.

Currently, LAP is licensed in combination with capecitabine (Xeloda®, Roche) for patients with advanced or metastatic disease with progression following prior therapy, which must have included anthracyclines and taxanes and therapy with trastuzumab (TRA) (Herceptin®, Roche) in the metastatic setting.²⁹ It is not, however, recommended for first-line treatment by NICE.

In June 2010, the European Medicines Agency (EMA) granted conditional approval for the use of LAP in combination with an aromatase inhibitor (AI) for the first-line treatment of postmenopausal women with HR+/HER2+ mBC.^{30,31}

Trastuzumab

Trastuzumab is a recombinant humanised immunoglobulin G1 (IgG1) monoclonal antibody directed against HER2. It is administered by intravenous (i.v.) infusion, the regimen and dose is dependent on several clinical factors including the patient's weight, other medications and stage of disease. It is commonly administered every 3 weeks, with the infusion taking approximately 30–90 minutes each time.

The most common side effects of TRA are fatigue and diarrhoea. Recent clinical trial data suggest that patients require a left ventricular ejection fraction (LVEF) of > 55% for treatment with TRA and the summary of product characteristics for TRA states that cardiac monitoring is required every 12 weeks during treatment. However, the optimal frequency of cardiac monitoring in the clinical practice setting is not universally agreed.³²

Trastuzumab should be used with caution in patients with symptomatic heart failure, a history of hypertension, coronary artery disease and uncontrolled arrhythmias. Pregnancy should be avoided during treatment and breastfeeding should be avoided during treatment and for 6 months after.²⁸

Trastuzumab is currently licensed in the UK for the following indications:³³

1. the treatment of early breast cancer which over-expresses HER2
2. in combination with paclitaxel or docetaxel (Taxotere[®], Sanofi-Aventis), for mBC in patients with HER2+ tumours who have not received chemotherapy for mBC and in whom anthracycline treatment is inappropriate
3. in combination with an AI, for mBC in post-menopausal patients with HR+/HER2+ tumours not previously treated with TRA
4. as a monotherapy for mBC in patients with HER2+ tumours who have received at least two chemotherapy regimens including, where appropriate, an anthracycline and a taxane; women with ER+ breast cancer should also have received endocrine therapy.

The AG contacted the EMA for clarification about point 3 above, as the interpretation of this licence varied among NHS clinicians. In particular, it was not clear whether or not TRA was indicated for a woman who had been given TRA during the treatment of early breast cancer, who subsequently progressed to mBC. The EMA responded by stating that TRA was licensed for use in mBC in TRA-naïve patients. Of note, at the time the trials were recruiting, the use of TRA for patients with early or advanced breast cancer was relatively rare. In its submission, Roche also state that the majority (76%) of patients who present for mBC have not previously received TRA for adjuvant therapy based on its own market research,²⁰ although it is not clear over which time period this research was conducted.

Aromatase inhibitors

Aromatase inhibitors are not, per se, one of the technologies under assessment in this appraisal. However, they are being assessed in combination with LAP and TRA and are one of the comparators. NICE issued guidance regarding the use of AIs in 2006.³⁴ During this appraisal, the Appraisal Committee agreed that there is insufficient evidence to conclude that any one AI (used within the licensed indications) or treatment strategy is more clinically effective than another. As such, the AIs considered in this technology appraisal are assumed to be equally clinically effective. However, in practice only letrozole (LET) (Femara[®], Novartis) and anastrozole (ANA) (Arimidex[®], AstraZeneca) are commonly used as first-line treatments for women with mBC (and they may also be offered as a second-line treatment), with exemestane (EXE) (Aromasin[®], Pharmacia & Upjohn, Kalamazoo, MI, USA) being mostly used as a second-line treatment.

Aromatase inhibitors are a form of endocrine therapy and act predominantly by blocking the conversion of androgens to oestrogens in the peripheral tissues. As such, they are classified as antioestrogen therapies. AIs are classified into irreversible steroidal inhibitors (e.g. EXE) and non-steroidal inhibitors (e.g. ANA and LET), the latter inhibiting the enzyme by reversible competition.

Letrozole is indicated as adjuvant treatment of HR+ early breast cancer in post-menopausal women, advanced breast cancer in post-menopausal women (including those in whom other endocrine therapy has failed), early invasive breast cancer in post-menopausal women after standard adjuvant tamoxifen (TAM) therapy and pre-operative treatment in post-menopausal women with localised HR+ breast cancer to allow subsequent breast-conserving surgery.

Cautions and contraindication include the avoidance of use during pregnancy and breastfeeding. Avoidance has also been advised in severe hepatic impairment, whereas caution has been advised if creatinine clearance is < 10 ml/minute.

Anastrozole is indicated as adjuvant treatment of ER+ early invasive breast cancer in post-menopausal women, adjuvant treatment of ER+ early breast cancer in post-menopausal women following 2–3 years of TAM therapy and in advanced breast cancer in post-menopausal women which are ER+ or responsive to TAM.²⁸

Caution has been advised for the use of ANA in patients susceptible to osteoporosis; bone mineral density should be measured before treatment and at regular intervals during treatment. ANA is contraindicated in pre-menopausal women. Its use should also be avoided in patients with moderate-to-severe hepatic impairment and renal impairment where creatinine clearance is < 20 ml/minute. As with LET, it should also be avoided in pregnancy and breastfeeding.

Common side effects of ANA include hot flushes, vaginal dryness, vaginal bleeding, hair thinning, anorexia, nausea, vomiting, diarrhoea, headache, arthralgia, bone fractures and rash (including Stevens–Johnson syndrome).²⁸

Exemestane is indicated as adjuvant treatment of ER+ early breast cancer in post-menopausal women following 2–3 years of TAM therapy and in advanced breast cancer in post-menopausal women where endocrine therapy has failed.

As with other AIs, EXE is contraindicated in pre-menopausal women and should be avoided in pregnant and breastfeeding women. Caution in its use is advised in patients with renal and hepatic impairment. Common side effects include nausea, vomiting, abdominal pain, dyspepsia, constipation, anorexia, dizziness, fatigue, headache, depression, insomnia, hot flushes, sweating, alopecia and rash.

Current service provision

The aim of current treatments for mBC is to palliate symptoms, prolong survival and maintain a good quality of life (QoL) with minimal adverse events (AEs). Choice of treatment depends on previous therapy, hormone receptor status, HER2 status and the extent of the disease.

The National Institute for Health and Clinical Excellence²³ recommends that endocrine therapy (such as TAM or an AI) is offered as a first-line treatment to the majority of women with ER+ advanced breast cancer. However, providing patients understand and are prepared to accept the toxicity of chemotherapy, this is also recommended as first-line treatment when the ER+ mBC is life-threatening or requires early relief of symptoms because of significant visceral organ involvement.

For patients who are receiving treatment with TRA for advanced breast cancer, NICE recommends¹⁵ that treatment with TRA is discontinued at the time of disease progression outside

the central nervous system, but that TRA is continued if disease progression is within the central nervous system alone.

In practice, for patients with HR+/HER2+, TRA is commonly given in combination with chemotherapy (paclitaxel or docetaxel). However, variation in management of patients by age has also been reported.^{35,36} Variation in practice regarding continued use of TRA at the time of disease progression also exists,³⁷ partly because of uncertainty about mechanisms of resistance and whether or not this is partial or absolute.

As already noted, TRA, in combination with an AI, has been licensed for the treatment of post-menopausal patients with HR+/HER2+ mBC not previously treated with TRA.³³ Given the growing number of patients who are treated with TRA in the early breast cancer setting, this may result in a decreasing number of patients being eligible for treatment with either LAP or TRA in combination with an AI. According to the estimates from the manufacturers of these drugs, the number of patients eligible for LAP or TRA in combination with an AI is currently expected to be < 100 women each year.

Chapter 2

Definition of the decision problem

Decision problem

Interventions

The following two interventions are being considered:

- LAP + AI
- TRA + AI.

Population including subgroups

The population of interest is patients with mBC receiving first-line treatment who must:

- have HR+ tumours, and
- have tumours over-expressing the ErbB2 receptor, i.e. HER2+.

Relevant comparators

For LAP + AI, the relevant comparators are:

- AIs alone
- TRA + AI.

For TRA + AI, the relevant comparators are:

- AIs alone
- LAP + AI.

Outcomes

The NICE scope identified the following relevant outcomes:

- overall survival (OS)
- progression-free survival (PFS)
- time to progression (TTP)
- response rate, which (although not specified in the scope) may further be broken down to:
 - overall response rate (ORR)
 - complete response (CR)
 - partial response (PR)
- AEs
- clinical benefit rate (CBR)
- health-related QoL.

Key issues

It is important to note that the following criteria were to be fulfilled a priori.

- Only trials that measure clinical effectiveness in the population of interest were to be included in the systematic review, i.e. women must have mBC, have tumours that are HR+/HER2+ and have had no prior treatment for mBC.
 - Women were to be considered to have HR+ breast cancer if they had ER+ or PgR+ tumours.
- Where head-to-head comparisons do not exist, indirect comparisons were to be attempted.
- Cost-effectiveness of treatments was to be expressed in terms of incremental cost per quality-adjusted life-year (QALY) gained.
- The time horizon for estimating clinical effectiveness and cost-effectiveness was to be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.
- Costs were to be considered from an NHS and Personal Social Services (PSS) perspective.

Overall aims and objectives of assessment

The remit of this appraisal is to review the clinical effectiveness and cost-effectiveness evidence base for LAP in combination with an AI (LAP + AI) and TRA in combination with an AI (TRA + AI) within their licensed indications for the first-line treatment of patients who have HR+/HER2+ mBC.

Chapter 3

Assessment of clinical effectiveness

Methods for reviewing effectiveness

Evidence for the clinical effectiveness of LAP + AI and TRA + AI for the first-line treatment of patients with HR+/HER2+ mBC was assessed by conducting a systematic review of published research evidence. The review was undertaken following the general principles published by the Centre for Reviews and Dissemination's (CRD's) guidance for undertaking reviews in health care.³⁸

Identification of studies

Randomised controlled trials (RCTs) were identified by searching major electronic medical databases including MEDLINE, EMBASE and the Cochrane Library. The search strategy was broad and not limited to RCTs. Information on studies in progress, unpublished research or research reported in the grey literature were sought by searching a range of relevant databases including the National Research Register and Controlled Clinical Trials. In addition, bibliographies of previous reviews and retrieved articles were searched for further studies. The search strategy used for MEDLINE is presented in *Appendix 1*. The same search strategies were used to identify economic evaluations.

Further attempts to identify studies were made by contacting clinical experts and examining the reference lists of all retrieved articles. The manufacturers' submissions (MS) were assessed for unpublished data.

Inclusion and exclusion criteria

Two reviewers (NF/MM) independently screened all titles and abstracts. Full-paper manuscripts of any titles/abstracts that were considered relevant by either reviewer were obtained where possible. The relevance of each study was assessed (NF/MM) according to the criteria in *Table 1*. Studies that did not meet the criteria were excluded and their bibliographic details were listed alongside reasons for their exclusion. These are listed in *Appendix 2*. Any discrepancies were resolved by consensus.

Data abstraction strategy

Data were extracted by one reviewer (MM) using a standardised data extraction form in Microsoft WORD 2007 (Microsoft Corporation, Redmond, WA, USA) and checked independently by a second reviewer (NF). Disagreements were resolved by discussion.

Critical appraisal strategy

The quality of the individual clinical effectiveness studies was assessed according to criteria based on the CRD's guidance for undertaking reviews in health care.³⁸ The assessment of risk of bias was conducted independently by both reviewers (MM/NF). Disagreements were resolved through discussion.

TABLE 1 Inclusion criteria (clinical effectiveness) based on the decision problem

Study design	RCTs
Population(s)	Post-menopausal women with HR+/HER2+ mBC who have not previously received treatment for metastatic disease and for whom treatment with an AI is suitable. The following broad subgroups are considered if data permit: <ul style="list-style-type: none"> ■ patients based on disease characteristics such as tumour burden ■ number of metastatic sites ■ disease-free interval (length of time prior to onset of metastatic disease)
Intervention(s)	LAP in combination with an AI TRA in combination with an AI
Comparators	The two interventions will be compared with each other The interventions will also be compared with AIs
Outcomes	The outcome measures to be considered include: <ul style="list-style-type: none"> ■ OS ■ PFS ■ TTP ■ ORR ■ CBR ■ AEs ■ QoL

Methods of data synthesis

The results of the data extraction and quality assessment for each study are presented in structured tables and as a narrative summary. The possible effects of study quality on the effectiveness data and review findings are discussed.

It was intended by the Assessment Group (AG) that meta-analyses would be conducted in which direct evidence would be pooled using a standard meta-analysis³⁹ and, where a direct comparison between LAP + AI and TRA + AI was not possible, by indirect comparisons.⁴⁰ However, the AG considered it inappropriate to conduct either of these analyses, as discussed further in the next section.

Results

Quantity and quality of research available

Identification of studies

Once duplicates were removed, a total of 2069 references were identified (*Figure 1*); a scan of the titles and abstracts resulted in 11 potential records.^{41–51} Four of these citations^{48–51} reporting on two trials [the efficacy and safety of lapatinib combined with letrozole (EGF30008)⁴⁹ trial and the efficacy and safety of trastuzumab combined with anastrozole (TAnDEM)⁵⁰ trial] met the inclusion criteria and a further trial [efficacy and safety of letrozole combined with trastuzumab (eLEcTRA)⁵² trial], reported only as a conference abstract, was also suitable for inclusion following information passed on to the AG by Roche at the NICE consultation meeting in February 2010. Thus, three trials were included in the systematic review. Additional data on these trials were submitted to NICE from the manufacturer of LAP (GlaxoSmithKline¹⁹) and the manufacturer of TRA (Roche²⁰), including the relevant clinical study report (CSR) for the EGF30008⁴⁹ and the TAnDEM.⁵⁰ Of the seven excluded citations, three^{45–47} were excluded either because they did not examine LAP or TRA in combination with an AI or because it was a conference report in relation to the TAnDEM.⁵⁰ Four citations^{41–44} were excluded because they could not be obtained. Each was a Physician Data Query (identified through The Cochrane

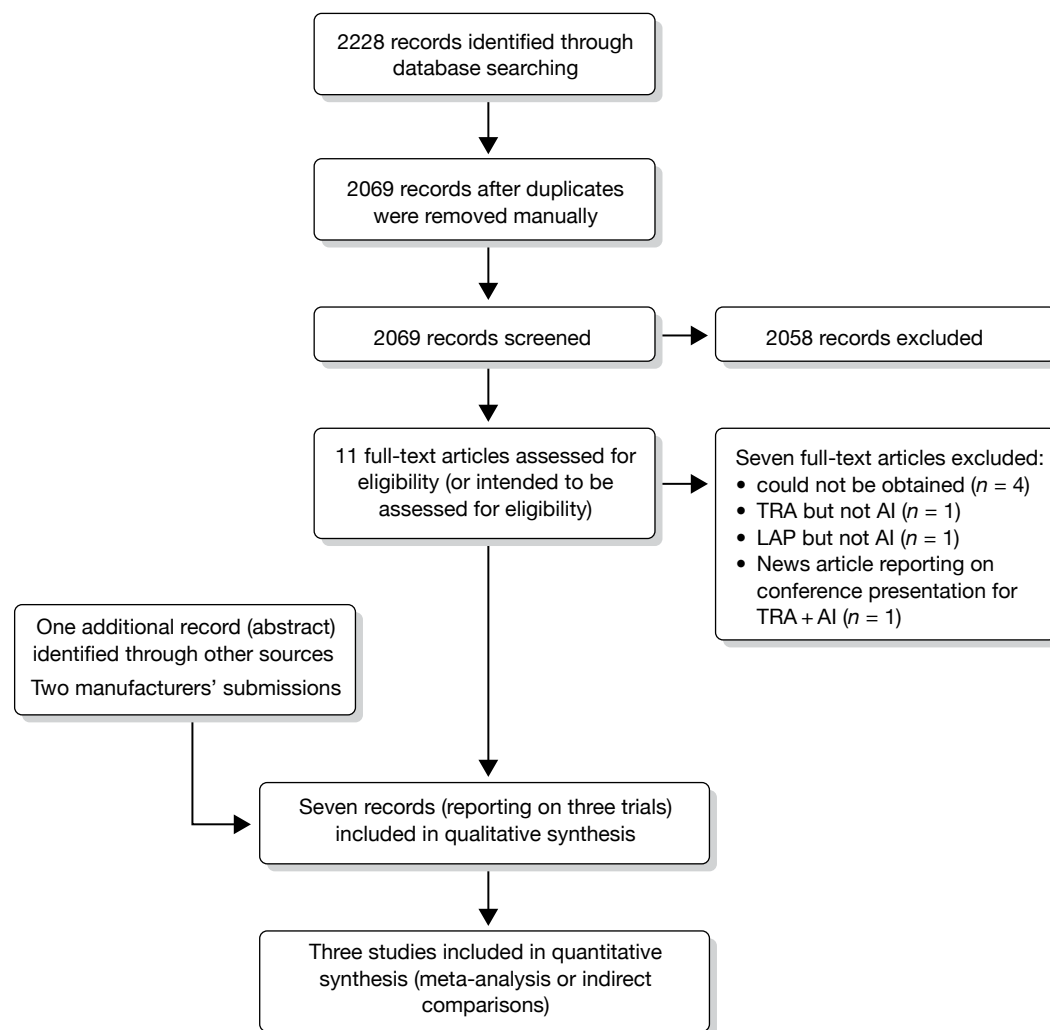


FIGURE 1 Identification of eligible studies.

Library) relating to the three included trials and indexed prior to the final study publication dates. In their submissions, both Roche and GlaxoSmithKline identified additional studies that they utilised as indirect evidence. The majority of these trials had also been identified by the AG's search, but as none were limited to the HR+/HER2+ mBC population (or at least did not include subgroup analysis on the HR+/HER2+ population), they did not meet the review inclusion criteria. Reasons outlining all of the excluded citations, including those identified and included by the manufacturers, are given in *Appendix 2*.

Included trials

Key characteristics of the included trials are summarised in *Table 2*.

All three trials (the EGF30008,⁴⁹ the TAnDEM⁵⁰ and the eLEcTRA⁵²) were multicentre and multinational trials (between 7 and 29 countries) enrolling post-menopausal patients receiving first-line treatment for mBC; all three trials included patients who had HR+/HER2+ mBC, although the EGF30008⁴⁹ and the eLEcTRA⁵² also included patients who were HR+/ human epidermal growth factor receptor 2 negative (HER2-). The trials were designed to evaluate the efficacy and safety of the addition of LAP + LET to LET (EGF30008⁴⁹), TRA + ANA to ANA (TAnDEM⁵⁰) and TRA + LET to LET (eLEcTRA⁵²). In all trials, treatment was administered at

TABLE 2 Included studies

Study and principal citation	Type of study and years of recruitment	Population	Interventions, dose and duration	Size of study	Notes
EGF30008 ⁴⁹	Double-blind multicentre trial conducted internationally: 212 sites in 29 countries, 2003–6	First-line post-menopausal HR+/HER2+ mBC	LAP + LET vs LET + placebo LAP = 1500 mg/day (oral) LET = 2.5 mg/day (oral) Placebo = pill (oral) Treatment was planned to continue until disease progression or study withdrawal	<i>n</i> = 219 ^a (LAP + LET = 111; LET = 108)	The trial was funded by GlaxoSmithKline and excluded patients with extensive symptomatic visceral disease, including hepatic involvement and pulmonary lymphangitic spread of tumour, or the disease was considered by the investigator to be rapidly progressing or life-threatening Second-line treatment was permitted following disease progression
TAnDEM ⁵⁰	Open-label multicentre trial conducted internationally: 77 sites in 22 countries (including eight sites in the UK), 2001–4	First-line post-menopausal HR+/HER2+ mBC	TRA + ANA vs ANA TRA = 4 mg/kg loading dose (i.v.) followed by 2 mg/kg/week (i.v.) or 8 mg/kg on day 1 followed by 6 mg/kg 3-weekly ANA = 1 mg/day (oral) Treatment was planned to continue until disease progression	<i>n</i> = 208 ^b (TRA + ANA = 103; ANA = 104)	The trial was funded and conducted by Roche and permitted patients in the ANA group to cross over to TRA + ANA following disease progression and patients in both groups were permitted chemotherapy following disease progression, i.e. patients were permitted second-line treatment A greater proportion of patients in the ANA group received second-line treatment
eLEcTRA ⁵²	Open-label multicentre trial conducted internationally: 32 sites in seven countries, 2003–7	First-line post-menopausal HR+/HER2+ mBC	TRA + LET vs LET TRA = 4 mg/kg loading dose (i.v.) followed by 2 mg/kg/week (i.v.) or 8 mg/kg on day 1 followed by 6 mg/kg 3-weekly LET = 2.5 mg/day (oral) Treatment was planned to continue until disease progression	<i>n</i> = 57 ^c (TRA + LET = 26; LET = 31 ^c)	The trial was funded by Novartis, with Roche described as a collaborator, and halted prematurely because of slow recruitment Patients were permitted to receive second-line TRA following disease progression A greater proportion of patients in the LET group received second-line treatment

a Also included another 1059 patients with HR+/HER2– mBC who received either LAP + LET or LET.

b One patient did not receive study drug.

c Also included another 35 patients with HR+/HER2– mBC who received LET.

licensed doses until disease progression, at which point patients received second-line therapy which included chemotherapy; for patients in the ANA group, TRA + ANA was also a second-line treatment option. Both chemotherapy and TRA were second-line treatment options in the EGF30008 trial.⁴⁹

Clinical end points, including OS, PFS and TTP, which are commonly used in trials of breast cancer, were utilised in at least one of the trials included in this appraisal. However, the only efficacy end points common to all three, and reported on by all three, were the secondary end points, CBR and ORR. All three trials also reported on AEs. The eLEcTRA⁵² trial intended to report on OS, but, to date, no findings for OS have been reported, possibly because this trial was halted prematurely because of slow recruitment. Only the EGF30008⁴⁹ trial reported on QoL.

As patients received second-line treatment once their disease had progressed, data on OS should be treated with caution as clearly this extra treatment could potentially impact on OS. Differences in second-line therapies received were clearly evident across the trials, with a greater proportion of patients receiving chemotherapy in the EGF30008⁴⁹ trial (Table 3).

Data on PFS, TTP, CBR and ORR in all trials should be treated with caution because of the way these end points were measured. This is discussed in more detail below.

Overall, the risk of bias assessment conducted by the AG (Table 4) found the EGF30008⁴⁹ to be of a good standard. Some small imbalances in baseline characteristics between the LAP + LET vs LET arms in the HR+/HER2+ population were noted (ECOG performance status ≥ 1 : 46% vs 53%; Diseases stage, lymph node: 51% vs 40%; Previous therapy, chemotherapy: 55% vs 40%, other: 10% vs 4%), which did not exist between groups in the population as a whole. The imbalances were not however deemed to be of clinical significance by the study authors or the AG. However, while the study was a double-blind study, because of the significantly increased incidences of diarrhoea and rash in the LAP + LET group (see below), the effectiveness of blinding may be questioned.

The TAnDEM⁵⁰ was similarly considered to be of good standard, the weakest aspect being the lack of blinding. As LAP is administered orally, the EGF30008⁴⁹ was able to blind treatment by also administering a placebo pill with LET. To have blinded treatment for TRA, however, a placebo i.v. therapy would have been required, which may arguably have been difficult to justify from an ethical perspective. Generally, baseline characteristics were well balanced across the

TABLE 3a Summary of second-line treatments received by patients in the HR+/HER2+ population in the EGF3008 trial

^a EGF30008 ⁴⁹	LAP + LET (n=103)	LET (n=98)
Any medication (%)	78	74
Chemotherapy (%)	57	60
Hormone therapy (%)	44	33
TRA (%)	17	28

TABLE 3b Summary of second-line treatments received by patients in the HR+/HER2+ population in the TANDEM trial

TAnDEM ⁵⁰	TRA + ANA	ANA
Any medication (%)	Not reported	Not reported
Chemotherapy (%)	8	32
TRA ^b (%)	1	70
Hormone therapy (%)	Not reported	Not reported

TABLE 3c Summary of second-line treatments received by patients in the HR+/HER2+ population in the eLEcTRA trial

eLEcTRA ⁵²	TRA + LET (n=26)	LET (n=31)
Any medication (%)	Not reported	Not reported
Chemotherapy (%)	Not reported	Not reported
TRA (%)	31	52
Hormone therapy (%)	Not reported	Not reported

a Data on second-line treatment were provided by the GlaxoSmithKline at the AG's request – the exact combinations of therapies are unknown.

b In 82% of instances, it is known that TRA was provided in combination with chemotherapy.

TABLE 4 Risk of bias table for included studies

Criteria	EGF30008 ⁴⁹	TAnDEM ⁵⁰	eLEcTRA ⁵²
Was the method used to assign participants to the treatment groups really random?	✓	✓	?
Was the allocation of treatment concealed?	✓	NA (open label)	NA (open label)
Was the number of participants who were randomised stated?	✓	✓	✓
Were details of baseline comparability presented in terms of prognostic factors?	✓	✓	✓
Was baseline comparability achieved in terms of prognostic factors?	✓	✓	×
Were the eligibility criteria for study entry specified?	✓	✓	✓
Were any co-interventions identified that may influence the outcomes for each group?	✓	✓	✓
Were the outcome assessors blinded to the treatment allocation?	✓/×	✓/×	×
Were the individuals who administered the intervention blinded to the treatment allocation?	✓/×	×	×
Were the participants who received the intervention blinded to the treatment allocation?	✓	×	×
Was the success of the blinding procedure assessed?	×	NA (open label)	NA (open label)
Were at least 80% of the participants originally included in the randomisation process followed up in the final analysis?	✓	✓	×
Were the reasons for withdrawals stated?	✓	✓	Trial was stopped prematurely
Is there any evidence to suggest that the authors measured more outcomes than they reported?	✓/× ^a	✓	✓
Was an ITT analysis included?	✓	✓	×

✓, yes (item properly addressed); ×, no (item not properly addressed); ✓/×, partially (item partially addressed); ?, unclear or not enough information; ITT, intention to treat; NA, not applicable.

a Data on TTP were only included in the MS from GlaxoSmithKline,¹⁹ which also included data on QoL outcomes that were previously reported separately in conference abstracts.

TRA + ANA and ANA arms although there were a small number of imbalances (Site of therapy, lung: 41.7% vs 46.2%, bone: 62.1% vs 51.0%, other: 69.9% vs 62.5%; Previous therapy, hormonal: 60.2% vs 66.3%, chemotherapy: 53.4% vs 59.6%, anthracycline: 44.7% vs 51.0%). Clinical advice received by the AG was that these were not a cause for concern in terms of biasing any results.

The eLEcTRA⁵² trial was deemed to be of poorer quality compared with the EGF30008⁴⁸ and the TAnDEM trials.⁵⁰ This may be a reflection of poor-quality reporting rather than trial design, as this trial was only published as an abstract, with limited additional data subsequently available from Roche.²⁰ However, the fact that the trial ended prematurely because of slow recruitment did affect quality. Firstly, slow recruitment is attributed in the Roche submission²⁰ to the fact that investigators believed TRA + LET was superior to LET (although no evidence is presented to support this claim) and investigators were reluctant to continue randomising patients into the LET group. This could have introduced selection bias. Secondly, because <25% of the intended patients were recruited, the trial lacked statistical power and finally, there were large differences in baseline comparability between the TRA + LET and LET groups in the HER2+ population [ECOG performance status ≥ 1: 69% vs 45%; median (range) time from primary diagnosis to randomisation, months: 3 (0–486) vs 30 (0–75); Site of metastases, locoregional: 46% vs 29%, liver: 19% vs 39%, soft tissue: 31% vs 36%; Previous therapy, any adjuvant: 42% vs 71%, adjuvant endocrine therapy: 31% vs 65%].

Comparing baseline characteristics across the three trials was problematic because of differences in how measures were defined and/or reported and so the characteristics have not been presented in this report. However, it was noticeable that the median age of patients in the TAnDEM⁵⁰ differs to that of the other two trials, the median age being around 55 years compared with around 60 years in the other two trials. There also appears to be more patients with soft tissue metastases in the TAnDEM⁵⁰ than the EGF30008.⁴⁹

Arguably, of greater significance were the aforementioned differences in second-line treatment and the choice of exclusion criteria in the EGF30008⁴⁸ trial. According to the MS,¹⁹ the EGF30008⁴⁹ excluded patients with symptomatic visceral disease and patients in whom the disease was considered by the investigator to be rapidly progressing or life-threatening.¹⁹ The potential importance of second-line treatment and/or this criterion became apparent when analysing median OS, which was reported to be ≤ 23.9 months [unadjusted intention-to-treat (ITT) population] or 28.6 months (centrally confirmed hormone receptor status) in the TAnDEM⁵⁰ trial compared with 32.3 months in the EGF30008⁴⁹ trial. If it is assumed that there is a 'class effect' (and certainly for early breast cancer where NICE guidance³⁴ exists on the use of AIs, it is indeed assumed that LET and ANA are equally effective), then if the populations were truly similar, a similar median OS would be expected for patients in the LET and ANA arms of the different trials.

The generalisability of the trials to the UK population may also be questioned as it is unclear whether or not patients at imminent risk of death, as some patients may have been in the TAnDEM trial,⁵⁰ would be eligible for treatment with LAP + AI or TRA + AI. However, clinical advice received by the AG was that some clinicians would offer TRA or LAP with an AI if patients were deemed to be too unfit for chemotherapy, even if they were at risk of imminent death. Equally, those who were not at risk of imminent death, as in the EGF30008 trial,⁴⁹ may also be offered TRA or LAP with an AI. Hence, both study populations appear generalisable to the UK.

In summary, although study designs appear appropriate for the comparison of LAP + AI versus AI or TRA + AI versus AI, key differences in the trials led the AG to the conclusion that it would not be appropriate to pool data or make meaningful comparisons, directly or indirectly, across the two completed trials. This decision was primarily based on apparent differences in patient populations – the key factors being the differences in second-line treatment received and the explicit exclusion of patients with symptomatic visceral disease and/or in whom the disease was considered by the investigator to be rapidly progressing or life-threatening from the EGF30008⁴⁸ trial (but not the other trials). As the eLEcTRA⁵² trial was halted prematurely some data were not available/reported and data which were reported should be treated with extreme caution. For these reasons, the AG decided to focus on discussing the trials individually.

Assessment of effectiveness

EGF30008: lapatinib in combination with letrozole versus letrozole alone

Patients were recruited into the EGF30008⁴⁹ trial between December 2003 and December 2006, during which time there were amendments to the original protocol. One amendment led to increased target enrolment, from 760 to 1280 subjects, in order to ensure adequate statistical power in the HR+/HER2+ subgroup (October 2005). The decision to focus on the HR+/HER2+ subgroup was made as a result of pre-clinical studies and clinical studies suggesting that LAP modulates its effect in breast cancer primarily via ErbB2.^{53,54} Another significant amendment was the definition of the HR+/HER2+ population as the primary population of interest, at which time the primary end point was changed from TTP to PFS (October 2007); PFS was defined as the

time from randomisation until the earliest date of disease progression or death from any cause, if sooner. The decision to change the primary end point was made because, unlike TTP, PFS includes death (and is thus a better correlate with OS) and is, therefore, preferred by the US Food and Drug Administration (FDA)⁵⁵ and the Committee for Medicinal Products for Human Use.⁵⁶ All of the EGF30008⁴⁹ trial amendments were carried out prior to un-blinding and are less likely to increase risk of bias than if amendments had occurred after blinding.

The findings from the EGF30008⁴⁹ trial are summarised in *Table 5*, where it can be seen that data were available for the HR+/HER2+ population as well as the wider population of patients recruited, which included patients who were HR+/HER2-. The wider population in the study was referred to as the ITT population.

No significant differences were reported in terms of OS between the groups, although there was a possible trend in favour of LAP + LET compared with LET.¹⁹ A pre-planned analysis within known prognostic factor subpopulations reported consistently improved OS with LAP + LET compared with LET in the following groups: the European Cooperative Oncology Group (ECOG) performance status score < 1 and patients with fewer than three metastatic sites; site of disease (non-visceral/visceral) did not significantly affect OS.¹⁹ It should be noted that OS data were not mature at the time of data cut-off, as only 104 subjects (47%) had died and 41% were still being followed for survival. It should also be reiterated that once study medication had been discontinued, 153 patients (76%) in the HR+/HER2+ population received second-line treatment, mostly chemotherapy (around 60% of all patients), which may have affected OS.

TABLE 5 Summary of efficacy results from the EGF30008⁴⁹ trial

Outcome	HR+/HER2+ population ^a			All patients (i.e. including those who are HR+/HER2- ^b)		
	LAP + LET (n=111)	LET (n=108)	HR/OR (95% CI); p-value	LAP + LET (n=644)	LET (n=642)	HR/OR (95% CI); p-value
OS (months) ^c	33.3	32.3	HR = 0.74 (0.5 to 1.1); p = 0.113	Not reported	Not reported	Not reported
PFS (months) ^c	8.2	3.0	HR = 0.71 (0.53 to 0.96); p = 0.019 Cox regression analysis (adjusting for known baseline prognostic factors) HR = 0.65 (0.47 to 0.89); p = 0.008	11.9	10.8	HR = 0.86 (0.76 to 0.98); p = 0.026
TTP (months) ^c	8.2 ^d	3.0 ^d	HR = 0.71 (0.53 to 0.96); p = 0.019	Not reported	Not reported	Not reported
ORR (%) ^e	28	15	OR = 0.4 (0.2 to 0.9); p = 0.021	33	32	OR not reported; p = 0.726
CR (%)	5	4		5	4	
PR (%)	23	11		28	27	
SD ≥ 6 months (%) ^e	20	14	Not reported	26	25	Not reported
CBR (%) ^f	48	29	OR = 0.4 (0.2 to 0.8); p = 0.003	58	56	OR not reported; p = 0.761

CI, confidence interval; OR, odds ratio; SD, stable disease.

a Median follow-up of 1.8 years.

b Median follow-up of 2 years.

c Median (95% CIs were not presented).

d TTP data only presented in the GlaxoSmithKline submission.

e Data presented only as percentages.

f CBR = CR, PR or SD ≥ 6 months.

For the HR+/HER2+ population, the EGF30008⁴⁹ trial reported significant improvements in PFS in the LAP + LET group when compared with the LET group.⁴⁹ When adjusted for baseline prognostic factors, the stepwise Cox regression analysis for PFS confirmed the benefit of LAP + LET compared with LET.⁵¹ A pre-planned analysis within known prognostic factor subpopulations reported consistently improved PFS with LAP + LET compared with LET in the following groups: patients with an ECOG performance status score >0, patients without bone as the only site of metastasis, patients with and without liver metastases, patients with fewer than three metastatic sites and patients having received prior endocrine therapy for < 6 months.⁵¹ Significant differences were also reported for differences in PFS in the ITT population,⁴⁹ but here the differences between the groups were less pronounced. In particular, it was noticeable that the PFS was greater in the ITT population than in the HR+/HER2+ population, particularly for patients receiving LET (the difference in PFS between the ITT and HR+/HER2+ populations here was 7.8 months compared with 3.7 months between the same two populations among patients receiving LAP + LET).

Because only one subject of the HR+/HER2+ population died from a cause other than breast cancer in this study, the TTP findings were almost identical to those reported for PFS.¹⁹ In the same population, ORR was significantly improved for patients treated with LAP + LET compared with LET, as was CBR. However, the differences in ORR and CBR between treatment groups were not significant in the ITT population.

Because assessment of disease progression is liable to subjectivity, introducing an observation bias, which needs to be considered when interpreting PFS, TPP, ORR and CBR, blinded independent review has been recommended in order to circumvent such problems.^{57,58} In the EGF30008 trial,⁴⁹ investigator assessment and a blinded Independent Radiological Review Committee (IRC) were employed. The main reasons for differences in PFS assessments between the investigators and IRC, as noted in the CSR, were primarily because of differences in the censoring methods used. The differences were, however, constant across both treatment arms, which reduces the risk of bias.

Patients who received LAP + LET were more likely to experience AEs, with nearly all patients in the HR+/HER2+ population experiencing an AE compared with around three-quarters of patients who received LET (*Table 6*). Serious adverse events (SAEs), however, were relatively rare in both groups. Only three patient deaths were attributed to treatment, one of these taking LAP + LET in the HR+/HER2+ population.

TABLE 6 Summary of AEs from the EGF30008⁴⁹ trial

Adverse events	HR+/HER2+ population		All patients (i.e. including those who are HR+/HER2-)	
	LAP + LET (n=111)	LET (n=108)	LAP + LET (n=644)	LET (n=642)
Any AE (%)	96 ^{a,b}	77 ^{a,b}	Not reported	Not reported
SAEs (%)	Not reported	Not reported	8 ^{b,c}	4 ^{b,c}
Discontinued treatment because of AE (%)	Not reported	Not reported	2 ^{b,c,d}	1 ^{b,c,d}
Treatment-related deaths, n	1 (<1%)	0	1 (<1%)	2 (<1%)

a Data taken from Schwarzberg *et al.*⁵¹ and so only available for HR+/HER2+.

b Data presented only as percentages.

c Data available only for all patients, i.e. including those with HR+/HER2-.

d Data for those discontinuing treatment due to an AE is only presented for those with diarrhoea, it is not known if other AEs resulted in discontinuation of treatment.

In patients with HR+/HER2+ mBC, and in all patients as a whole (i.e. including HR+/HER2–mBC), the most common AEs were diarrhoea, rash, nausea, arthralgia and fatigue, of which the majority were grade 1 or 2 (Tables 7 and 8). In particular, incidences of diarrhoea, rash and nausea were significantly higher in patients receiving LAP + LET. It was reported by Johnston *et al.*⁴⁹ that 15% of all 60 patients with grades 3 or 4 diarrhoea discontinued LAP + LET as a result, i.e. around 1% of all patients. For the remainder of patients, diarrhoea was managed by dose reduction (19%), dose interruption (36%) or supportive intervention without treatment dose adjustments (31%).

An additional 8 months of data beyond trial reporting had been collected (through to 3 February 2009) and presented in the GlaxoSmithKline submission.¹⁹ These data remain consistent with the initial study results, although more patients in the LET group reported AEs than before [629 (96%) patients reported an AE in the LAP + LET group compared with 537 (86%) in the LET group].

Overall, therefore, no new safety issues were identified, the safety profile of LAP + LET being consistent with the safety profiles of both drugs when given as single agents and with safety data from previously reported LAP studies.

Finally, QoL was also assessed in the EGF30008 trial,⁴⁹ utilising the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire.¹⁹ Within the HR+/HER2+ population, QoL scores and changes from baseline were reported to be generally stable over time for subjects who stayed in the study in both the LAP + LET and LET groups, suggesting maintenance of QoL. The Quality-Adjusted Time Without Symptoms of Disease or Toxicity of Treatment (Q-TWIST) difference between treatment groups for the HR+/HER2+ population ranged from 8 weeks to

TABLE 7 Most common AEs recorded in the HR+/HER2+ population in the EGF30008^{49,a} trial

AEs	LAP+LET (n=111)		LET (n=108)	
	Total (any grade) (%)	Grade 3 or higher (%)	Total (any grade) (%)	Grade 3 or higher (%)
Diarrhoea	68	7	8	0
Rash	46	0	8	0
Nausea	27	0	18	<1
Fatigue	22	4	14	0
Arthralgia	18	4	20	<1
Back pain	17	2	9	<1
Vomiting	17	<1	7	0
Headache	14	0	11	<1
Asthenia	14	2	9	0
Pruritus	13	0	5	<1
Dizziness	12	0	8	0
Cough	11	0	9	0
Alopecia	11	0	4	0
Musculoskeletal pain	10	<1	5	0
Epistaxis	10	<1	2	0
Dyspnoea	9	<1	10	4
Hot flush	6	0	12	0
Alanine aminotransferase increase	11	<1	6	<1
Aspartate aminotransferase increase	10	<1	5	2

a Events reported in $\geq 10\%$ of patients in any group taken from Schwarzbeg *et al.* 2010.⁵¹

9.5 weeks, favouring LAP + LET over LET for all hypothetical utility levels, although none of the findings were reported to be statistically significant.⁵⁹

TAnDEM: trastuzumab in combination with anastrozole versus anastrozole alone

Between March 2001 and May 2006, the TAnDEM⁵⁰ trial enrolled 207 HR+/HER2+ patients, of whom 103 were randomly assigned to TRA + ANA and 104 to ANA. According to the CSR, prior to any patient being recruited into the trial, there had already been amendments to the protocol, including a request at the behest of the FDA that the primary end point was changed from TTP to PFS. PFS was defined as the time between random assignment and the date of progressive disease (PD), clinical or radiographic, or death. There were also amendments following recruitment of the first patient. The most significant was perhaps the amendment that allowed for the crossover of patients from ANA to TRA + ANA following disease progression, thus, impacting on the size of the OS results. No statistical methods were described to address this issue of crossover a priori, the trial simply being separated into two treatment phases: main and extension. The main phase was defined as the first 24 months of treatment or until disease progression, and the extension phase was defined as the treatment period after 24 months or the treatment period after disease progression, whichever came earliest. Patients had a safety follow-up assessment 28 days after their last dose of treatment. Subsequently, post-hoc analyses were performed by Roche which attempted to take into account the effects of crossover, as described further below.

TABLE 8 Most common AEs recorded in all patients in the EGF30008⁴⁹ trial

AEs	LAP+LET (n=111)		LET (n=108)	
	Total (any grade) (%)	Grade 3 or higher (%)	Total (any grade) (%)	Grade 3 or higher (%)
Diarrhoea ^a	64	9	20	1
Rash ^a	45	1	13	0
Nausea ^a	31	1	21	1
Arthralgia	19	1	23	1
Fatigue	20	2	17	0
Back pain	16	2	16	<1
Vomiting ^a	17	1	11	<1
Headache	14	<1	13	0
Cough	12	<1	14	0
Hot flush ^a	11	0	15	0
Asthenia	12	1	11	1
Pain in extremity	10	<1	11	1
Dyspnoea	10	1	12	<1
Pruritus ^a	12	<1	9	0
Alopecia ^a	13	<1	7	0
Constipation	9	0	11	<1
Anorexia	11	1	9	<1
Dry skin	13	<1	4	0
Epistaxis	11	<1	2	0
Nail disorder	11	<1	1	0

a A statistically significant ($p < 0.05$) effect was reported between treatment groups for the total incidence of these AEs in Johnston *et al.* 2009.⁴⁹

The findings from the TAnDEM⁵⁰ trial are summarised in *Table 9*. No significant differences in terms of OS were found between the groups. However, it should be noted that 70% of the patients randomised to ANA subsequently received TRA + ANA in the extension phase of the trial and this may have impacted on the findings. In addition, around one-third (32%) of ANA patients went on to receive chemotherapy compared with a minority of patients who had been randomised to TRA + ANA (8%). With some legitimacy, the manufacturer of TRA argued that this could impact on the size of the OS estimates because, in this situation, the ITT results will be significantly compromised and will either underestimate or overestimate the treatment effect between groups. Roche contended that this would underestimate the treatment effect and show a reduced incremental gain from TRA + ANA over ANA. Thus, unplanned exploratory post-hoc analyses were performed by Roche to investigate the impact of this crossover from the control group of the trial on OS.

Currently there is no uniform agreement about which is the best method(s) to use for adjusting for crossover. In a study by Kaufman *et al.*,⁵⁰ an attempt to highlight the impact of crossover

TABLE 9 Summary of efficacy results from the TAnDEM^{50,a} trial

Outcome	TRA + ANA (n=103)	ANA (n=104)	HR (95% CI); p-value
OS (range) months, ^a unadjusted ITT population ^b	28.5 (22.8–42.4)	23.9 (18.2–37.4)	HR = 0.84 (0.59 to 1.20); p = 0.325
OS (range) months, ^a centrally confirmed hormone receptor status ^b	34.1 (23.9–52.0)	28.6 (17.4–40.0)	HR = 0.85 (no CIs); p = 0.451
OS (range) months, ^a adjusted for crossover by RPSFT	28.52 ^c	21.98 ^c	HR = 0.73 (0.51 to 1.04); p = not reported
OS (range) months, ^d PP analysis (patients who did not cross over)	28.5 (22.8–42.4)	17.2 ^e	p = 0.218; ^f p = 0.048 ^g
PFS (range) months, ^a ITT population ^b	4.8 (3.7–7.0)	2.4 (2.0–4.6)	HR = 0.63 (0.47 to 0.84); p = 0.0016
PFS (range) months, ^a centrally confirmed hormone receptor status ^b	5.6 (3.8–8.3)	3.8 (2.0–6.3)	HR = 0.62 (no CIs); p = 0.006
PFS (range) months, ^a updated ^d	5.8 (4.6–8.3)	2.9 (2.1–4.5)	HR = 0.55 (0.41 to 0.74); p < 0.0001
TTP (range) months, ^a ITT population ^b	4.8 (3.7–7.7)	2.4 (2.0–4.6)	HR not reported; p = 0.0007
TTP (range) months, ^a centrally confirmed hormone receptor status ^b	5.6 (3.8–8.3)	3.9 (2.1–6.3)	HR = 0.62 (no CIs); p = 0.0007
	TRA + ANA (n=74)	ANA (n=73)	OR (95% CI); p-value
ORR centrally confirmed hormone receptor status (%) ^b	20	5	OR not reported; p = 0.018
CR (%)	0	0	
PR (%)	20	5	
SD ≥ 6 months (%)	38	38	Not reported
CBR (range) %, ^h ITT population ^b	43 (33–53)	28 (20–38)	OR not reported; p = 0.026

CI, confidence interval; OR, odds ratio; RPSFT, rank preserving structural failure time; SD, stable disease.

a Median (95% CI).

b For both the unadjusted ITT population and centrally confirmed hormone receptor status, PFS is derived from data in which the tumour response/date of progression was determined locally by the investigator and confirmed by the blinded Response Evaluation Committee.

c The RPSFT adjustment was made only in the submission by Roche.²⁰ No CIs were presented for median OS.

d The end of study update was performed after the main phase of the study; therefore, the tumour response was solely based on local investigator assessment.

e n = 31; no CIs presented for OS.

f Log-rank test.

g Wilcoxon test.

h CBR = CR, PR or SD ≥ 6 months.

on OS was explored using a per protocol (PP) analysis approach, in which the median OS for patients receiving TRA + ANA (28.5 months, $n = 103$) from randomisation was compared with the subgroup of patients who initially received ANA and did not cross over to receive TRA (17.2 months, $n = 31$). By log-rank testing, there was no significant difference in the OS analysis ($p = 0.218$). However, because of the small number of patients with long survival times available for analysis, the Wilcoxon test was also used as this gives more weight to early time points than the log-rank test. The analysis using the Wilcoxon test resulted in a modestly statistically significant difference ($p = 0.048$). Similarly, comparing patients in the ANA group who crossed over to receive TRA + ANA ($n = 73$) with those who did not ($n = 31$) resulted in an OS estimate of 25.1 months and 17.2 months, respectively. These differences were reported to be not statistically significant using the log rank test ($p = 0.358$), but were statistically significant using the Wilcoxon test ($p = 0.040$). The AG notes that where there is a relatively large proportion of patients who cross over, these PP approaches are prone to selection bias.

In their submission, the crossover adjustment employed by Roche²⁰ was based on a rank-preserving structural failure time (RPSFT) approach initially proposed by Robins and Tsiatis⁶⁰ and later modified by Mark and Robins.⁶¹ Using the RPSFT approach (ITT population), median OS in the TRA + ANA group becomes 28.52 months and the median OS in the ANA group becomes 21.98 months. The RPSFT method is an accelerated failure time model, a form of randomisation-based analysis that more effectively preserves the integrity of randomisation than do PP analyses. However, its validity has been questioned when imbalances occur post randomisation, e.g. when there is an unequal distribution of patients receiving second-line treatment across the arms.⁶²

The use of the RPSFT approach in the current appraisal was justified by the manufacturer as it has also been used for two other NICE appraisals: sunitinib for the treatment of gastrointestinal stromal tumours⁶³ and everolimus for the second-line treatment of advanced renal cell carcinoma.⁶⁴ However, in the former appraisal, only 7% of patients crossed over to receive sunitinib whereas, in the latter, 81% of patients crossed over to receive everolimus. In the sunitinib appraisal,⁶³ because so few patients crossed over from the control arm to sunitinib, the Appraisal Committee had confidence in the results from the RPSFT as well as the PP analysis, which was also performed. For everolimus,⁶⁴ two different methods were employed to adjust for crossover by the manufacturer, the inverse probability censoring weight (IPCW) approach⁶⁵ and the RPSFT approach. Because 81% of people had crossed over to receive everolimus, the Appraisal Committee agreed that it was appropriate to adjust the results utilising statistical methods such as these to control for crossover. However, as both methods gave different OS estimates,⁶⁴ it was unclear which method, if either, was most suitable.

A recent paper by Morden *et al.*⁶² explored various approaches to adjusting for crossover using a simulation exercise. Methods tested included PP approaches and accelerated failure time model methods. The authors found that that when there is crossover from the control group, commonly adopted approaches such as censoring at the time of crossover, or considering treatment as a time-dependent covariate, may be associated with biased estimates of the true treatment effect, where the reasons for the crossover are strongly related to their underlying prognosis. Where patients who cross over are excluded from the analysis altogether (i.e. a PP analysis), biases were reported to be small in situations with a low proportion of switchers (as was the case, for example, with sunitinib). However, as the number of patients who switch increases, the risk of bias was also reported to increase.

Specifically, with regard to accelerated failure time model methods, three methods were considered by Morden *et al.*:⁶² the RPSFT developed by Robins and Tsiatis,⁶⁰ the iterative parameter estimation algorithm approach⁶⁶ (which is a modification of the RPSFT method in

which the test-based estimation is replaced with a likelihood-based analysis) and a parametric randomisation-based method (which as an extension to the previous two methods).⁶⁷ The findings from their simulation exercise suggested that the RPSFT⁶⁰ and the iterative parameter estimation algorithm⁶⁶ gave estimates close to the true treatment effect, whereas the parametric randomisation-based method⁶⁷ overestimated the true treatment effect. The iterative parameter estimation algorithm⁶⁶ appeared to be the most accurate method when the proportion of patients who crossed over was relatively high.

In the TAnDEM trial,⁵⁰ the AG notes that some imbalances appear to have occurred post-randomisation, e.g. four times as many patients in the ANA arm received chemotherapy as a second-line treatment compared with TRA + ANA (32% compared with 8%). The AG also notes that the proportion of patients who crossed over was relatively high, being 70%, which, as Morden *et al.*⁶² report, increases the likelihood of bias. However, the AG does agree that attempts to adjust for crossover are worthwhile – ideally different randomisation-based methods should be used to compute and compare a range of OS estimates to assess sensitivity of treatment effects, the applicability of each individual method employed depending on the trial circumstances and characteristics – in the MS such sensitivity is not investigated. It should be noted that in order to undertake such analyses, individual patient data are required. Such data were not available to the AG and thus the AG was unable to employ any of the aforementioned approaches. Thus, the AG has utilised its own method for adjusting for crossover for the purposes of conducting its economic analysis. This is described further in *Chapter 4, Specific model features and parameters: trastuzumab in combination with anastrozole versus anastrozole alone*.

As the assessment of disease progression (and therefore PFS, TTP, ORR and CBR) may be prone to subjectivity, and thus to observation bias, three universally accepted methods^{57,58} and procedures for assessing disease progression were employed in the TAnDEM⁵⁰ trial to minimise the risk: an investigator assessment (ITT), a centrally confirmed assessment by a Response Evaluation Committee (REC) and, in situations in which the investigator assessment was different from the REC assessment, an independent oncologist was appointed to make a reconciliation assessment. Patients in the TRA + ANA group experienced significant improvement in PFS and TTP. Significant differences were also reported in terms of ORR and CBR in the ITT population, although, interestingly, no CR was recorded for any patient, the difference occurring as a result of improvements in PR in the TRA + ANA group.

Patients who received TRA + ANA were more likely to experience AEs, with nearly 90% experiencing an AE compared with 65% of patients who received ANA (*Table 10*). SAEs were also more common in the TRA + ANA group, nearly 25% experiencing an SAE compared with < 10% of patients receiving ANA. There were no treatment-related deaths in either group.

The most frequently reported AEs in both groups were fatigue, diarrhoea, vomiting and arthralgia, of which the majority were grades 1 or 2 (*Table 11*). AEs were more common in the TRA + ANA group than in the ANA group, although it should also be noted that duration of

TABLE 10 Summary of AEs from the TAnDEM⁵⁰ trial

Adverse events	TRA + ANA (n=103)	ANA (n=104)
Any AE (%)	87	65
SAEs (%)	23	6
Discontinued treatment because of AEs (%)	9	1
Treatment-related deaths (%)	0	0

TABLE 11 Most common AEs recorded in patients in the TAnDEM^{50,a} trial

AEs	TRA+ANA (n=103)		ANA (n=104)	
	Total (any grade) (%)	Grade 3 or higher (%)	Total (any grade) (%)	Grade 3 or higher (%)
Fatigue	21	1	10	0
Diarrhea	20	1	8	0
Vomiting	21	3	5	1
Arthralgia	15	0	10	1
Pyrexia	18	0	7	0
Back pain	15	2	7	2
Dyspnoea	13	2	9	0
Nausea	17	1	5	0
Cough	14	0	6	0
Headache	14	0	6	0
Nasopharyngitis	17	0	2	0
Bone pain	11	2	6	0
Constipation	12	0	5	0
Chills	15	1	0	0
Hypertension	7	2	4	4

a Most common AEs are those of any grade occurring at an incidence rate of > 10% in either treatment group and/or those of grade 3 or 4 occurring at a frequency of > 2% in either treatment group.

Note AEs reported in the ANA group were only recorded prior to crossover.

treatment was longer in the TRA + ANA group and that the open-label design of the study meant that AEs in the ANA group were only reported until the patients crossed over to TRA + ANA.

Overall, therefore, no new safety issues were identified, the safety profile of TRA + ANA being consistent with the safety profiles of both drugs when given as single agents and with safety data from previously reported TRA studies.

eLEcTRA: trastuzumab in combination with letrozole versus letrozole alone

The eLEcTRA⁵² trial planned to enrol 370 patients with HR+ mBC, but between 2003 and 2007 enrolled only 92 patients, at which point the study was halted because of slow recruitment. The slow recruitment is attributed in the Roche submission²⁰ to the fact that investigators believed that TRA + LET was superior to LET (although no evidence is presented to support this claim). When the trial was halted, patients who were HR+/HER2+ had been randomly assigned to TRA + LET ($n=26$) or LET ($n=31$) and patients who were HR+/HER2- had been assigned to receive LET ($n=35$).

The findings from the eLEcTRA⁵² trial are summarised in *Table 12*: a large difference in TTP was observed between the two treatment groups [although this difference was not statistically significant (HR = 0.67; $p=0.23$)]. Interestingly, however, significant differences were reported in TTP between the two cohorts of patients that received LET (median 3.3 months vs 15.2 months for HR+/HER2+ mBC vs HR+/HER2- mBC, respectively; HR = 0.71; $p=0.03$). Large differences were also observed between TRA + LET and LET for ORR and CBR, but again these differences were not statistically significant ($p=0.3124$ and $p=0.0636$, respectively).

Patients who received TRA + LET were slightly more likely to experience SAEs and/or 'clinically significant AEs' (which were not defined) (*Table 13*). The most common AEs for patients in

TABLE 12 Summary of efficacy results from the eLEcTRA⁵² trial

Outcome	TRA + LET (<i>n</i> =26)	LET (<i>n</i> =31)
TTP (months) ^a	14.1	3.3
ORR (%)	27	13
CBR (%) ^b	65	39

a Median (no 95% CIs presented).

b CBR not defined.

TABLE 13 Summary of AEs from the eLEcTRA⁵² trial

Adverse events	TRA + LET (<i>n</i> =26)	LET (<i>n</i> =31)
SAEs (%)	27	23
SAEs and/or clinically significant AEs (%) ^a	39	36
Discontinued treatment because of SAEs and/or clinically significant AEs (%) ^a	4	0
Death during treatment (%)	0	3.2

a Clinically significant AEs not defined.

either group were musculoskeletal and connective tissue disorders and gastrointestinal disorders, whereas infections were also relatively common in both groups, particularly the TRA + LET group (*Table 14*). Fatigue was a problem particular to TRA + LET patients and around 15% experienced hepatobiliary disorders, whereas no patient in the LET group experienced these AEs.

Notwithstanding the caveats raised by the AG in comparing data across trials, it is also impossible to compare the AE profiles of TRA + LET in the eLeCTR⁵² trial with TRA + ANA in the TAnDEM⁵⁰ trial or LET in the EGF30008⁴⁹ trial because of the different ways in which AEs have been categorised, with the possible exceptions of fatigue and headaches. However, comparisons with the eLEcTRA⁵² trial are arguably still inappropriate given the small number of patients in this trial and the fact that the trial was halted early.

As noted above, there are known concerns about cardiac safety associated with TRA, but there were fewer cardiac events recorded in the TRA + LET group than in the LET group.

Overall, therefore, no new safety issues were identified, the safety profile of TRA + LET being consistent with the safety profiles of both drugs when given as single agents and with the safety data from previously reported TRA studies.

Although there were three trials^{49,50,52} identified that compared the interventions of interest with a comparator of interest in the relevant population, only two of these trials^{49,50} were completed as intended. These two trials were primarily sponsored by the manufacturers of LAP (GlaxoSmithKline) and TRA (Roche) and it was from these two manufacturers that the MS^{19,20} were received. In both of the MS, the manufacturers reported and appraised each of the pivotal trials individually, an approach also undertaken by the AG. Unlike the AG, however, Roche also performed a meta-analysis and both manufacturers also conducted indirect comparison analyses in order to compare LAP + AI with TRA + AI.

TABLE 14 Adverse events recorded in patients in the eLEcTRA⁵² trial

AEs	TRA + LET (n=26) (%)	LET (n=31) (%)
Musculoskeletal and connective tissue disorders	57.7	38.7
Gastrointestinal disorders	57.7	32.2
Infections	30.8	16.1
Fatigue	26.9	0.0
Metabolism disorders	20.0	3.2
Headache	19.2	9.7
Hepatobiliary disorders	15.4	0.0
Bone fractures	7.7	6.5
Psychiatric disorders	3.8	16.1
Hot flushes	7.7	3.2
Cardiac events	7.7	9.7

Meta-analysis (Roche)

The fixed-effect standard meta-analyses undertaken by Roche²⁰ examined PFS and were conducted for ANA versus TAM (two trials^{68,69}) and ANA versus megestrol acetate (Magace[®], Bristol-Myers Squibb) (two trials^{70,71}). There were insufficient trials to conduct meta-analyses for any other comparisons, such as LAP + LET versus LET or TRA + AI versus AI.

For the meta-analysis, forest plots for HR for individual studies and pooled studies were presented. The I^2 statistic was calculated to assess the potential heterogeneity between studies. The studies⁶⁸⁻⁷¹ included in these meta-analyses appeared to be associated with statistical and clinical heterogeneity. No significant differences were found for PFS between treatment groups in either meta-analysis.

Given that ANA was being compared with TAM or megestrol acetate, and given that it was unclear how many patients were HR+/HER2+, the AG believes that the relevance of these analyses to the current appraisal is limited. They were, however, relevant to the Roche submission²⁰ because the results from these meta-analyses were used in its indirect comparison analyses.

Indirect comparisons analyses

Both manufacturers performed indirect comparisons analyses, although different approaches were employed, as summarised in *Table 15*.

A complex network meta-analysis using the methods described by Puhan *et al.*⁷⁵ was planned by GlaxoSmithKline,¹⁹ but was not possible because of the lack of data for the outcomes of interest: OS and PFS/TTP. Thus, adjusted indirect comparisons analyses were performed for single outcomes as available, using the methods and principles as described by Bucher *et al.*⁷³ and incorporating data from five studies; the EGF30008⁴⁹ and the TAnDEM⁵⁰ trials were included as well as one study comparing LET (2.5 mg/day) with TAM (20 mg/day)⁷⁶ and two studies comparing ANA (1 mg/day) with TAM (20 mg/day).^{68,69} The eLEcTRA⁵² study was not included in the GlaxoSmithKline analyses as it was published only as an abstract and the AG agrees with the manufacturer's argument that a lack of data from this trial justifies its exclusion.

TABLE 15 Comparison of indirect comparisons approaches undertaken by the manufacturers

Approach taken	GlaxoSmithKline	Roche
Population included	Post-menopausal women with HR+ mBC who have not received prior therapy for advanced or mBC, i.e. patients for whom treatment with endocrine therapy was considered appropriate	Post-menopausal women with HR+ mBC
Outcomes analysed	PFS/TTP, OS TTP has been used where possible and, when TTP was not reported, PFS has been used assuming this was similar to TTP. Used Cox results not log-rank results	PFS, OS PFS = TTP, if TTP was explicitly defined as the time from randomisation to disease progression or death from any cause (if the reason for death was not reported, it was assumed that the death was from any cause) Where HRs were unavailable, summary statistics were used based on Parmar <i>et al.</i> ⁷²
Included studies	Five studies were included in both the PFS and OS analyses	Seven studies were included in PFS analysis, 11 studies in the PFS/TTP analysis and 12 studies in the OS analysis
Synthesis methodology	No direct meta-analysis Series of the adjusted indirect comparisons, using the methods and principles as described by Bucher <i>et al.</i> ⁷³	For indirect comparisons, analyses were performed using Bayesian network meta-analyses (also known as mixed-treatment comparisons), as described by Sutton and Higgins ⁷⁴
Assessment of homogeneity and similarity between included studies	No assessment was reported, although the manufacturer stated in the methods that it anticipated systematic differences between studies (i.e. heterogeneity). Thus, a random-effects model was used for the calculation of RR. Heterogeneity was intended to be assessed by measuring the degree of inconsistency in the studies' results (I^2 statistic). However, neither the I^2 statistic nor measures of RR were calculated; HRs were calculated and utilised in the analysis instead	For indirect comparisons, the manufacturer discussed with clinical experts and assessed statistically (from the posterior median variance of the random effects) the suitability of including particular trials in the analyses. A series of sensitivity analysis were performed to explore the nature of heterogeneity
Manufacturers' quality assessment	The manufacturer discussed the limitations of its indirect comparisons. These included failure to fulfil basic assumptions of homogeneity, similarity and consistency for the indirect comparisons	The manufacturer utilised clinical experts to assess the suitability of trials to be included in their analyses. The manufacturer discussed the limitations of their direct and network meta-analyses and sensitivity analyses were performed
AG comment	The studies included in the indirect comparisons analysis included trials in which the HR+/HER2+ status was unknown; only two trials included analyses of this specific population – the EGF30008 ⁴⁹ and the TAnDEM ⁵⁰ trials	The manufacturer also utilised clinical experts to assess the suitability of trials to be included in their analyses. However, there were only three trials in which the HR+/HER2+ status of patients analyses was known – the EGF30008, ⁴⁹ the TAnDEM ⁵⁰ and the eLEcTRA ⁵² trials

RR, relative risk.

The findings for both OS and PFS/TTP presented by the manufacturer suggest that there are no significant differences between any of the interventions for OS. Both LAP + LET and TRA + LET result in significantly improved outcomes for PFS/TTP when compared with ANA, LET and TAM. For reasons discussed below, the AG believes these findings should be treated with extreme caution and so the findings are not presented in this report.

Roche²⁰ employed an indirect network meta-analyses based on a Bayesian approach,⁷⁴ in which a number of different analyses were performed for OS (base case of 12 trials^{49,50,68–71,77–82}) and PFS (base case of seven trials^{49,50,68–70,78,81}). A number of assumptions were made and tested by sensitivity analyses. These included an assumption that PFS = TTP (which enabled four additional trials^{52,77,79,80} to be considered) and that OS findings for the TAnDEM⁵⁰ trial based on the RPSFT adjustment should be used in the base case. In addition, for every outcome, the assumption that AIs hold a 'class effect' (i.e. LET = ANA, as suggested by clinical experts and as found in a head-to-head trial of second-line ANA vs LET⁸²) was tested. This assumption related to the mixed HER2 status population (i.e. the population in which the proportion of patients with

HER2+ breast cancer was unknown, as in the aforementioned ANA vs LET trial⁸²). The mixed HER2 population was chosen because the HR+/HER2+ population was too specific to allow the inclusion of any trials other than the EGF30008,⁴⁹ the TAnDEM⁵⁰ and the eLEcTRA trials.⁵²

The findings presented by the manufacturer in which a 'class effect' was assumed for AIs and which were derived from the EGF30008⁴⁹ and the TAnDEM⁵⁰ for OS and PFS and from the EGF30008,⁴⁹ the TAnDEM⁵⁰ and the eLEcTRA⁵² for PFS/TTP suggest that there are no significant differences between LAP + LET and TRA + ANA for OS, PFS or PFS/TTP. For reasons discussed below, the AG believes these findings should be treated with extreme caution and so findings are not presented in this report.

Aside from the fact that the EGF30008⁴⁹ and the TAnDEM⁵⁰ trials were too dissimilar in terms of patient populations, the AG believes that both the manufacturers' indirect comparisons analyses had one other major limitation, namely that the basic requirement for indirect comparisons with regard to exchangeability of relative treatment effect between trials in the two MS could not be assumed. This is a limitation recognised by the manufacturers themselves^{19,20} and is amplified when patient population characteristics are considered. Crucially, it was unknown how many patients with HR+/HER2+ mBC were included in the trials. Only three trials^{49,50,52} presented data for patients with HR+/HER2+ mBC. The other trials^{68-71,76,77,78,82-90} included patients of mixed/unknown status. The importance of missing data on HR+/HER2+ status is twofold. Firstly, patients with HR+/HER2+ mBC are the population of interest to this review and, as Roche has acknowledged (MS, p. 18):²⁰ 'All results should be treated with extreme caution when applied to the HR+/HER2+ population as there is no evidence base capable of informing this analysis in the population specified by the decision problem.' Secondly, both the EGF30008⁴⁹ and the eLEcTRA⁵² trials suggest that the effects of LET in patients with HR+/HER2+ mBC tumours are significantly compromised when compared with those with HR+/HER2- mBC. Thus, the indirect comparisons analyses may be overstating the benefit of AIs and, if so, there is a need to adjust for the results based on HER2+ status. However, given that the proportion of such patients is unknown, such adjustments are currently impossible. It is important to note, as Roche has also stated (MS, p. 18):²⁰ '...understanding of HER2 was not fully developed at the period when most of the evidence base identified was formed as many of the trials conducted were not stratified for HER2 positivity and it is clearly plausible that an imbalance in this strong indicator of extremely poor prognosis could have biased the estimates of relative efficacy generated'.

Roche²⁰ also acknowledges a number of additional limitations to its indirect comparisons analyses, namely 'the low number of trials by pairwise comparison, the heterogeneity in the length of follow-up observed in the selected studies and the different methods used to adjust for cross-over in the individual studies' (MS, p. 17). A final limitation is the fact that not all trials included patients receiving first-line treatment. In fact, two trials^{78,82} were second line, including the trial by Rose *et al.*,⁸² which was a key trial for suggesting a 'class effect' for AIs. The AG believes that pooling trials with different lines of treatment is inappropriate and misleading; thus, these results should be interpreted with caution.

In summary, given the limitations described above, the AG believes that conducting indirect comparisons analyses with the limited data available is inappropriate. Therefore, any findings generated from these analyses should be treated with caution.

Summary

The findings from the three main trials examining the efficacy of LAP + LET (EGF30008⁴⁹), TRA + ANA (TAnDEM⁵⁰) and TRA + LET (eLEcTRA⁵²) all suggest that LAP + AI or TRA + AI

results in improved outcomes when compared with AIs alone (LET or ANA). In the EGF30008 and the TAnDEM trials,^{49,50} although these differences were not significant for OS, statistically significantly different outcomes were reported for PFS and TTP and large differences were reported between TRA + LET and LET patients in the eLEcTRA trial;⁵² this trial lacked statistical power to adequately test for significant differences. In addition, both ORR and CBR appeared to be improved for patients taking LAP + AI or TRA + AI. No new safety concerns were identified from the trials, although both AEs and SAEs were more common in the LAP + LET and TRA + AI groups than in the groups treated with AIs alone. For LAP + LET, the most significant AE was diarrhoea, experienced by around two-thirds of all patients. The impact this may have had on patient QoL is difficult to estimate, as to date the findings have been presented only as a conference abstract.⁵⁹ However, it would appear there are no significant differences between patients in either treatment group. Indeed, the majority of cases of AEs (including diarrhoea) were of grades 1 or 2 severity. Nevertheless, diarrhoea did result in around 1% of all patients who received LAP + LET discontinuing their treatment as a result; all other patients were managed by dose reduction, dose interruption or supportive intervention without treatment dose adjustments. For TRA + ANA patients, the most frequently reported AEs were fatigue, diarrhoea and vomiting, experienced by around one-fifth of all patients, of which the majority were grades 1 or 2 severity. Fatigue was also a problem for around one-quarter of patients who received TRA + LET, but infections, gastrointestinal disorders and musculoskeletal and connective tissue disorders were even more common; over half of TRA + LET patients experienced these last two AEs. Around one-third of LET patients also reported gastrointestinal disorders and musculoskeletal and connective tissue disorders.

However, extreme caution must be exercised in comparing the aforementioned findings across trials. Thus, for example, it would be wrong to assume that because TRA + ANA appears to have comparable efficacy and a more preferable side-effects profile than LAP + LET or TRA + LET, it is therefore superior to other treatments, for a number of reasons.

- Such a comparison would be considered to be too simplistic and naive as it breaks the randomisation procedure and would not account for differences in baseline characteristics in treatment groups across the trials. To compare the outcomes more accurately, a direct comparison or indirect comparisons analyses would need to be considered.
- The ORR hides the fact that none of the patients in the TAnDEM⁵⁰ trial examining TRA + ANA were CRs, unlike in the EGF30008 trial,⁴⁹ in which 5% of LAP + LET and 4% of LET patients were CRs. It was not known if any patients taking TRA + LET or LET were CRs in the eLEcTRA⁵² trial because this trial did not report ORR by CR and PR.
- Trials did not always report data in the same way, so it is unclear, for example, if a greater proportion of patients in the eLEcTRA⁵² trial experienced gastrointestinal disorders than in other trials because such a category of AE did not exist (instead there were data on diarrhoea and vomiting, etc.). A similar problem was encountered in trying to compare baseline characteristics across trials.
- It is difficult to compare the results of the eLEcTRA⁵² trial with those of the other two trials because this trial was halted prematurely because of slow recruitment.
- Most crucially, it was apparent from the exclusion criteria that there may have been differences in the patients included in the EGF30008 and the TAnDEM trials.^{49,50} This appeared to be supported by data reported by the two trials, which suggested large differences in median OS in the AI arms (LET and ANA, respectively). Notwithstanding the dangers of crude comparisons across trials just highlighted, if patients were similar in terms of their baseline characteristics, we would expect similar estimates for OS in the AI-only arms trials given that the evidence to date suggests that there is no difference between LET and ANA in terms of efficacy, albeit in early HR+ breast cancer.^{34,91} However, depending

on which estimate for OS was used in the TAnDEM trial,⁵⁰ differences of between 3.7 and 10.4 months were observed in the AI arms of the EGF30008⁴⁹ and TAnDEM trials.⁵⁰

Alternative explanations for differences in OS are that there are real differences between LET and ANA, or that differences between the AI groups occurred as a result of differences in second-line treatment received following progression. In relation to the first alternative, there appears to be a broad consensus within clinical practice that there is little to choose between LET and ANA, certainly in terms of efficacy, and there is also evidence of a 'class effect' (i.e. LET = ANA), albeit from studies of early HR+ breast cancer.^{34,91} In relation to the second possible explanation, patients in both the EGF30008⁴⁹ and the TAnDEM⁵⁰ trials were permitted to receive second-line treatment and this appears to differ between the trials, with chemotherapy being more common in the EGF30008 trial.⁴⁹

The fact that patients were able to cross over in the TAnDEM⁵⁰ trial and the fact that in both trials second-line therapy was permitted has added an extra complication in interpreting and comparing the findings, namely how much of the benefit in OS is attributable to the first-line treatment and how much of the benefit is attributable to subsequent treatment following disease progression? Post-hoc attempts have been made by both Kaufman *et al.*⁵⁰ and Roche²⁰ to address this issue in the TAnDEM trial,⁵⁰ but no such attempts were made for the EGF30008 trial.⁴⁹

Kaufman *et al.*⁵⁰ compared the median OS between those receiving TRA + ANA with those who initially received ANA but did not cross over to receive TRA, and those in the AI group who crossed over to receive TRA + ANA with those who did not. Significant differences, when the Wilcoxon test was employed, were reported in favour of TRA + ANA and those in the ANA group who crossed over. The AG believes this was an inappropriate method as it is prone to selection bias. A different method was employed by Roche,²⁰ namely the RPSFT method, which allowed for a comparisons between the TRA + ANA and ANA groups. Using this method OS gains were found to be greater than when no adjustment was made. However, the main justification for employing the RPSFT approach appears to be that it has been used in previous submissions to NICE.^{63,64} The AG notes that other, possibly more appropriate, methods exist and believes that different randomisation-based methods should ideally be used to compute and compare a range of OS estimates to assess sensitivity of treatment effects. Therefore, the AG believes that the findings from the RPSFT approach should be treated with caution.

Because crude comparisons of OS across trials are too simplistic, both manufacturers conducted adjusted indirect comparisons analyses,^{19,20} with Roche employing a network meta-analysis based on a Bayesian approach,⁷⁴ in which a number of different analyses and sensitivity analyses were performed and in which it was assumed, and tested, that there was a 'class effect' for AIs. The findings from both the manufacturers' approaches appeared to support the trial findings suggesting that LAP + LET and TRA + AI were better than AIs alone in terms of PFS and/or TTP, but not OS. In addition, their analyses suggested that there was little difference between LAP + LET, TRA + ANA and TRA + AI. However, the AG believes that these indirect comparisons must also be treated with caution for a number of important reasons. First and foremost, as discussed above, the AG believes that the patient populations are not sufficiently similar in the EGF30008⁴⁹ and the TAnDEM trials.⁵⁰ Hence, these trials should not be compared with each other at all. On the other hand, if there are differences in efficacy between LET and ANA, then there may be grounds to conduct an indirect comparisons analysis if the other trials are sufficiently similar. However, both indirect comparisons analyses had one other major limitation, recognised by the manufacturers themselves,^{19,20} namely that the basic requirement for indirect comparisons with regard to exchangeability of relative treatment effect between trials in the two MS could not be assumed. Crucially, it was unknown how many patients with HR+/HER2+ mBC

were included. Both the EGF30008⁴⁹ and the eLEcTRA⁵² trials suggest that the effects of LET in patients with HR+/HER2+ mBC tumours are significantly compromised when compared with those with HR+/HER2- mBC. As has been acknowledged by Roche,²⁰ 'it is clearly plausible that an imbalance in this strong indicator [HER2+] of extremely poor prognosis could have biased the estimates of relative efficacy generated' (MS, p. 18). Other areas of heterogeneity include the proportion of patients with advanced breast cancer, length of follow-up and proportion of patients receiving first-line treatment.

Thus, overall, the AG believes comparisons across trials cannot be made and that only the individual findings from each trial should be considered.

Chapter 4

Assessment of cost-effectiveness

Systematic review of existing cost-effectiveness evidence

In this section, firstly, a critical appraisal of the available economic evidence describing (1) LAP + LET and (2) TRA + ANA is described. Secondly, the AG's critique of the two economic evaluations submitted by the manufacturers is presented.

Review of published cost-effectiveness studies

Full details of the search strategy conducted by the AG and the methods used for selecting evidence are presented in *Chapter 3, Quantity and quality of research available*. The AG concluded that none of the 107 economics studies identified from the electronic searches were eligible for inclusion in the literature review as they did not include any of the relevant interventions (LAP + AI or TRA + AI). The authors of the GlaxoSmithKline MS noted that 'no economic evaluations of lapatinib plus an AI were identified' (MS, p. 100). The authors of the Roche MS stated that, although they summarised the characteristics and results of five studies,⁹²⁻⁹⁶ 'four were of poor relevance to the decision problem as they were not in the population of relevance and were not set in the UK' (MS, p. 209). The only study that Roche deemed to be relevant to the review was the poster by Hastings *et al.*,⁹⁶ which is discussed below.

The AG notes that the poster presented at American Society of Clinical Oncology (ASCO) conference (June 2010) by Hastings *et al.*⁹⁶ is relevant to the technologies under assessment. It is noted that the authors of this poster are employees of GlaxoSmithKline, yet the poster was only discussed in the MS submitted by Roche.

Summary and critique of Hastings poster

The Hastings *et al.*⁹⁶ poster describes an indirect comparison of the cost-effectiveness of LAP + LET versus TRA + ANA in post-menopausal women with HR+/HER2+ mBC who have not received prior treatment. The perspective of the economic analysis is the UK NHS. The evidence network used to estimate treatment effectiveness appears to be the same as that described in the MS submitted by GlaxoSmithKline and includes both the EGF30008⁴⁹ and the TAnDEM trials;⁵⁰ the utility values for PFS and post-progression survival (PPS) health states are also the same. Base-case results are shown in *Table 16* and are different to the estimates provided in the MS by GlaxoSmithKline. Hastings *et al.*⁹⁶ conclude that LAP + LET is cheaper and more clinically effective than TRA + ANA and is therefore dominant. The AG is of the opinion that the results of the indirect analysis performed by Hastings *et al.*⁹⁶ are unreliable as the studies which make up the evidence network are inappropriate (for more details see *Chapter 3*). In addition, the

TABLE 16 Base-case results from Hastings *et al.* poster presentation⁹⁶

Measure	LAP + LET	TRA + ANA	Difference
Total QALYs (discounted)	2.626	2.330	0.296
Total costs (£) (discounted)	60,614	64,003	-3.389
Cost per QALY (£)			Dominant

AG notes that without access to more detailed information on costs, it is difficult to comment on the reliability of the cost-effectiveness results in this study.

Conclusions of the review of existing cost-effectiveness evidence

There is no relevant, currently available, published cost-effectiveness evidence to describe the use of LAP + LET or TRA + ANA in women who are HR+/HER2+ with mBC.

Overview and critique of GlaxoSmithKline economic evaluation

Overview of submitted economic evaluation and economic model

The purpose of the manufacturer's model is to assess the cost-effectiveness of first-line treatment with LAP + LET in HR+/HER2+ patients with mBC. In the MS, the combination of LAP + LET is compared with the following interventions: LET monotherapy, TRA + ANA and ANA monotherapy. A decision-analytic model was developed by the manufacturer to estimate PFS, OS, lifetime costs of treatment of mBC and QALYs. The model schema is presented in *Figure 2*. The model features three health states: alive and no progression, alive with progression and dead. The manufacturer estimates costs from the perspective of the NHS and PSS and health outcomes in terms of life-years, progression-free life-years (PFLYs), post-progression life-years (PPLY) and QALYs; variables are estimated daily for 10 years. The economic evaluation has a time horizon of 10 years and both costs and benefits are discounted at 3.5% per annum. The manufacturer's reference case adequately reflects the NICE reference case⁹⁷ (*Table 17*).

Summary and critique: clinical effectiveness data

Direct clinical evidence: lapatinib in combination with letrozole versus letrozole alone

The key clinical data (PFS, OS and AEs) used in the manufacturer's economic model comparing LAP + LET versus LET are taken directly from the EGF30008 trial.⁴⁹ The AG's description and critique of the EGF30008⁴⁹ trial is presented in *Chapter 3* of this report.

Progression-free survival and OS estimates for patients receiving LET were estimated by fitting Weibull survival functions to patient-level failure time data for HR+/HER2+ patients in the EGF30008 trial.⁴⁹ PFS and OS estimates for patients receiving LAP + LET were obtained by applying the HRs for LAP + LET versus LET to the PFS and OS curves for LET for HR+/HER2+ patients in the EGF30008 trial.⁴⁹ In general, the AG's preferred approach to projective modelling is to assess PFS and PPS separately and then combine them in order to get a more reliable estimate of OS, rather than simply modelling OS as a single entity.

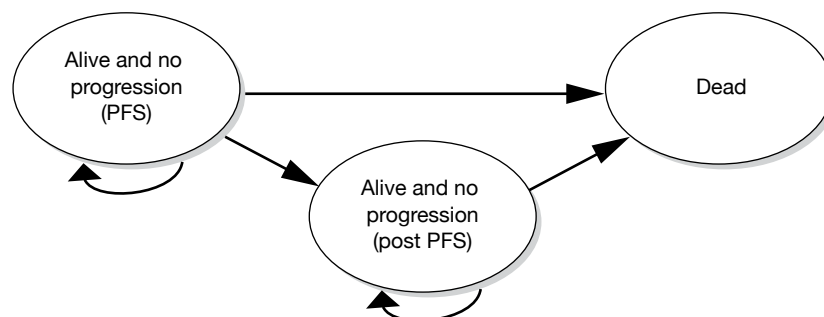


FIGURE 2 The structure of the model submitted by GlaxoSmithKline.

TABLE 17 Reference case checklist for GlaxoSmithKline economic evaluation

NICE reference case requirements	Reference case ⁹⁷	Does the de novo economic evaluation match the reference case?
Defining the decision problem	The scope developed by the institute	Yes
Comparators	Therapies routinely used in the NHS, including technologies currently regarded as best practice	Yes. Intervention is LAP + LET Best practice: Als. New intervention also under appraisal: TRA + ANA
Perspective on costs	NHS and PSS	NHS and PSS
Perspective on outcomes	All health effects on individuals	All health effects on individuals
Type of economic evaluation	Cost-effectiveness analysis	Cost-utility analysis
Synthesis of evidence on outcomes	Based on a systematic review	Based on a systematic review and an adjusted indirect comparisons exercise
Measure of health benefits	QALYs	QALYs
Source of data for measurement of QoL	Reported directly by patients and/or carers	(1) Utilities are reported directly by patients from the EGF30008 ⁴⁹ trial for PFS health states (2) published utilities are used for PPS health states
Source of preference data for valuation of changes in QoL	Representative sample of general public	Algorithm used to map FACT-G values into EQ-5D values; EQ-5D valuations are based on values from representative values of general public
Discount rate	An annual rate of 3.5% on both costs and QALYs	An annual rate of 3.5% on both costs and QALYs
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit

EQ-5D, European Quality of Life-5 Dimensions; FACT-G, Functional Assessment of Cancer Therapy-General Scale.

Indirect clinical evidence: lapatinib in combination with letrozole versus trastuzumab in combination with anastrozole/anastrozole alone

An indirect comparisons analysis was carried out by the manufacturer to compare LAP + LET with other drugs. In order to perform the indirect comparison and derive (PFS, OS and AEs) parameter estimates for TRA + ANA and ANA monotherapy, data from the TAnDEM⁵⁰ and other published AI trials (with or without an anti-HER2 therapy and mixed HER2 populations) were used. A summary and critique of the evidence network employed by the manufacturer is presented in *Chapter 3* of this report.

As noted earlier, the AG is not confident that the results of the indirect comparisons analysis conducted by the manufacturer are reliable. Firstly, the TAnDEM⁵⁰ trial is included in the network and this trial does not explicitly exclude patients who have extensive symptomatic visceral or rapidly progressing or life-threatening disease, which means that the patient populations of the studies in the network may be different; in particular, the patients in the TAnDEM⁵⁰ and the EGF30008⁴⁹ trials are not comparable. Secondly, there were large differences in the second-line treatment received in these trials. A further criticism is that in the indirect comparisons analysis, it is likely that the AI trials include patients who are both HER2+ and HER2-; the AG is of the opinion that the inclusion of HER2- patients is inappropriate given that the decision problem is focused on treating women who are HER2+ and it is becoming apparent^{49,52} that an AI as monotherapy is less effective in women who are HER2+ than in women who are HER2-. Finally, it should be noted that GlaxoSmithKline uses the TAnDEM⁵⁰ trial data published in 2009 that does not use the RPFST method to adjust (for crossover) OS estimates for patients receiving ANA in the TAnDEM trial.⁵⁰

In summary, the AG considers that the submitted model results for the comparison of LAP + LET versus LET is the only comparison that is wholly valid to inform decision-making in this area because of the limited comparative clinical effectiveness data available.

Summary and critique: costs and resource use

The manufacturer estimates the following costs for each treatment strategy: acquisition and administration of medications, patient monitoring, treatment of AEs, other costs during PFS and PPS and total costs. The key cost parameters used in the model are summarised in *Table 18*.

The economic model makes use of pre- and post-progression cost data from the Remak and Brazil study;¹⁰⁰ however, the manufacturer does not comment on the relevance and/or generalisability of the assumptions employed in this study to HR+/HER2+ patients with mBC in England and Wales.

In summary, the AG notes that in the MS, the methods used by the manufacturer to identify, measure and value cost items are not fully described. The AG notes that further information is provided in the manufacturer's accompanying cost-effectiveness report. *Table 19* identifies key costs which could have been discussed in further detail by the manufacturer.

Summary and critique: utilities

Utility values for PFS without AEs were estimated using data from the EGF30008⁴⁹ trial on the Functional Assessment of Cancer Therapy-General Scale (FACT-G)¹⁰¹ plus Breast Cancer subscale (FACT-B)¹⁹ and an algorithm was used to map from the FACT-G to patient preference-based utilities.^{102,103} The pre-progression utility value used in the model was 0.86.

In the EGF0008 trial,⁴⁹ FACT assessments were routinely completed by patients only until withdrawal of study medications (i.e. typically at disease progression). This means that post-progression utility values for patients are largely unavailable, and the manufacturer states that the generalisability of the values that are available is uncertain. In order to identify a utility

TABLE 18 Key cost parameters used in the model

Item	Most (£)	Source
LAP (250 mg) 70 pack	804.30/pack; 11.49 per tablet	BNF 59 ²⁸
LET (2.5 mg) 28 pack	66.50/pack; 2.38 per tablet	BNF 59 ²⁸
TRA (150-mg vial)	407.40	BNF 59 ²⁸
ANA (1 mg) 28 pack	68.56/pack; 2.45 per tablet	BNF 59 ²⁸
Dispensing costs	8.50	PSSRU (15 minutes of community pharmacist time, £34.00/hour) ⁹⁸
ECHO/MUGA monitoring costs	46.50/month	<i>NHS reference costs 2008–2009</i> ⁹⁹ (50% : 50%, testing every 3 months)
Total pre-progression cost	562.00/month of PFS	Remak and Brazil ¹⁰⁰ /PSSRU ⁹⁸
Total post-progression cost	803.92/month of PPS	Remak and Brazil ¹⁰⁰ /PSSRU ⁹⁸
Non-severe AE (e.g. chills, constipation, cough, epistaxis, hot flushes, nasopharyngitis)	99	Probability for hospitalisation for grade 3 or higher AEs was based on data from the EGF30008 trial. ⁴⁹ Visit and hospitalisation costs for grade 3 or higher AEs based on <i>NHS reference costs 2008–2009</i> ⁹⁹
Alopecia	158	
Dyspnoea	722	
Headache	255	
Nausea	420	
Vomiting	1398	

BNF, *British National Formulary*; ECHO, echocardiogram; MUGA, multigated acquisition scan; PSSRU, Personal Social Services Research Unit.

TABLE 19 Examples of limited costing methods described in the MS by GlaxoSmithKline

Assumption made	Limitation
Economic evaluation uses a 4 mg/kg loading dose of TRA followed by subsequent doses of 6 mg/kg in a 3-weekly scenario	SPC states that a 8 mg/kg loading dose be used then followed by subsequent doses of 6 mg/kg in a 3-weekly scenario. In the model a 10 mg/kg loading dose is costed (4 mg/kg + 6 mg/kg)
MS describes costs of PFS and PPS using cost categories described in Remak and Brazil ¹⁰⁰ paper	Remak and Brazil ¹⁰⁰ paper also describes cost categories related to end-of-life treatment which are not included in the economic evaluation
MS appears to assume that patients did not receive second-line chemotherapy or post-progression treatments as further treatments are not discussed	Inappropriate assumption – (1) not a valid assumption for clinical practice in England and Wales as often patients go on to receive additional treatments and (2) high proportion of patients received second-line chemotherapy treatment in the TAnDEM trial, ⁵⁰ which gives first-line treatment in a similar setting to patients with mBC
MS assumes a 14-day wastage of oral tablets	GlaxoSmithKline model uses drug costs on a per tablet basis. As drugs can only be bought in packs (and any unused drugs cannot be shared) this is inappropriate. The full (rather than half) pharmacy dispensing cost should also be included in the cost associated with wastage
GlaxoSmithKline estimates drug costs per tablet which leads to inaccuracies: Daily cost per tablet (ANA) = £2.45 Daily cost per tablet (LET) = £2.38 28-day cost (ANA) = £68.60 28-day cost (LET) = £66.64	Pack prices from BNF 59: ²⁸ 28-day cost (ANA) = £68.56 28-day cost (LET) = £66.50
GlaxoSmithKline assumes that delivery of TRA is always an outpatient procedure. Delivery of simple parenteral chemotherapy [SB12Z Deliver parenteral chemotherapy at first attendance (£272) and SB15Z Deliver subsequent elements of a chemotherapy cycle (£272)]	Depending on patient condition and local circumstance, delivery could be on a day-case basis. A weighted average of outpatient and day-case costs would be more meaningful
Monitoring costs in the economic model are £46.50 per month for both LAP + LET and TRA + ANA patients	In the base case, GlaxoSmithKline assumes that cardiac monitoring occurs every 3 months and that both MUGA and ECHO scans are used in equal proportions. AG clinical advisors have stated that MUGA scans are used less frequently (30%) than ECHOs (70%)
AEs	No real information is presented in MS to explain methods used to cost concurrent events; all AEs appear to be costed as individual episodes, which is unrepresentative of clinical practice

BNF, *British National Formulary*; ECHO, echocardiogram; MUGA, multigated acquisition scan; SPC, summary of product characteristics.

decrement for PD to apply to patients with PD, the manufacturer used the results of a study by Lloyd *et al.*¹⁰⁴ of societal preferences for different stages of mBC in the UK. The absolute reduction in utility compared with no progression used in the model was 0.23; this means that PP utility value can be no higher than 0.62.

Disutility values from grades 3 or higher AEs were obtained from published and unpublished sources,¹⁰⁴⁻¹⁰⁶ and where no data were available, assumptions were made. The utility decrements employed in the economic model include nausea (0.1), vomiting (0.1), diarrhoea (0.1), alopecia (0.11), asthenia/fatigue/lethargy (0.12), and skin and nail disorders (0.15).

The AG notes that the manufacturer does not sufficiently describe the results of the FACT assessments from the EGF30008 trial,⁴⁹ nor does the manufacturer adequately describe (or test the sensitivity of) the mapping exercise undertaken. Therefore, it is difficult to comment on the usefulness of the PFS utility values.

For PPS, the AG agrees with the manufacturer that the paper by Lloyd *et al.*¹⁰⁴ describing UK-based societal preferences is relevant to health-care decision-making in the UK. However, as (1) the health states described in the Lloyd *et al.*¹⁰⁴ paper were derived from literature reviews,

exploratory interviews with physicians and an oncology focus group made up of specialist nurses and (2) the health states were gender neutral and there was no mention of ‘cancer’ in the health-state descriptions, the AG is also very aware that health-state descriptions and the valuations of the general public may not fully reflect the experiences of patients with cancer nor the true preferences of the general public.

Summary and critique: results

The manufacturer presents detailed summaries of costs and outcomes (PFLYs, PPLYs, Life-years and QALYs) for the following regimens: LAP + LET, LET monotherapy, TRA + ANA and ANA monotherapy. Base-case results for the pair-wise comparisons are reported in *Table 20*. The results show that LAP + LET is not cost-effective compared with any of the AIs. LAP + LET appears to be cost-effective compared with TRA + ANA; however, as there is much uncertainty about the reliability of the indirect comparison results, these results are not considered by the AG to be meaningful.

Summary and critique: sensitivity analysis and probabilistic sensitivity analysis

The AG notes that 51 scenarios were examined by the manufacturer using sensitivity analysis. The results of the sensitivity analysis are presented in table 41 of the MS. For the comparison with LET monotherapy, the incremental cost per QALY is in the range of £41,877 to LAP + LET being dominated by LET monotherapy. The cost per QALY gained versus ANA monotherapy ranges from £38,170 to £378,674. For the comparison with TRA + ANA, the range is LAP + LET dominating the comparator to a cost per QALY estimate of £45,106. The approach to sensitivity

TABLE 20 Base-case results: pair-wise comparisons

Outcomes, costs and ICER	LAP + LET	LET	TRA + ANA	ANA	Incremental comparisons: LAP + LET vs		
					LET ^a	TRA + ANA	ANA
Outcomes							
PFLYs	1.181	0.738	1.042	0.592	0.444	0.139	0.589
PPLYs	2.218	2.079	2.004	2.065	0.138	0.214	0.153
Life-years	3.399	2.817	3.045	2.657	0.582	0.354	0.742
QALYs	2.389	1.923	2.137	1.788	0.467	0.252	0.601
Costs							
Acquisition costs (£)	30,219	688	23,818	576	29,531	6401	29,643
Administration costs (£)	260	83	4236	66	177	-3976	194
Monitoring costs (£)	659	0	581	0	659	78	659
Treatment-specific AE costs (£)	113	71	109	67	42	4	46
Other progression-free costs (£)	7966	4975	7026	3991	2991	940	3975
Other post-progression costs (£)	21,396	20,060	19,330	19,919	1336	2066	1447
Total costs (£)	60,614	25,878	55,101	24,620	34,737	5513	35,995
ICER							
Cost per LYG (£)					59,684	15,590	48,478
Cost per PFLYG (£)					78,317	39,532	61,074
Cost per QALY gained (£)					74,448	21,836	59,895

LYG, life-year gained; PFLYG, progression-free life-year gained.

a AG only considers the results of the LAP + LET vs LET comparison to be valid (highlighted in bold).

analysis adopted by the manufacturer makes it difficult for the AG to acquire any real insight into the true drivers affecting the size of the incremental cost-effectiveness ratios (ICERs).

A summary of the probabilistic sensitivity analysis (PSA) is presented in *Figure 3* and the cost-effectiveness acceptability curve (CEAC) is shown in *Figure 4*. The CEAC shows that, at a cost-effectiveness threshold of £30,000 per QALY gained, the probability of LAP + LET being cost-effective is very low (< 25%) compared with any AI and low (approximately 50%) compared with TRA + ANA.

Summary and critique: end-of-life treatment criteria

The AG notes that the manufacturer has not requested that LAP + LET be considered by NICE as an end-of-life treatment.

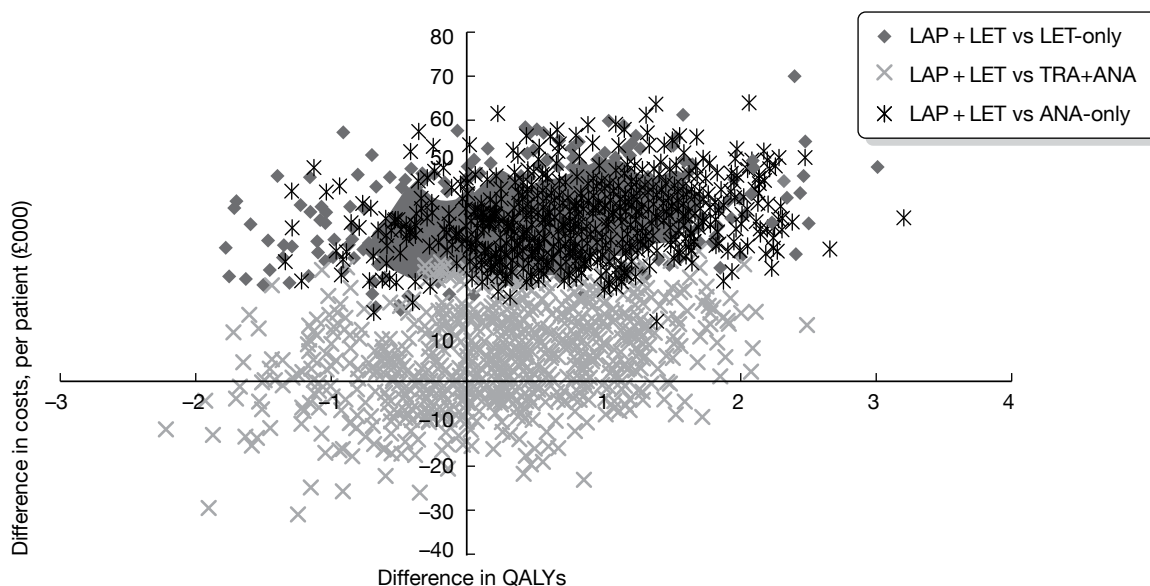


FIGURE 3 Incremental cost-effectiveness ratios for LAP + LET versus comparators.

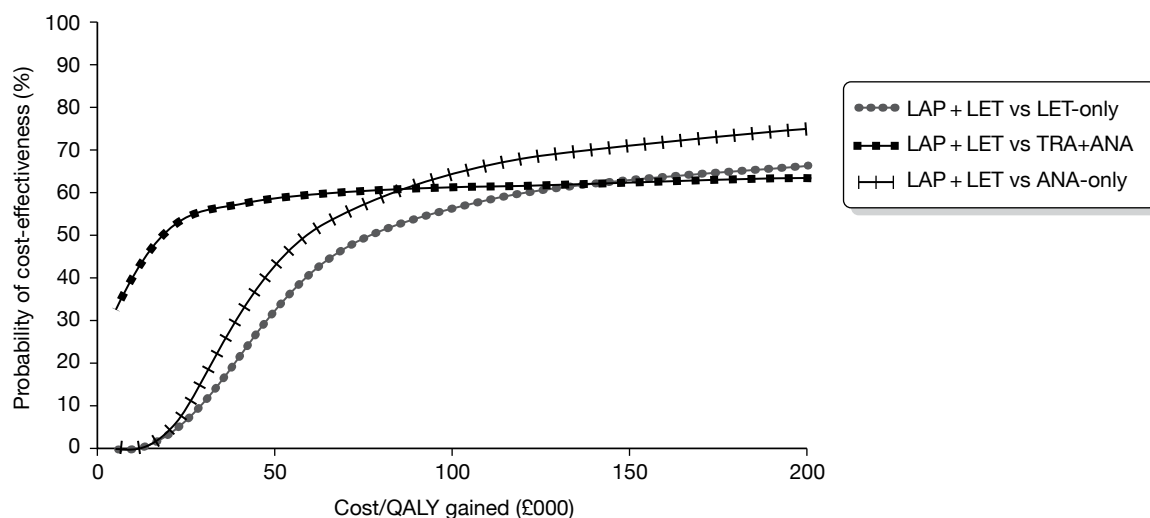


FIGURE 4 Cost-effectiveness acceptability curve for LAP + LET versus LET, TRA + ANA and ANA.

Conclusions of the Assessment Group

From the information presented in the MS, the AG agrees with the manufacturer that LAP + LET is not cost-effective when compared with LET.

The AG also considers that the methods used in the indirect analysis undertaken by the manufacturer are unreliable and concludes that the ICERs derived from the remaining comparisons (LAP + LET vs TRA + ANA; LAP + LET vs ANA) are not meaningful.

GlaxoSmithKline did not make a case for LAP to be considered as an end-of-life treatment.

Overview and critique of Roche economic evaluation

Overview of submitted economic evaluation and economic model

The purpose of the manufacturer's model is to assess the cost-effectiveness of first-line treatment with TRA + ANA in HR+/HER2+ patients with mBC. In the MS, the combination of TRA + ANA is compared with the following interventions: ANA monotherapy, LAP + LET and LET monotherapy. An area under the curve (AUC) model was designed to calculate the present value of the health outcomes and NHS/PSS costs attributable to each possible treatment option calculated. The model schema is presented in *Figure 5*. The model features three health states (PFS, PD and death) and has a cycle length of 1 month. The manufacturer estimates costs from the perspective of the NHS/PSS and health outcomes in terms of life-years gained (LYG) and QALYs. The economic evaluation has a time horizon of 15 years and both costs and benefits are discounted at 3.5% per annum (implemented monthly). The manufacturer's economic evaluation adequately reflects the NICE reference case⁹⁷ (*Table 21*).

Summary and critique: clinical effectiveness data

Direct clinical evidence

The key clinical data (PFS and OS) used in the MS are taken directly from the TAnDEM⁵⁰ trial and utilise some previously unpublished data as the model inputs were taken from an April 2008 data cut (the published paper from the trial uses an older data cut). As the PFS curves from the TAnDEM⁵⁰ trial were practically complete, the Kaplan–Meier PFS curves for the two regimens were used directly to model the majority of disease progression of patients within the economic model (uncertainty in the Kaplan–Meier PFS curves was addressed in the sensitivity analysis). In general, the AG's preferred approach to projective modelling would be to assess PFS and PPS separately and then combine them in order to get a more reliable estimate of OS, rather than simply modelling OS as a single entity.

In the TAnDEM⁵⁰ trial estimates of OS were affected by (1) high rates of crossover of patients from ANA to TRA + ANA and (2) second-line chemotherapy imbalance by trial group. Both

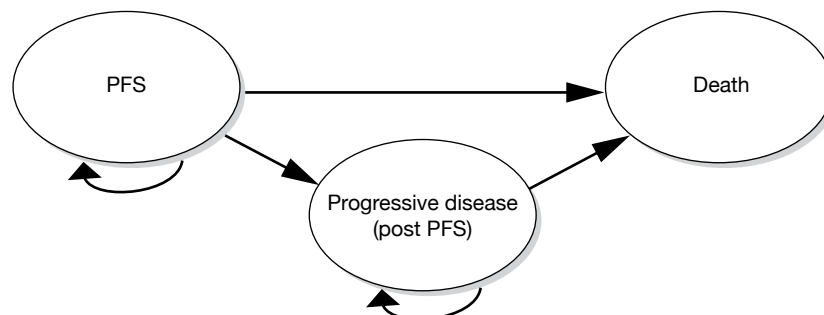


FIGURE 5 The structure of the model submitted by Roche.

TABLE 21 Reference case checklist for Roche economic evaluation

NICE reference case requirements	Reference case ⁹⁷	Does the de novo economic evaluation match the reference case?
Defining the decision problem	The scope developed by the institute	Yes
Comparators	Therapies routinely used in the NHS, including technologies currently regarded as best practice	Yes. Best practice: Als. New intervention also under appraisal: LAP + LET
Perspective on costs	NHS and PSS	NHS and PSS
Perspective on outcomes	All health effects on individuals	All health effects on individuals
Type of economic evaluation	Cost-effectiveness analysis	Cost-utility analysis
Synthesis of evidence on outcomes	Based on a systematic review	Based on a systematic review and indirect analysis exercise
Measure of health benefits	QALYs	QALYs
Source of data for measurement of QoL	Reported directly by patients and/or carers	Health-state descriptions derived from reviews of the literature and lay and professional focus groups
Source of preference data for valuation of changes in QoL	Representative sample of general public	Representative sample of general population
Discount rate	An annual rate of 3.5% on both costs and QALYs	An annual rate of 3.5% on both costs and QALYs (implemented monthly)
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit

of these factors have been considered by the AG in *Chapter 3, Quantity and quality of research available*. The AG is aware that the OS estimates for TRA + ANA used in the base case are the adjusted values; use of the RPSFT approach reduced the OS HR of TRA + ANA versus ANA. To date, the manufacturer has been unable to account for the second-line therapy imbalance using quantitative methods. As the Kaplan–Meier OS curves were not complete, parametric fitting of the curves was carried out to allow extrapolation beyond the follow-up period. The manufacturer concluded that the exponential distribution most accurately portrayed the OS curves of the two regimens for the time period beyond the availability of the Kaplan–Meier OS curves.

The AG considers that the manufacturer's approach to adjusting for cross-over in the TAnDEM⁵⁰ is limited and requires further exploration/justification before confidence can be placed in the OS results generated.

Indirect clinical evidence

As the manufacturer's systematic review found no network capable of linking all of the regimens in the population of interest, the manufacturer assumed that LET and ANA hold an 'AI class effect' in terms of PFS and OS and that the PFS and OS curves observed for ANA patients in the TAnDEM⁵⁰ trial would therefore hold for LET patients. In order to integrate the combination therapies into the evidence network, the manufacturer also assumed that HER2 status is independent of the relative treatment effect of the AI therapies. The AG's critique of the manufacturer's evidence approach to indirect analysis is discussed fully in *Chapter 3, Quantity and quality of research available*.

In summary, the AG is not confident that the results of the indirect comparisons analyses conducted by the manufacturer are reliable. Firstly, the EGF30008⁴⁹ trial is included in the network and this trial explicitly excludes patients who have extensive symptomatic visceral or rapidly progressing or life-threatening disease, which means that the patient populations in the EGF30008⁴⁹ and the TAnDEM⁵⁰ trials may not be comparable. Secondly, the AG agrees with

the manufacturer that ‘given ... mixing of heterogeneous populations, the results produced by the [indirect] analysis should be treated with caution’ (MS, p. 216). Specifically, the AG is of the opinion that inclusion of evidence derived from HER2– patients is inappropriate given that the decision problem is focused on treating women who are HER2+ and it is becoming apparent^{49,52} that an AI as monotherapy is less effective in women who are HER2+ than in women who are HER2–.

In summary, the AG considers that the submitted model results for the comparison of TRA + ANA versus ANA is the only comparison that is wholly valid to inform decision-making in this area.

Summary and critique: resource use and costs

The manufacturer presents a detailed and comprehensive description of resource use and costs used in the economic model. The cost categories are presented as follows: monthly drug costs, treatment duration, administration and monitoring costs, pharmacy preparation, response

TABLE 22 Key parameters used by Roche

Item	Cost (£)	Source
LAP ^a (250 mg)	11.49 per tablet purchased; 12.32 per tablet taken; 2249.53/month	BNF 59 ²⁸
LET ^a (2.5 mg)	2.38 per tablet purchased; 2.55 per tablet taken; 77.50/month	BNF 59 ²⁸
TRA ^b (150-mg vial)	1956.33/month (vial sharing used in model); 2230.16/month (full wastage)	BNF 59 ²⁸
ANA ^a (1 mg)	2.45 per tablet purchased; 2.62 per tablet taken; 79.90/month	BNF 59 ²⁸
ECHO/MUGA monitoring costs	46.31/month	Ward <i>et al.</i> ; ¹⁰⁷ NHS reference costs 2008–2009 ⁹⁹ (70%:30%, testing every 4 months)
Total subsequent monthly cost (administration, cardiac monitoring, pharmacy preparation)	92.99 (ANA/LET) 273.58 (LAP + LET) 297.87 (TRA + ANA)	NHS reference costs 2008–2009, ⁹⁹ PSSRU ¹⁰⁸ and Clinician Advisory Board
Progressive disease costs (second-line treatment with EXE monotherapy)	92.88	Roche Advisory Board; BNF 59 ²⁸
PFS BSC costs	192.83/month	NICE CG No. 81; ²³ PSSRU 2009 ¹⁰⁸
Post-progression BSC costs	542/month	NICE CG No. 81; ²³ PSSRU 2009 ¹⁰⁸
End-of-life costs	3418/last 14 days of life	NICE CG No. 81 ²³
Examples of AE costs		
Back pain	194	NHS reference costs 2008–2009 ⁹⁹ (PS05A)
Cardiac failure	370	NHS reference costs 2008–2009 ⁹⁹ (EB05Z)
Chest pain	400	NHS reference costs 2008–2009 ⁹⁹ (PA22Z)
Hypertension	560	NHS reference costs 2008–2009 ⁹⁹ (EB041)
Vomiting	553	NHS reference costs 2008–2009 ⁹⁹ (PA28B)
Utility values		
Cooper <i>et al.</i> ¹⁰⁹ /NICE ²³ (base case)	PFS = 0.73; PD = 0.45; SD = 0.65	
Hastings <i>et al.</i> ⁹⁶ (sensitivity analysis)	PFS = 0.86; PD = 0.62	

BNF, *British National Formulary*; BSC, best supportive care; CG, clinical guidance; EB041, Healthcare Resource Group (HRG) code for hypertension; EB05Z, HRG code for cardiac arrest; ECHO, echocardiogram; MUGA, multigated acquisition scan; PA22Z, HRG cost code for chest pain; PA28B, HRG code for feeding difficulties and vomiting without complications and comorbidities; PS05A, HRG code for developmental disorders with length of stay 1 day or less; PSSRU, Personal Social Services Research Unit; SD, stable disease.

a 6.72% of dispensed oral tablets are wasted (based on the TAnDEM⁵⁰ data).

b 80% of patients receiving TRA do so in vial sharing centres.

assessment, cardiac monitoring, PFS best supportive care, AEs, progressed disease costs and end-of-life costs. The key cost parameters used in the economic model are summarised in *Table 22*. In terms of costs, the key difference between the treatment regimens is the acquisition costs of the drugs (LAP and TRA are much more expensive than the AIs), followed by administration costs (i.v. TRA is much more expensive to administer than the other oral drugs) and finally, the costs of 'PD, BSC and second-line treatment' (post-PFS costs are higher for the patients taking LAP and TRA).

The AG notes that the economic evaluation in the MS uses a 3-weekly schedule for TRA; although this is not the weekly schedule used in the TAnDEM trial,⁵⁰ the AG agrees that the 3-weekly schedule is typically used in clinical practice in England and Wales.

Table 23 summarises the key costs that the AG believes the manufacturer could have considered in more detail in the MS.

Summary and critique: utilities and adverse events

The TAnDEM⁵⁰ conducted by Roche did not collect data using a generic health-utility instrument. In order to estimate utility values for HR+/HER2+ patients, the manufacturer undertook a focused review of the literature, identified 20 relevant studies (1996–2009) and presented utility values from six of these published studies (MS, p. 247). However, as no studies were identified as being relevant specifically to HR+/HER2+ patients, the manufacturer made a decision to use the assumptions of Winstanley and Murray in the recent breast cancer publication²³ and to apply utilities as identified by Cooper *et al.*;¹⁰⁹ this decision was made to ensure alignment with the most recent relevant piece of research²³ commissioned by NICE in breast cancer. In the sensitivity analysis, the manufacturer made use of the utility values cited by

TABLE 23 Examples of limited costing methods employed in MS by Roche

Assumption made	Limitation
Wastage (tablets)	Roche uses an average pill count per month to compare with a notional number of whole packs – this is not correct and underestimates wastage
Subsequent administration of TRA	Roche uses estimate from old interim local source instead of the correct NHS reference cost
Roche estimates drug costs per tablet purchased/taken which leads to inaccuracies	Only pack prices are available from the BNF 59 ²⁸ and drug usage would be more accurately costed accordingly
Roche assumes that delivery of TRA is always a day-case procedure and uses day-case costs	Depending on patient condition and local circumstance, delivery could be on an outpatient basis. A weighted average of outpatient and day-case costs would be more meaningful
Cardiac monitoring costs used in the economic model	In the base case, Roche assumes that cardiac monitoring occurs every 4 months and that MUGA and ECHO scans are used in unequal proportions (30%:70%). AG clinical advisors have stated that cardiac monitoring occurs every 3 months
MUGA cost = £316.64 based on uplifted cost from Ward <i>et al.</i> ¹⁰⁷	NHS reference costs 2008–2009; ⁹⁹ ^a RA37Z OP = £203.05 is more appropriate
AEs are limited and poorly described and sourced AE costs described by Roche appear to be underestimates	Examples: Back pain uses 'paramedic attendance' cost and ignores inpatient/outpatient/day-case episode costs In MS, hypercalcaemia cost is given hypertension cost (model); hypercalcaemia cost is not estimated in model

BNF, *British National Formulary*; ECHO, echocardiogram; MUGA, multigated acquisition scan; OP, outpatient; PSSRU, Personal Social Services Research Unit.

a This is the HRG code for RA37Z nuclear medicine category 3: procedures requiring diagnostic level radiation protection, technologist time of up to two hours, gamma camera with single photon emission computed tomography and/or medium isotope costs. For cardiac procedures, cardiology supervision is included.

Hastings *et al.*⁹⁶ in the indirect comparison of LAP + LET versus TRA + ANA. The values used by Hastings *et al.*⁹⁶ were derived via mapping FACT-G¹⁰¹ data collected in the EGF30008⁴⁹ trial to European Quality of Life-5 Dimensions (EQ-5D). Both sets of values are shown in *Table 22*. Disutility from AEs is not a feature of the economic model developed by Roche.

The Cooper *et al.*¹⁰⁹ paper pools utilities from many different sources (all derived from oncology nurses using the standard gamble technique). In contrast, the AG notes that the paper by Lloyd *et al.*,¹⁰⁴ identified by the manufacturer, asks 100 members of the general public to rank health states using the standard gamble technique to determine utility values. As the study by Lloyd *et al.*¹⁰⁴ is a large preference study designed to obtain UK-based societal preferences for distinct stages of mBC, the AG considers the paper by Lloyd *et al.*,¹⁰⁴ with caveats previously mentioned, to be the most useful evidence available that could help to inform the decision problem.

In the Roche model, only grade 3 or grade 4 AEs are considered. In the MS it is assumed that the AEs recorded for TRA + ANA are the same for LAP + LET and that the AEs recorded for ANA can be applied to LET. For comparison of TRA and LAP this seems unlikely as episodes of diarrhoea are reported more often for LAP patients. The AG also notes that the costs of several of the AEs listed in the MS (e.g. anaemia, cardiac failure, hypercalcaemia and hypertension) are not the cost inputs used in the economic model ('AE cost data'). In summary, the AG is of the opinion that the AE costs used in the economic model are underestimated and require revision to make them reliable.

Results: summary and critique

The manufacturer presents detailed summaries of estimated costs and outcomes (time in PFS, time in PD, life-years, QALYs in PFS, QALYs in PD and total QALYs) for the following regimens: TRA + ANA, LAP + LET, ANA monotherapy and LET monotherapy (*Table 24*). As there are four regimens of interest, the manufacturer has chosen to represent the results of the economic evaluation in terms of the efficiency frontier. The efficiency frontier links the regimens that are not dominated. *Figure 6* shows that, using this approach, LAP + LET does not lie on the efficiency frontier and that the key comparison is between TRA + ANA versus LET. When TRA + ANA is compared with LET, the ICER is estimated at approximately £54,336 per QALY gained. When TRA + ANA is compared with LAP + LET, it appears to be cost-effective.

Summary and critique: sensitivity analysis and probabilistic sensitivity analysis

Sensitivity analysis

Twenty-three different parameters were modified in the univariate sensitivity analysis. The results are presented only for the comparison of TRA + ANA versus LET. The base-case ICER was most sensitive to variation in PFS utility values (£50,099–£59,355) and the rate used to discount health outcomes (£48,664–£58,400).

TABLE 24 Incremental cost-effectiveness ratios (cost per QALY gained)

Total costs and QALYs	TRA + ANA	LAP + LET	ANA	LET
Total costs (£)	54,748.92	51,882.53	23,340.88	23,327.52
Total QALYs	1.87	1.71	1.29	1.29
ICER				
TRA + ANA vs LAP + LET	£17,914/QALY gained			
TRA + ANA vs ANA	£54,151/QALY gained			
TRA + ANA vs LET	£54,174/QALY gained			

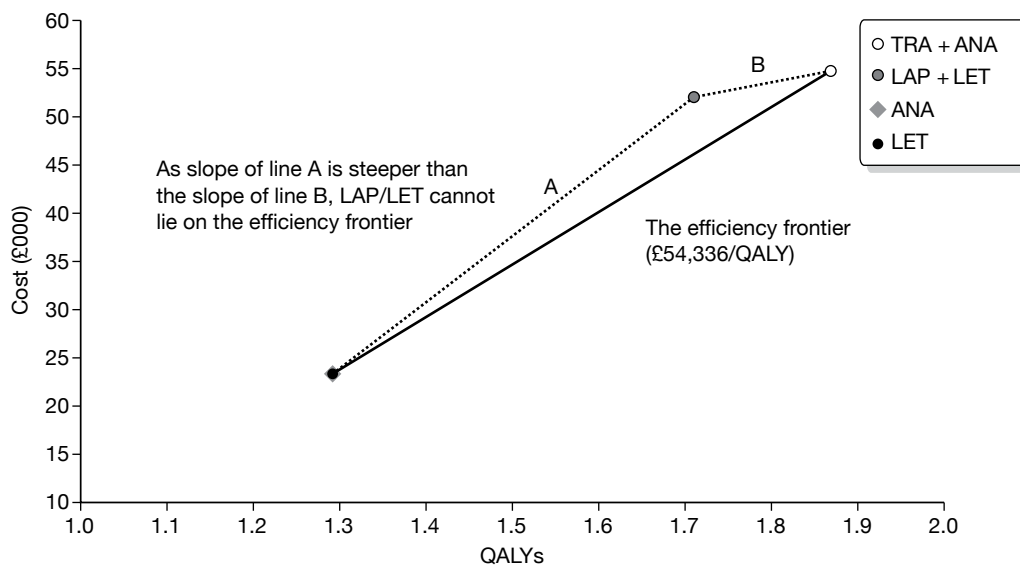


FIGURE 6 Cost-effectiveness plane.

Note: although ANA is, technically speaking, dominated by LET, it is only marginally more expensive, and in this diagram the separation between ANA and LET is indistinguishable.

The manufacturer also described three multivariate/scenario analyses. The implementation of the HRS derived from the indirect comparisons analysis for PFS and OS into the model (using the ANA curve from the TAnDEM50 as a baseline; the Roche analysis shows LET is slightly preferred to ANA) leads to a change in the efficiency frontier and the results are as follows: ANA represents a cost-effective option up to a threshold of £3594; LET is the most cost-effective option from £3594 to £57,773; >£57,773 TRA + ANA represents the most cost-effective treatment.

When pessimistic (PFS = 0.65; PD = 0.35) and optimistic (PFS = 0.8; PD = 0.55) utility values are used in the multivariate analysis, the ICER ranges from £48,715 to £62,239. The manufacturer estimates that the base-case ICER would fall to £44,497 if the utility values used in the Hastings *et al.*⁹⁶ paper are employed (these values do not fall within the $\pm 10\%$ of PFS and PD values used in the univariate sensitivity analysis).

Finally, the manufacturer attempts to account for the confounding influence of the imbalance in second-line chemotherapy in the TAnDEM⁵⁰ trial and demonstrates that the base-case ICER could fall to around £49,426.

Probabilistic sensitivity analysis

The PSA carried out by the manufacturer is summarised in the MS (p. 278). The CEAC (MS, p. 279) shows that at a threshold of £30,000 per QALY gained, the combination therapies (LAP + LET or TRA + ANA) are never cost-effective. At a threshold of £55,000 per QALY gained, TRA + ANA was shown to be cost-effective in approximately 35% of simulations (i.e. had a low probability of cost-effectiveness).

End-of-life treatment criteria: summary and critique

This section provides an overview and critique of the manufacturer's case for TRA + ANA as an end-of-life maintenance treatment for patients mBC. The NICE end-of-life treatment criteria have three key points:

- the treatment is indicated for patients with a short life expectancy, normally < 24 months, and
- there is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment, and
- the treatment is licensed or otherwise indicated for small patient populations.

Patient life expectancy of less than 24 months

The published literature¹¹⁰ on prognosis after a diagnosis of mBC, confirms that the disease is incurable and patient life expectancy is short. In a previous scope¹¹¹ issued by NICE (LAP for the treatment of previously treated women with advanced, metastatic or recurrent breast cancer), it was stated that ‘...The average life expectancy after diagnosis of mBC is 18–24 months. This is reduced by up to 50% for patients with tumours over-expressing HER2’.

The manufacturer cites data from the comparator (ANA) group of the TAnDEM⁵⁰ trial to support the argument that patients with mBC who are HR+/HER2+ have a very poor prognosis. Median OS is shown to range between 17.2 months (excluding all patients who crossed over) and be ≤ 32.1 months (excluding all patients with liver metastases); other OS estimates are also generated depending on the methodology used to undertake survival analysis (Table 25). The AG notes that although data from the EGF30008⁴⁹ trial show that patients with mBC who are HR+/HER2+ have a median OS of 33.3 months, this trial explicitly excludes patients who have extensive symptomatic visceral or rapidly progressing or life-threatening disease. The AG acknowledges that use of second-line therapies may also influence estimates of OS.

Life extension of at least 3 months

The manufacturer attempts to demonstrate that there is sufficient evidence from the TAnDEM⁵⁰ trial to indicate that TRA + ANA offers an extension to life of at least an additional 3 months, compared with current NHS treatment. In the TAnDEM trial,⁵⁰ unadjusted median OS gained and RPFST-adjusted median OS gained were estimated to be 4.6 months and 6.54 months, respectively.

The AG is of the opinion that TRA + ANA compared with ANA yields a life extension of at least 3 months for patients who are HR+/HER2+ and who have had no prior treatment for mBC.

Licensed for a small patient population

The size of the patient population eligible for treatment with TRA + AI in England and Wales, i.e. women with HR+/HER2+ mBC, is estimated to be around 50 patients by both GlaxoSmithKline and Roche. However, TRA has indications in mBC, metastatic gastric cancer and early breast cancer. The manufacturer reports that, in England and Wales, across all the indications, 7158 patients are eligible to receive TRA each year (2333 from mBC, 506 from metastatic gastric cancer and 4319 from early breast cancer). It was difficult for the AG to verify these population figures as the references cited were not included in the references package as part of the MS; the data were from pharmaceutical company reports that the AG could not easily access.

TABLE 25 Overall survival (AI monotherapy)

Trial	Median OS: ANA Unadjusted	Median OS: ANA Centrally confirmed status	Median OS: ANA RPFST-adjusted	Median OS: ANA Excluding all patients who crossed over	Median OS: LET
TAnDEM ⁵⁰	23.9 months	28.6 months	21.98 months	17.2 months	n/a
EGF30008 ⁴⁹	n/a	n/a	n/a	n/a	33.3 months

n/a, not applicable.

Conclusions of the Assessment Group

From the information presented in the MS, the AG agrees with the manufacturer that TRA + ANA is not cost-effective when compared with ANA. The AG also considers that the methods used in the indirect analysis undertaken by the manufacturer are unreliable and concludes that the ICERs derived from the remaining comparisons (TRA + ANA vs LET; TRA + ANA vs LAP + LET) are not meaningful.

The manufacturer submitted a case for TRA + ANA to be considered as an end-of-life treatment for women with HR+/HER2+ mBC. The AG agrees that TRA + ANA meets the criteria as a treatment for patients with a short life expectancy and that it extends life by an additional 3 months when compared with current NHS treatment. However, the AG makes no comment on whether or not the criterion of a small patient population is met.

Independent economic assessment

Each of the novel treatment regimens considered in this AG report relies on clinical evidence derived from a single small RCT (the EGF30008⁴⁹ or the TAnDEM⁵⁰ trial). Moreover, the comparator treatments differ between these trials, albeit both drugs were drawn from the same class of compounds. These disparities alone suggest the need for caution when generalising these results of the RCTs. However, an even greater difficulty arises if the two study populations do not appear to match.

As discussed in earlier sections, there is reason to believe that, in some important respects, the protocol criteria governing the selection of subjects for these two trials were sufficiently dissimilar as to be likely to generate non-equivalent patient populations. In particular, the requirement in the EGF30008⁴⁹ trial to exclude patients with extensive symptomatic visceral disease including rapidly progressing or life-threatening disease is not explicitly matched by a similar exclusion in the TAnDEM⁵⁰ protocol.

As a result, it is reasonable to expect that patients in the EGF30008⁴⁹ trial may have been somewhat fitter and with better prognoses than those recruited into the TAnDEM trial.⁵⁰ However, direct comparison of patient characteristics in the trials is restricted by differences in how measures were defined and/or reported in the two CSRs. Tables setting out the number and location of metastatic lesions at baseline in the two trials are available. However, they cannot be compared with full confidence as they are defined somewhat differently. There is strong evidence of a significant difference in the mean age of the populations. There is also evidence of a greater incidence of soft-tissue metastases in the TAnDEM⁵⁰ trial patients (43.5% vs 30.14%, $p = 0.004$), although metastases at other sites are broadly comparable. Overall, the frequency of metastatic sites affected per patient (1.77 in the EGF30008⁴⁹ vs 2.40 in the TAnDEM⁵⁰ trial) also suggests more severe advanced disease in the TAnDEM⁵⁰ patients, although this could be an artefact of differing reporting methods.

Coupled with the serious problems identified in earlier sections relating to the indirect comparison of treatment effects, these uncertainties led the AG to conclude that although two separate assessments of cost-effectiveness, each based on one of the principal RCTs, could be undertaken with some confidence, the evidence base is too insecure to allow a meaningful comparison of the two innovative compounds against each other. In this section, two separate cost-effectiveness analyses are reported, using a common modelling framework and common parameter values, but employing effectiveness data drawn from only a single RCT (either the TAnDEM⁵⁰ or the EGF30008⁴⁹ trial).

Methods: common model features and parameters

Model design

A common model structure has been adopted for both de novo cost-effectiveness analyses (Figure 7) and, wherever possible, has been implemented using the same parameter values. The de novo model employs outcome data derived from the relevant clinical trial in the form of Kaplan–Meier estimated survival values augmented by projected survival estimates calibrated against the observed data. The preferred approach uses PFS and PPS estimates directly as the basis for calculating expected OS in each group of the RCT. PFS and PPS values then furnish the information required to calculate all components of health service costs and also to estimate the expected future patient utility. These survival estimates are calculated separately for each date on which a resource is expected to be used (e.g. when prescriptions are dispensed or when a hospital visit or test takes place), avoiding the need for a general model cycle or for mid-cycle corrections.

Both of the manufacturers' models use PFS and OS as the primary sources for survival information, and derive time in PPS as the difference between OS and PFS. The AG finds this approach generally liable to generate substantial bias in OS estimates when projective parametric modelling is used. This is because recorded OS data are a result of combining patient experience in two distinct phases in which hazard rates would be expected to exhibit quite different dynamics (in PFS the patient is likely to have reduced event risks although the active drug continues to be effective, but in PPS event risks are more likely to revert to higher levels of uncontrolled disease progression). In most cases, standard parametric statistical models cannot accurately represent an outcome measure (such as OS) which is a compound of two very different processes, and modelled OS projected over several decades can result in very large cumulative errors. By contrast, in advanced disease the risk profile of patients entering PPS is usually quite stable and allows projective modelling with greater confidence [i.e. narrow confidence intervals (CIs)] and limits the risk of some of the more extreme estimates of long-term survival which can occur when modelling OS directly. At a pragmatic level, deriving PPS as the difference between OS and PFS can sometimes lead to modelling anomalies with negative estimates of PPS during projection, an error which cannot occur when PFS and PPS estimates are summed.

Undiscounted and discounted (3.5% per annum for costs and outcomes) deterministic results were generated for each year of remaining life up to 30 years. A PSA was carried out for all model variables for which sampling uncertainty could be estimated, and a range of univariate sensitivity analyses were performed for other variables and assumptions.

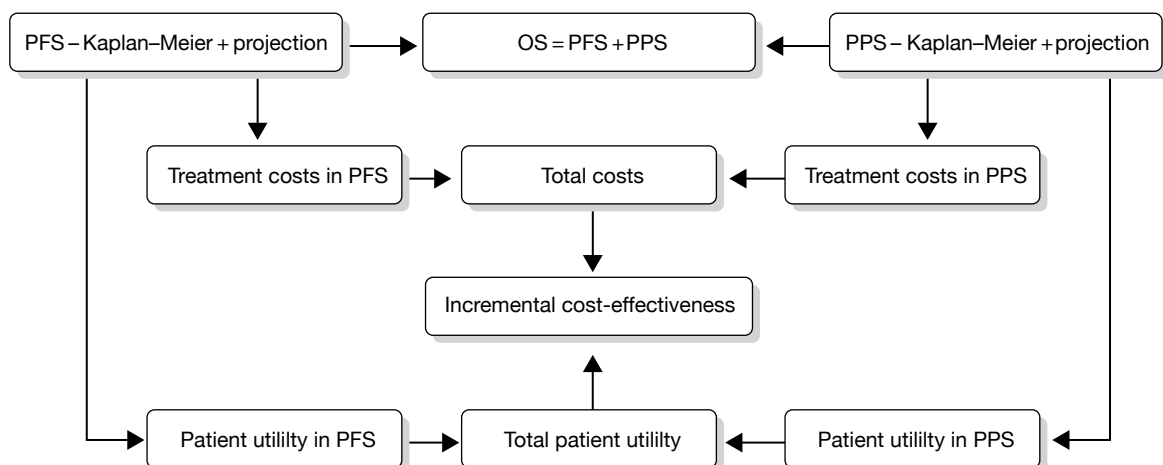


FIGURE 7 A schematic of the AG's model structure for each treatment option.

Cost parameter values

Model costing variables common to both models are listed in *Table 26* with the parameter values used in the base-case analyses and the data sources employed.

Patient utility valuation

The AG considered a number of sources for utility values for breast cancer patients referenced by the manufacturers and conducted an exploratory (but not systematic) search which failed to identify any useful additional material. Overall, there appears to be a particular dearth of relevant utility studies appropriate to this appraisal and conforming to the NICE recommended⁹⁷ approach (UK data capturing population preferences using EQ-5D or either time trade-off or standard gamble methodology). Several standard gamble studies have been reported, but normally use a very small sample of health professionals to assess quite general health states, not particularly focused on advanced disease. The AG concluded that the best available option was the study reported by Lloyd *et al.*¹⁰⁴ published in 2006, which considered health states and a limited set of treatment-related AEs specific to mBC, and developed a mixed model using data collected from a sample of 100 UK residents broadly similar in age and gender to the general population. The values presented have face validity for both absolute values and interstate differences. The particular benefit is that they furnish an integrated system of utility estimates (rather than adopting values from disparate sources as is often the case).

The Lloyd *et al.*¹⁰⁴ model includes age and treatment response as model variables. However, it is important to note that the relevant age is not that of the patient, but of the study participant. To ensure consistency with the UK EQ-5D standard value scheme, the AG adopted the average age of respondents to the original multivessel disease study¹¹² of just over 47 years in arriving at utility

TABLE 26 Costing parameter values and sources common to both AG economic models

Cost item	Value	Source
Pharmacy dispensing costs (£)	9.00 from hospital pharmacy 6.90 from community pharmacy	Roche MS, based on hourly cost of pharmacist time ¹⁰⁸ and 12 minutes per script dispensed
Frequency of cardiac monitoring	Every 3 months	Clinical advisor opinion
ECHO : MUGA proportion of cardiac scans	70 : 30	Clinical advisor opinion
Unit cost per ECHO scan (£)	74.37	NHS reference costs 2008–2009, ⁹⁹ direct access diagnostics code DA02
Unit cost per MUGA scan (£)	203.05	NHS reference costs 2008–2009, ⁹⁹ OP nuclear medicine code RA37Z
Frequency of OP follow-up (including CT scan) in PFS	Every 3 months	Clinical advisor opinion
Unit cost per OP follow-up visit (£)	98.51	NHS reference costs 2008–2009, ⁹⁹ consultant-led follow-up attendance, non-admitted, face to face, code 800 (clinical oncology)
Unit cost per CT scan (£)	138.27	NHS reference costs 2008–2009, ⁹⁹ code RA12Z – OP CT scan (two areas with contrast)
Annual cost of BSC in PFS (£)	1831.54	NICE guideline, ²³ updated for inflation ¹⁰⁸
Annual cost of BSC in PPS (£)	5597.82	NICE guideline, ²³ updated for inflation ¹⁰⁸
Terminal care costs (last 2 weeks of life) (£)	1788.55	Remak and Brazil, ¹⁰⁰ updated for inflation ¹⁰⁸
Unit cost of EXE (per 30-tablet pack) (£)	88.80	BNF 59 ²⁸
Wastage per patient (half pack) (£)	44.40	BNF 59 ²⁸
Proportion of PPS patients receiving EXE (%)	50	Modelling assumption
Discounting rate (costs)	3.5% per annum	NICE methods guide ⁹⁷
Discounting rate (outcomes)	3.5% per annum	NICE methods guide ⁹⁷

BNF, *British National Formulary*; BSC, best supportive care; CT, computed tomography; ECHO, echocardiogram; MUGA, multigated acquisition scan; OP, outpatient.

parameter values. For patients who are pre-progression it was necessary to calculate a weighted average of the model values for stable disease and treatment response, based on the reported response rate (CR + PR) in each group of each trial (see *Specific model features and parameters: lapatinib in combination with letrozole versus letrozole alone* and *Specific model features and parameters: trastuzumab in combination with anastrozole versus anastrozole alone*). A common health-state utility value was obtained for post-progression patients of 0.496 [standard error (SE) 0.160] for use in both models.

Specific model features and parameters: lapatinib in combination with letrozole versus letrozole alone

The manufacturer of LAP provided full details of survival analyses (PFS, PPS and OS) requested by the AG relating to data from the EGF30008 trial.⁴⁹ The AG employed these data to estimate the components of mean survival that could be expected over the lifetime of a patient, the results of which are presented below. Note that these may differ in detail from those generated by the AG model because of the approximations required to implement the continuous mathematical survival functions in a structure designed around discrete cycle periods.

Expected progression-free survival

Examination of the Kaplan–Meier estimates of PFS over time (data provided in confidence) shows an early advantage for the combination therapy (LAP + LET) compared with LET alone, but also indicates that this benefit steadily eroded over time until the two treatments were indistinguishable beyond about 16 months. The AG decided that the most reliable estimate of the mean expected PFS would be obtained by using the difference between the Kaplan–Meier AUC estimates up to the time of convergence (505 days). Thereafter, a single exponential model of PFS was applied to both the intervention and the comparator in the AG model, calibrated on pooled Kaplan–Meier data for the period > 500 days.

This approach yielded estimates of PFS up to 505 days:

- 198.5 (SE 17.6) PFS days for LET only
- 266.2 (SE 16.1) PFS days for LAP + LET,

i.e. a gain of 67.6 (SE 16.9) PFS days attributable to the use of LAP.

For the period beyond 505 days, a further 67.8 (SE 5.0) days PFS must be applied to all patients irrespective of treatment to obtain the overall mean PFS estimates per patient:

- 266.4 (SE 18.3) PFS days for LET only
- 334.0 (SE 16.9) PFS days for LAP + LET.

Expected post-progression survival

Examination of the Kaplan–Meier analysis of PPS in the EGF30008⁴⁹ trial indicated that following disease progression, patients in both groups of the trial were at the same risk of death, which appears to be constant over time. Therefore, a single exponential model was calibrated from the pooled trial data for use in the AG model, yielding an estimated mean survival for patients in PPS of 764.8 (SE 5.0) days. This is applied only to patients whose progression event is non-fatal.

Expected overall survival

As no cross-over following disease progression was permitted in the EGF30008 trial,⁴⁹ and there is no evidence of significant imbalance in post-progression therapies, no further adjustments to PFS and PPS estimates are necessary.

The best estimate of OS is obtained by summing PFS and PPS, after adjusting PPS to exclude patients dying at or before disease progression:

- 1009.6 (SE 18.9) OS days for LET only
- 1050.6 (SE 17.6) OS days for LAP + LET,

i.e. a gain of 41.0 (SE 25.8) OS days attributable to the use of LAP.

Patient utility values

Health-state utility values for patients in PFS, obtained from the Lloyd *et al.*¹⁰⁴ model, differ slightly between the EGF30008⁴⁹ groups because of differential treatment response rates:

- 0.7749 (SE 0.1125) in the LET group
- 0.7794 (SE 0.1118) in the LAP + LET group.

Adverse events

Examining the incidence of the six grades 3/4 AEs featured in the Lloyd *et al.*¹⁰⁴ model (fatigue, diarrhoea/vomiting, stomatitis, febrile neutropenia, hand-foot syndrome and alopecia), showed generally low incidence in all categories with the exception of diarrhoea/vomiting, which was six times more common in the combination group than the LET group. However, the absolute difference in estimated utility per study patient is very small (<0.01) with a wide CI, so the AG decided to examine the influence of the disutility of this AE through sensitivity analysis rather than through setting a value in the base case. A similar approach was taken to the differential cost per patient of AEs.

Cost of lapatinib: acquisition

The acquisition cost of LAP is £804.30 per pack of 70 tablets. The standard dose requires patients to take six tablets per day. In the AG model it is assumed that LAP is prescribed to non-progressed patients every 28 days, with sufficient packs to complete treatment for the next 4 weeks (taking account of any unused tablets from previous prescriptions). This requires two or three packs to be prescribed at each visit. Wastage is automatically included in this calculation as the dispensed tablets are unused at the time of progression (14 days' supply on average), and no mid-cycle correction is necessary. It is assumed that prescriptions will be dispensed by a hospital pharmacist.

Cost of letrozole: acquisition

The acquisition cost of LET is £66.50 per pack of 28 tablets. It is assumed that one pack is dispensed every 28 days to all patients remaining in PFS on that day. This implies that wastage is limited to an average 14 days of treatment per patient. It is assumed that prescriptions will be dispensed by a community pharmacist, except for the first prescription, which is provided in the hospital.

Actual and expected delivery of treatment

Information provided by the manufacturer of LAP indicates that adjustments made to the dose intensity of treatments in the EGF30008⁴⁹ trial were based on similar pill counts to those discussed in the next section in relation to ANA. The AG has no reason to consider these data are any more reliable than those for ANA, which were assessed at the individual patient level. The AG, therefore, decided not to make adjustments to calculations based on 100% compliance with the treatment protocol. This ensures a consistent approach in both appraisals.

Specific model features and parameters: trastuzumab in combination with anastrozole versus anastrozole alone

Expected progression-free survival

The manufacturer of TRA provided full details of the survival analyses (PFS, PPS and OS) requested by the AG relating to data from the TAnDEM trial.⁵⁰ The AG employed these data to estimate the components of mean survival that could be expected over the lifetime of a patient, the results of which are presented below. Note that these may differ in detail from those generated by the AG model because of the approximations required to implement the continuous mathematical survival functions in a structure designed around discrete cycle periods.

Examination of the cumulative hazard plots for PFS suggested an early relatively high risk of progression, followed by a more regular slowly reducing hazard trend in both trial groups. It was found that a two-parameter Weibull model offered an acceptable representation of the long-term trend in both groups (using data provided in confidence). The AG decided that the most reliable estimate of the mean expected PFS would be obtained by using the Kaplan–Meier AUC estimate up to the last recorded event in each group, and then adding the area under the projected long-term Weibull model curve at later times.

This approach yielded estimates of:

- 189.6 (SE 21.4) PFS days for ANA only
- 514.8 (SE 64.1) PFS days for TRA + ANA,

i.e. a gain of 325.1 (SE 67.6) PFS days attributable to the use of TRA.

Expected post-progression survival

Examination of the cumulative hazard plots for PPS indicated that disease progression was not associated with any variation in risk away from a continuous long-term trend. However, analysis confirmed that simple exponential models (i.e. linear trends in cumulative hazard) were not adequate to describe the observed PPS data. Two-parameter Weibull models were fitted to data from both trial groups and offered an acceptable representation. The AG decided that the most reliable estimate of the mean expected PPS would be obtained by using the Kaplan–Meier AUC estimate up to the last recorded event in each group, and then adding the area under the projected long-term Weibull model curve at later times.

Using this approach generated estimates of:

- 869.6 (SE 46.3) PPS days for ANA only
- 649.6 (SE 63.1) PPS days for TRA + ANA,

i.e. a loss of 220.0 (SE 78.3) PPS days attributable to the use of TRA.

Expected overall survival

By combining estimates of mean PFS and mean PPS in each group and adjusting for the minority of patients who die at or before progression (5.77% in the ANA group and 5.83% in the TRA + ANA group), combined estimates for OS were obtained:

- 1009.0 (SE 50.5) OS days for ANA only
- 1126.5 (SE 85.6) OS days for TRA + ANA,

i.e. a gain of 117.5 (SE 100.9) OS days attributable to the use of TRA.

The manufacturer of TRA has drawn attention to two factors in the TAnDEM⁵⁰ trial that are considered likely to distort the estimation of PPS in the comparator group:

1. a large number of patients in the comparator (ANA) group chose to 'cross over' to TRA + ANA therapy following disease progression and are likely to gain additional benefit in terms of extended PPS
2. a greater proportion of patients in the comparator group received second-line chemotherapy, also potentially extending PPS.

In the MS, the results of applying a statistical technique to attempt to counter the first of these confounding factors were presented, but no attempt was made to make any further adjustment to overcome the second-line chemotherapy imbalance.

As discussed in *Chapter 3, Assessment of effectiveness*, the suggested statistical adjustment is not universally accepted as the most suitable method to employ and may rely on restrictive assumptions that are not valid for use in the TAnDEM trial.⁵⁰ The AG asked for additional survival analyses to be undertaken in order to explore the sensitivity of OS estimates to other approaches to correcting PPS for crossover and imbalance in second-line chemotherapy; how the results of the survival analyses were used by the AG are discussed below.

Crossover: Separate Kaplan–Meier analyses of patients in the comparator group of the TAnDEM trial,⁵⁰ split by whether or not they did or did not receive crossover TRA following progression, demonstrated a clear advantage for crossover patients. However, the data suggest that, after about 6 months has elapsed, this advantage diminishes, and it disappears altogether after about 3 years. The AG found that these complex trends in PPS could be well described by fitting bi-phase exponential models, from which it is possible to estimate the mean survival gain attributable to crossover for patients in the post-progression phase.

The net benefit of crossover (i.e. the area between the two modelled PPS lines) is estimated as 150.5 days. However, this advantage only accrues to those patients who do not die at or before progression (94% of the total), so that the mean PPS adjustment which may be subtracted in the calculation of OS in the control group is 141.8 (SE 12.8) days.

Second-line chemotherapy: Four Kaplan–Meier analyses of the TAnDEM⁵⁰ patients, stratified by treatment group and post-progression use of second-line chemotherapy, were compared. No clear distinctions were apparent, though in both trial groups those receiving second-line therapy seemed to have a modest advantage. Generally, the hazard time profiles did not markedly differ from linearity indicating that an exponential parametric model would be appropriate. The AG chose to compare all patients receiving second-line chemotherapy to all patients who did not, recognising that this is necessarily only an exploratory analysis lacking a full standardisation. However, in view of the small numbers of patients in each stratum, more detailed analysis would most likely be unproductive. Exponential survival parameters were estimated suggesting a HR of 0.83 in favour of chemotherapy and a gain in PPS of 145.2 (SE 31.1) days. This figure must be adjusted for three factors:

1. the difference in the use of second-line chemotherapy between the trial groups is 24% (32% – 8%)
2. examination of the trial data indicated that the majority (82%) of chemotherapy patients also benefited from crossover TRA, and for these patients the effect of chemotherapy is already included in the crossover adjustment discussed above
3. the absolute difference in PPS only applies to patients who did not die at or before disease progression.

The net effect of these adjustments is an estimated additional second-line chemotherapy gain in PFS in the comparator group of 5.9 (SE 1.2) days.

When the adjustments for crossover and chemotherapy are included, the following final estimates for OS were obtained:

- 861.4 (SE 52.1) OS days for ANA only
- 1126.5 (SE 87.3) OS days for TRA + ANA,

i.e. a gain of 265.1 (SE 101.7) OS days attributable to the use of TRA.

Patient utility values

Health-state utility values for patients in PFS obtained from the Lloyd *et al.*¹⁰⁴ model, differ slightly from the TAnDEM⁵⁰ groups because of differential treatment response rates:

- 0.7639 (SE 0.1139) in the ANA group
- 0.7687 (SE 0.1133) in the TRA + ANA group.

Adverse events

Examining the incidence of the six grades 3/4 AEs featured in the Lloyd *et al.*¹⁰⁴ model (fatigue, diarrhoea/vomiting, stomatitis, febrile neutropenia, hand-foot syndrome and alopecia) showed very low incidence in all categories and no significant differences on which to base any estimate of differential disutility from AEs for this comparison; the AG decided to examine the potential importance of this issue via sensitivity analysis. A similar approach was taken to the differential cost per patient of AEs.

Cost of trastuzumab: acquisition and administration

The cost of TRA treatment was estimated using the distribution of body weight recorded at baseline in the TAnDEM trial.⁵⁰ These data indicated that a log-normal distribution was appropriate and parameters were estimated by the method of moments (i.e. a weighted average of the individual doses and vials of TRA which would be required to treat the population of patients without vial sharing was estimated). This calculation automatically incorporated drug wastage. For the initial loading dose (8 mg/kg), the cost per dose was estimated as £1657.86 and for a regular dose (6 mg/kg) the cost per dose is £1292.88. These costs were applied to all patients remaining in PFS at the beginning of each 3-week period.

The costs of administering TRA are derived from the *NHS reference costs 2008–2009*,⁹⁹ using average costs for day cases and outpatient weighted by national activity levels. For the loading dose, this uses Healthcare Resource Group code SB14Z, and for the regular dose, code SB12Z, as specified in clinical coders guidance.¹¹³ The unit cost per treatment is £284.66 (loading dose) and £198.63 (regular doses).

Cost of anastrozole: acquisition

The acquisition cost of ANA is £68.56 per pack of 28 tablets. It is assumed that one pack is dispensed every 28 days to all patients remaining in PFS on that day. This implies that wastage is limited to an average of 14 days of treatment per patient. It is assumed that prescriptions will be dispensed by a community pharmacist, except for the first prescription which is provided in the hospital.

Actual and expected delivery of treatment

In their submitted model, the manufacturer of TRA adjusted the quantity of each treatment by a multiplier to represent the ratio of treatment actually received by patients and that expected

during their time in PFS. This seems to be a compound of patient compliance, missed doses, dose adjustments and the lack of precision in the estimation of treatment volumes in their model. For TRA infusions this factor has a minor effect ($\times 0.987$), but the effect is more pronounced for ANA. The AG considered this issue carefully on the basis of the detailed individual treatment records included in the TAnDEM CSR.⁵⁰ In the case of TRA infusions, there are almost no occasions when scheduled infusions were not administered on time and at the prescribed dose. A few instances of a missed appointment (e.g. at Christmas holiday) were generally followed by a double dose administered at the next scheduled visit. It appears, therefore, that the trial data do not support the notion that there is any serious systematic discrepancy between planned and administered delivery of TRA. There may be some merit in a minor adjustment in the submitted model to take account of the approximation involved in estimating PFS at monthly intervals, but this problem does not arise in the AG's model which calculates PFS daily.

For ANA, the estimation of an adjustment factor appears to have been based on estimated compliance data using pill counts undertaken during the trial. The individual patient data track the issue of tablet packs at each patient visit and the number of tablets returned unused at the following visit. These data reveal that the method of calculating compliance is fundamentally unsound, as it takes no account of the occasional failure of patients to return unused tablets during the dosing period and a systematic failure to return unused tablets at the end of treatment. As a consequence, individual compliance figures ranging between 32% and 300% were estimated. Closer examination of individual patients' drug issues and returns shows a generally exemplary adherence to schedule in all patients.

The AG is satisfied that there is no evidential basis for making any adjustments to the calculated expected use of either treatment on the grounds of deviation from treatment protocol, or to correct for approximations arising from the model structure, as the AG model is designed to avoid such problems.

Results

The results obtained from modelling the costs and outcomes of each of the trial-based appraisals are shown separately in this section. No attempt has been made to make any comparisons between the groups of the two trials, as the populations are not considered to be directly comparable and reliable indirect comparisons of treatment effects could not be undertaken (see *Chapter 3, Quantity and quality of research available*). Therefore, the only questions that may be addressed legitimately are as follows.

1. Can LAP + LET be considered a cost-effective alternative to LET alone?
2. Can TRA + ANA be considered a cost-effective alternative to ANA alone?

Base-case result: lapatinib in combination with letrozole versus letrozole alone

The base-case cost-effectiveness results based on the AG model are shown in *Table 27*. A small expected mean health gain per patient (2 months' life extension and < 0.12 additional QALYs) is generated by an additional cost of $> \pounds 25,000$ per patient, most of which is incurred in the first 5 years. The cost-effectiveness ratio is stable over long time periods and exceeds $\pounds 225,000$ per QALY gained.

Univariate sensitivity analysis

Results from a sensitivity analysis covering the main model variables are shown in *Table 28*. The ICER is most sensitive to the health-state utility parameter values and to the cost of LAP, but is insensitive to most of the other variables. In all cases, the ICER remains $> \pounds 141,000$ per QALY,

TABLE 27 Cost-effectiveness results for base-case analysis of LAP + LET versus LET (discounted) using the AG's model

Treatment	Cost per patient (£)						Outcomes per patient		ICER
	Drugs	Monitoring	AEs	BSC	Terminal care	Total costs	Life-years	QALYs	£/QALY gained
<i>LET</i>									
10	685	702		12,485	1633	15,506	2.539	1.238	
20	686	702		12,620	1653	15,661	2.562	1.247	
30	686	702		12,621	1653	15,662	2.562	1.247	
<i>LAP + LET</i>									
10	26,051	1446	98	12,435	1620	41,650	2.704	1.354	
20	26,052	1446	98	12,574	1641	41,811	2.727	1.363	
30	26,052	1446	98	12,575	1641	41,812	2.728	1.363	
<i>Incremental</i>									
10	25,366	744	98	-51	-13	26,144	0.165	0.116	225,676
20	25,366	744	98	-46	-12	26,150	0.166	0.116	225,131
30	25,366	744	98	-46	-12	26,150	0.166	0.116	225,127

BSC, best supportive care.

TABLE 28 Univariate sensitivity analysis of the cost-effectiveness results of LAP + LET versus LET to variations in main variables in the AG's model (base case with a 20-year time horizon)

Model variable	Variation in value		ICER (£) for	
	Low	High	Low	High
Base case				225,131
Discount rate: costs	0%	6%	228,880	222,701
Discount rate: outcomes	0%	6%	219,215	228,988
Dispensing costs: community	£5	£10	225,087	225,210
Dispensing costs: hospital	£7	£11	224,912	225,351
Frequency of cardiac monitoring (per annum)	3	6	224,331	227,037
ECHO as % of scans	50	100	226,136	223,625
Frequency of PFS follow-up and CT scan (per annum)	2	6	223,912	226,080
Proportion of progressed patients on EXE	0%	100%	225,666	224,596
Net extra cost of AEs in LAP + LET group	£0	£1000	224,284	232,761
Net extra disutility of AEs in LAP + LET group	0	-0.01	211,246	229,503
Utility in PFS: LET only	-10%	+10%	157,265	396,037
Utility in PFS: LAP + LET	-10%	+10%	549,154	141,589
Utility in PFS: both groups	-10%	+10%	267,536	194,330
Utility in PPS	-10%	+10%	219,375	231,198
Acquisition cost of LAP	-10%	+10%	203,605	246,658
Cost of cardiac scan	-10%	+10%	224,710	225,553
BSC annual costs	-10%	+10%	225,118	225,145
Terminal care costs	-10%	+10%	225,142	225,121

BSC, best supportive care; CT, computed tomography; ECHO, echocardiogram.

indicating that uncertainty in any single parameter value is unlikely to alter the cost-effectiveness of LAP + LET relative to conventional thresholds.

Probabilistic sensitivity analysis

Probabilistic sensitivity was explored, running 1000 random iterations for all variables subject to measurable parameter uncertainty, using the base-case scenario over a 20-year time horizon. The PSA results are compared with the corresponding deterministic results in *Table 29*.

The scatterplot of iteration results in the cost-effectiveness plane as shown in *Figure 8*, the scatterplot, indicates that all iterations lie substantially outside the region normally considered cost-effective. *Figure 9* confirms that the probability of the combination therapy being cost-effective at a willingness-to-pay threshold of £50,000 per QALY gained is 0.1%, and does not reach 50% probability until £231,000 per QALY gained.

Base-case results: trastuzumab in combination with anastrozole versus anastrozole alone

The base-case cost-effectiveness results based on the AG model are shown in *Table 30*. A modest expected mean health gain per patient (< 8 months' life extension and about 0.5 additional QALYs) is generated by a substantial additional cost of > £35,000 per patient, most of which is incurred in the first 5 years. The cost-effectiveness ratio is stable over long time periods and exceeds £69,000 per QALY gained.

TABLE 29 Comparison of deterministic and probabilistic cost-effectiveness results for LAP + LET versus LET (base case with a 20-year time horizon)

Sensitivity analysis	Incremental cost (£)	Incremental QALYs	ICER (£)
Deterministic	25,150	0.116	225,131
Probabilistic	25,034	0.109	228,913

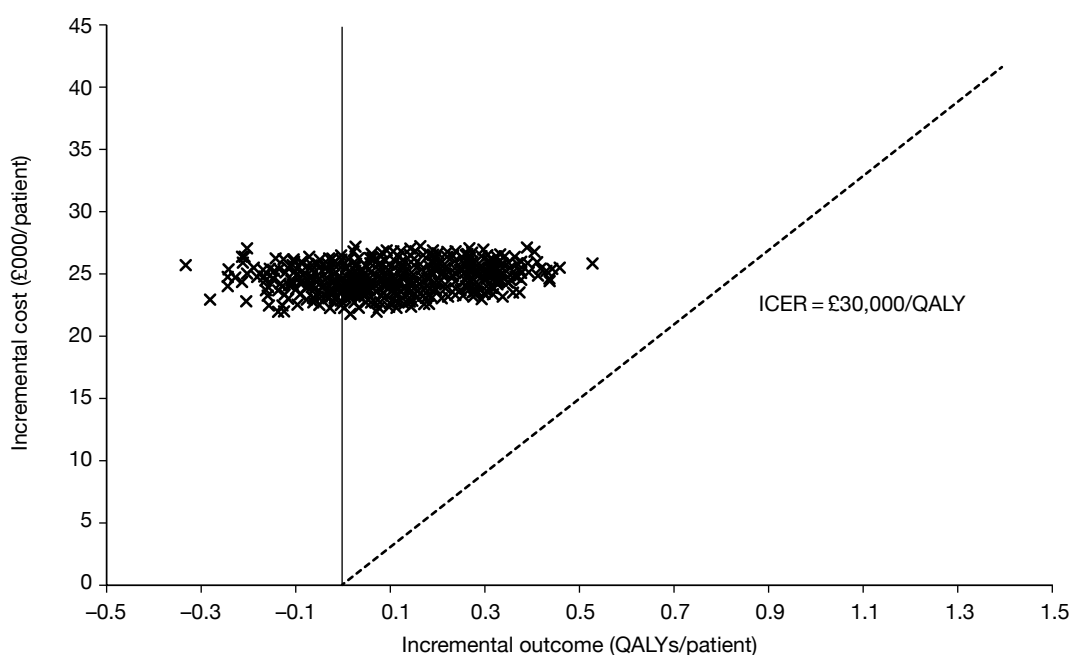


FIGURE 8 Probabilistic sensitivity analysis of LAP + LET versus LET only: scatterplot of 1000 probabilistic iterations.

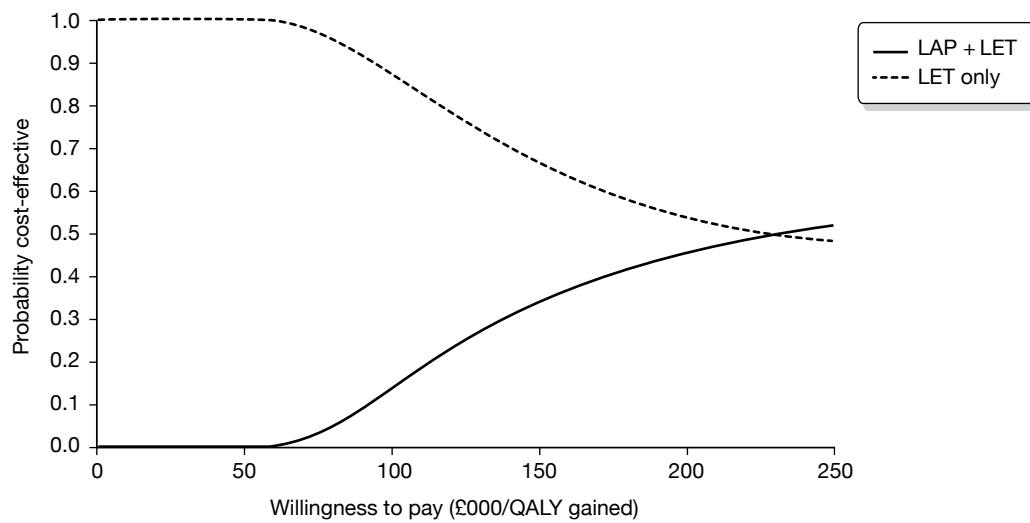


FIGURE 9 Probabilistic sensitivity analysis of LAP + LET versus LET only: CEAC.

TABLE 30 Cost-effectiveness results for base-case analysis of TRA + ANA versus ANA (discounted) using the AG's model

Treatment	Cost per patient (£)					Outcomes per patient			ICER
Time horizon (years)	Drugs	Monitoring	AEs	BSC	Terminal care	Total costs	Life-years	QALYs	£/QALY gained
ANA									
10	549	602		11,101	1632	13,884	2.204	1.235	
20	549	602		11,194	1647	13,992	2.220	1.243	
30	549	602		11,194	1648	13,993	2.220	1.243	
TRA + ANA									
10	35,197	1843	90	11,875	1695	50,699	2.848	1.757	
20	36,251	1898	92	11,953	1696	51,891	2.888	1.788	
30	36,370	1905	93	11,961	1696	52,025	2.893	1.791	
Incremental									
10	34,648	1241	90	774	63	36,815	0.644	0.522	70,463
20	35,702	1297	92	759	49	37,899	0.669	0.545	69,514
30	35,821	1303	93	767	49	38,032	0.673	0.549	69,333

BSC, best supportive care.

Univariate sensitivity analysis

Results from a sensitivity analysis covering the main model variables are shown in *Table 31*. The ICER is most sensitive to the health-state utility parameter values, to the cost of TRA and to discounting rates, but very insensitive to most of the other variables. In all cases, the ICER remains > £58,000 per QALY, indicating that uncertainty in any single parameter value is unlikely to alter the cost-effectiveness of TRA + ANA relative to conventional thresholds.

TABLE 31 Univariate sensitivity analysis of the cost-effectiveness results of TRA + ANA versus ANA to variations in main variables in the AG's model (base case with a 20-year time horizon)

Model variable	Variation in value		ICER (£) for	
	Low	High	Low	High
Base case				69,514
Discount rate: costs	0%	6%	76,076	66,870
Discount rate: outcomes	0%	6%	64,711	72,588
Dispensing costs: community	£5	£10	69,482	69,570
Dispensing costs: hospital	£7	£11	69,429	69,598
Frequency of cardiac monitoring (per annum)	3	6	69,249	70,051
ECHO as % of scans	50%	100%	69,778	69,117
Frequency of PFS follow-up and CT scan (per annum)	2	6	68,940	70,130
Proportion of progressed patients on EXE	0%	100%	69,628	69,399
Net extra cost of AEs in TRA + ANA group	£0	£1000	69,459	71,155
Net extra disutility of AEs in TRA + ANA group	0	-0.01	69,514	70,713
Utility in PFS: ANA only	-10%	+10%	64,744	75,042
Utility in PFS: TRA + ANA	-10%	+10%	85,113	58,747
Utility in PFS: both groups	-10%	+10%	78,071	62,647
Utility in PPS	-10%	+10%	68,852	70,188
Administration of TRA costs	-10%	+10%	68,661	70,367
Acquisition cost of TRA costs	-10%	+10%	63,997	75,030
Cost of cardiac scan	-10%	+10%	69,397	69,630
BSC annual costs	-10%	+10%	69,363	69,664
Terminal care costs	-10%	+10%	69,505	69,523

BSC, best supportive care; CT, computed tomography; ECHO, echocardiogram.

Probabilistic sensitivity analysis

Probabilistic sensitivity was explored, running 1000 random iterations for all variables subject to measurable parameter uncertainty, using the base-case scenario over a 20-year time horizon. The PSA results are compared with the corresponding deterministic results in *Table 32*.

The scatterplot of iteration results in the cost-effectiveness plane (*Figure 10*) indicates a strong positive correlation between incremental cost and incremental benefit. *Figure 11* confirms that there is no measurable probability of the combination therapy being cost-effective at a willingness-to-pay threshold of £40,000 per QALY gained, and only a 6.3% probability at £50,000 per QALY gained.

Summary of cost-effectiveness evidence

Cost-effectiveness review

In summary, the AG did not identify any relevant papers for inclusion in the cost-effectiveness review of LAP + AI or TRA + AI in patients who are HR+/HER2+ with mBC. The manufacturer of TRA identified a poster⁹⁶ that was presented at the ASCO 2010 conference; the study described compared LAP + LET versus TRA + ANA, using an indirect comparisons analysis. The AG is of the opinion that the results of the indirect analysis performed by Hastings *et al.*⁹⁶ are unreliable as the studies that make up the evidence network are inappropriate. In addition, the AG notes that

TABLE 32 Comparison of deterministic and probabilistic cost-effectiveness results for TRA+ANA versus ANA (base case with a 20-year time horizon)

Sensitivity analysis	Incremental cost (£)	Incremental QALYs	ICER (£)
Deterministic	37,899	0.669	69,514
Probabilistic	33,489	0.513	65,284

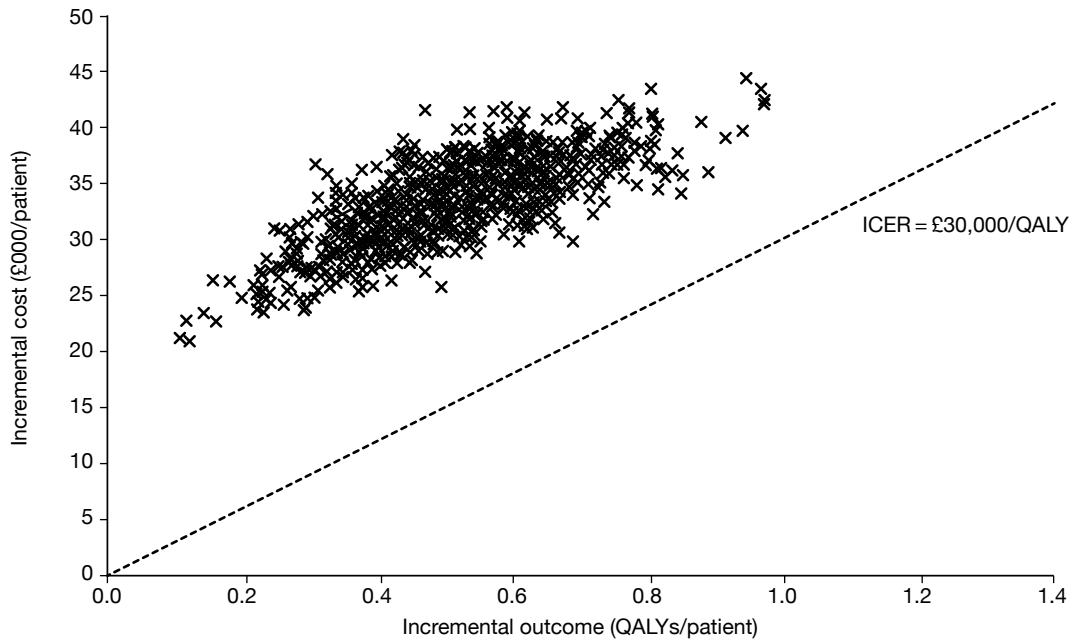


FIGURE 10 Probabilistic sensitivity analysis of TRA+ANA versus ANA only: scatterplot of 1000 probabilistic iterations.

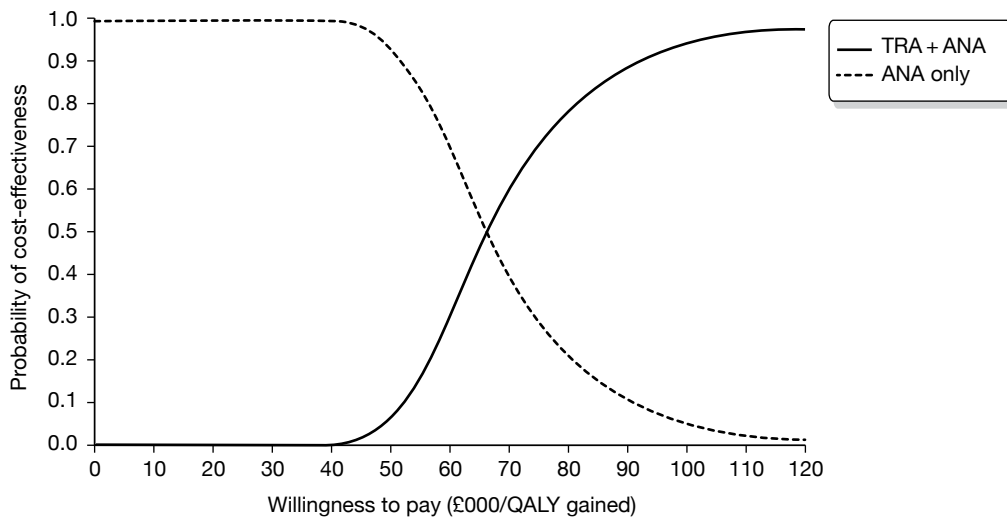


FIGURE 11 Probabilistic sensitivity analysis of TRA+ANA versus ANA only: CEAC.

without access to more detailed information on costs, it is difficult to comment on the reliability of the cost-effectiveness results in this study.

Submitted economic evaluations by manufacturers

The two economic evaluations submitted by the manufacturers appear to meet the NICE reference case criteria.⁹⁷ However, the AG is critical of the approaches used by the manufacturers to estimate OS in each of their models; the AG is of the opinion that projective modelling in this group of patients can lead to substantial bias in OS estimates. In addition, the AG also identified several costing inaccuracies and inconsistencies in both of the economic evaluations submitted.

For the direct comparisons, GlaxoSmithKline demonstrated that LAP + LET is not cost-effective compared with LET and Roche demonstrated that TRA + ANA is not cost-effective compared with ANA.

Both of the manufacturers undertook indirect comparisons analyses in order to be able to compare LAP + LET versus TRA + ANA. GlaxoSmithKline demonstrated that LAP + LET is cost-effective compared with TRA + ANA. Roche demonstrated that TRA + ANA is cost-effective compared with LAP + LET. The AG concludes that the indirect comparisons analyses conducted by the manufacturers are unreliable and that only the ICERs estimated from the direct comparisons are valid.

Roche makes the case for TRA + ANA to be considered as an end-of-life treatment for women with HR+/HER2+ mBC. The AG does not have sufficient information to verify whether or not all three NICE criteria for consideration of end-of-life treatments are met.

Assessment Group's cost-effectiveness results and sensitivity analysis

The AG reports the results of two separate de novo cost-effectiveness analyses using a common framework and common parameter values, but employing effectiveness data drawn only from a single RCT (the EGF30008⁴⁹ or the TAnDEM⁵³ trial). The AG model employs outcome data derived from the relevant clinical trial in the form of Kaplan–Meier estimated survival values augmented by projected survival estimates calibrated against the observed data. The AG uses PFS and PPS estimates directly as the basis for calculating expected OS in each group of the RCT.

As the AG is of the opinion that the evidence base is too unstable to allow meaningful comparison of LAP + AI versus TRA + ANA, the only questions that may be addressed legitimately are as follows.

- Can LAP + LET be considered a cost-effective treatment compared with LET alone?
- Can TRA + ANA be considered a cost-effective treatment compared with ANA alone?

Base-case result: lapatinib in combination with letrozole versus letrozole alone

The AG concludes that in HR+/HER2+ women with mBC, LAP + LET compared with LET is not cost-effective. Using a time horizon of 20 years, the AG estimates an ICER that exceeds £225,000 per QALY gained for the comparison of LAP + LET versus LET; the incremental total costs and QALYs per patient treated are estimated as £26,150 and 0.116, respectively.

Base-case result: trastuzumab in combination with anastrozole versus anastrozole alone

The AG concludes that in HR+/HER2+ women with mBC, TRA + ANA compared with ANA is not cost-effective. Using a time horizon of 20 years, the AG estimates an ICER that exceeds

£69,000 per QALY gained for the comparison of TRA + ANA versus ANA; the incremental total costs and QALYs per patient treated are estimated as £37,899 and 0.545, respectively.

Lapatinib in combination with aromatase inhibitor versus trastuzumab in combination with aromatase inhibitor

The AG emphasises, again, that the currently available clinical evidence base is too unstable to allow meaningful comparison of LAP + AI versus TRA + AI.

Sensitivity analyses undertaken by the Assessment Group

For the comparison of LAP + LET versus LET, the univariate sensitivity analysis shows that the ICER is most sensitive to the choice of health-state utility parameter values and the cost of LAP, but is insensitive to most of the other variables. In all cases, the ICER remains > £141,000 per QALY gained. The PSA shows that the probability of LAP + LET being cost-effective is 0.1% at a willingness-to-pay threshold of £50,000 per QALY gained; to achieve a 50% probability of LAP + LET being cost-effective, the willingness-to-pay threshold needs to increase to £231,000 per QALY gained.

For the comparison of TRA + ANA versus ANA, the univariate sensitivity analysis shows that the ICER is most sensitive to the choice of health-state utility parameter values, the cost of TRA and discounting rates only. In all cases, the ICER exceeds £58,000 per QALY gained. The PSA shows that there is no measureable probability of TRA + ANA being cost-effective compared with ANA at a willingness-to-pay threshold of £40,000.

Chapter 5

Discussion

The size of the relevant study population of interest to this appraisal is small. The manufacturers of both LAP and TRA are in agreement that the population of post-menopausal women with HR+/HER2+ mBC eligible for LAP or TRA in combination with an AI in England and Wales is < 100 patients per year. From the limited data available, the AG agrees that these estimates appear to be reasonable.

Only three RCTs^{49,50,52} have been identified that present head-to-head comparisons of the interventions of interest to this appraisal. It was not possible to compare the data across the trials because of differences in the patient populations. Nevertheless, all three^{49,50,52} trials suggest that either LAP or TRA in combination with an AI improves efficacy, in terms of PFS and/or TTP, over an AI alone. These findings are only statistically significantly different in two trials,^{49,50} as the eLEcTRA⁵² trial lacks statistical power owing to being halted early because of slow recruitment. The trials^{49,50} that measured OS did not report any statistically significant differences between treatment groups, although the OS data in the HR+/HER2+ population of the EGF30008 trial had yet to reach maturity. AEs were more common in the groups in which either LAP or TRA was given in combination with an AI, but on the whole, were of grades 1 or 2 severity. However, around 1% of patients taking LAP + LET had to discontinue their treatment as a result of AEs related to diarrhoea. No new safety concerns were reported in any of the trials.

The comparison of LAP + AI versus TRA + AI is also of interest to this appraisal and, as there are no head-to-head trials of these interventions, the manufacturers used indirect comparisons analyses using mainly clinical data from the EGF30008⁴⁹ and the TAnDEM⁵⁰ trials to assess this comparison. The AG believes that the results of any indirect comparisons analyses of LAP + LET versus TRA + ANA using data from the EGF30008⁴⁹ and the TAnDEM⁵⁰ trials are unreliable because of heterogeneous patient populations. The AG considers that there are apparent differences in the study populations of these two key trials that prohibit comparison of patients and therefore results; these differences may be explained by the fact that patients were explicitly excluded from the EGF30008⁴⁹ trial if they had extensive symptomatic visceral disease or their disease was rapidly progressing or life-threatening, or they may be explained by differences in second-line treatment received in the two trials.

In addition, to complete the evidence network in the indirect comparisons analyses presented in the submitted MS, the manufacturers had to use trials with mixed HER2- and HER2+ populations. The AG is of the opinion, that the use of clinical effectiveness evidence from a mixed population adds to the uncertainty regarding the results of the indirect analyses conducted by the manufacturers. To illustrate, in the EGF30008 trial,⁴⁹ which included both HR+/HER2+ and HR+/HER2- populations, the clinical effectiveness of LET appears to be compromised in patients who are HR+/HER2+ compared with patients who are HR+/HER2-; this was also apparent for patients in the LAP + LET arm of the trial, but to a lesser extent. The significance of this finding is unclear but from a purely clinical viewpoint, could suggest that an AI alone is relatively less effective in patients with HR+/HER2+ mBC.

In summary, the AG is of the opinion that it is not useful to compare findings across the two trials^{49,50} because of the heterogeneous patient populations. In addition, reliance on clinical

evidence from a mixed population adds to the uncertainty of the validity of the results for a HR+/HER2+ population. The AG, therefore, considers the results of the indirect comparisons analysis presented by the manufacturers to be unreliable.

A final issue that needs to be considered relates to the generalisability of these trials to the actual population of interest in the UK, namely post-menopausal women with HR+/HER2+ mBC who have not previously received treatment for mBC and for whom treatment with an AI is suitable. None of the patients in the EGF30008⁴⁹ or the TAnDEM⁵⁰ trials have received prior treatment with TRA; this is not surprising as, at the time the trials were recruiting, the use of TRA for patients with early or advanced breast cancer was relatively rare. This contrasts very much with what happens in clinical practice in the NHS today. Now, when a patient is diagnosed with early HER2+ breast cancer, TRA is the standard treatment of choice and in reality it is likely that only de novo patients with HR+/HER2+ mBC will be eligible for TRA + AI as per the wording of the EMA licence (i.e. TRA-naive), although Roche believes the majority (76%) of patients who present for mBC have not previously received TRA for adjuvant therapy based on its own market research.²⁰ Patients who have been treated with TRA previously are eligible for treatment with LAP + AI; however, whether or not the clinical effectiveness of LAP + AI is the same for patients who are and who are not TRA-naive is uncertain. An FDA post-approval commitment study, EGF114299, is currently being conducted by GlaxoSmithKline to compare the safety and efficacy of an AI in combination with LAP, TRA or both for the treatment of HR+/HER2+ mBC. However, the results from this study will not be available for many years as this study is not currently open for participant recruitment as of November 2011.¹¹⁴

From a health economics perspective, the AG has confirmed by its independent analyses the assertion made by both manufacturers that LAP + LET and TRA + ANA are not cost-effective compared with AIs alone for women with HR+/HER2+mBC. However, the ICERs estimated by the AG for LAP + LET versus LET and TRA + ANA versus ANA are higher than those estimated by the manufacturer.

The AG is of the opinion that the protocol criteria governing the selection of patients for the EGF30008⁴⁹ and the TAnDEM⁵⁰ trials, and subsequent treatment received on progression in these trials, are sufficiently dissimilar to be likely to generate non-equivalent patient populations. This means that the results of any indirect comparisons analyses that include both of these trials in the evidence network are unreliable. Consequently, the AG did not address the cost-effectiveness of LAP + LET versus TRA + ANA as there were insufficient comparative clinical data available to allow estimation of meaningful ICERs.

Chapter 6

Conclusions and research recommendations

Clinical effectiveness evidence from two good-quality RCTs^{49,50} and a third trial that was halted prematurely⁵⁸ demonstrates that LAP + LET or TRA + ANA improves median PFS and/or TTP compared with AI monotherapy in patients who are HR+/HER2+ mBC; it also appears that AIs alone may be less effective in patients with HR+/HER2+ tumours compared with HR+/HER2-^{49,52}. To date, the trials^{49,50} do not show a statistically significant benefit in terms of OS for patients taking LAP + LET versus AI monotherapy or TRA + ANA versus AI monotherapy, although the OS data in the HR+/HER2+ population of the EGF30008⁴⁹ trial had yet to reach maturity and no OS data were presented for the eLEcTRA trial,⁵⁸ presumably because this trial was halted prematurely. The results of the economic evaluations conducted by the manufacturers and confirmed by the AG demonstrate that LAP + LET is not cost-effective compared with AI monotherapy, nor is TRA + ANA cost-effective compared with AI monotherapy.

As a result of differences in the patient populations of the EGF30008⁴⁹ and the TAnDEM trials,⁵⁰ the AG believes the results of the indirect comparisons analyses conducted by the manufacturers are inappropriate and for the same reason believes that it would be unsound to compare LAP + LET versus TRA + ANA in an economic evaluation.

Recommendations for further research

Given the uncertainties in the evidence base, the AG suggests that the following research priorities should be addressed (in order of priority).

1. Given that most patients who present for HR+/HER2+ mBC are now likely to have been previously treated for early breast cancer and given that this is almost certain to have included TRA (unlike at the time the pivotal trials in this appraisal were conducted), further research may be required into treating mBC in the HR+/HER2+ population who are not TRA (or LAP) naive. It is noted that such a study (EGF114299) is planned by GlaxoSmithKline.
2. As, increasingly, trials allow patients to cross over following disease progression, attempts should be made to consider how to adjust for crossover at the trial design stage, rather than as a post-hoc analysis.
3. As the EGF30008⁴⁹ trial reports, there were large differences in PFS for HER2+ and HER2- patients receiving both LAP + LET and, in particular, LET. Further research may be warranted comparing the clinical effectiveness of AIs as monotherapy in patients with HER2+ and HER2- breast cancer.

Acknowledgements

The authors are pleased to acknowledge Janet Atkinson [Liverpool Reviews and Implementation Group (LRiG), University of Liverpool], who provided administrative support (including obtaining bibliographic sources) for this project. In addition, four referees considered and commented on the final version of this report post submission. The policy of the NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC) is not to name referees; however, individuals contributing peer review of HTA programme products are listed on the NETSCC website (www.netscc.ac.uk/). Finally, the authors would like to acknowledge the comments received by consultees prior to the first meeting of the NICE Appraisal Committee Meeting in November 2010, available from the NICE website (at <http://guidance.nice.org.uk/TA/Wave0/167>).

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 the 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 the background section and commented on draft versions of the final report.

Anne Armstrong Contributed to the analysis and interpretation of data and commented on draft versions of the final report.

Nicky Thorp Contributed to the background section, analysis and interpretation of data and commented on draft versions of the final report.

References

1. Germano S, O'Driscoll L. Breast cancer: understanding sensitivity and resistance to chemotherapy and targeted therapies to aid in personalised medicine. *Curr Cancer Drug Targets* 2009;**9**:398–418.
2. Cancer Research UK. *Breast cancer – risk factors*. 2010. URL: <http://info.cancerresearchuk.org/cancerstats/types/breast/riskfactors/> (accessed: 6 September 2010).
3. Ward S, Simpson E, Davis S, Hind D, Rees A, Wilkinson A. Taxanes for the adjuvant treatment of early breast cancer: systematic review and economic evaluation. *Health Technol Assess* 2007;**11**(40).
4. Pharoah PD, Antoniou A, Bobrow M, Zimmern RL, Easton DF, Ponder BA. Polygenic susceptibility to breast cancer and implications for prevention. *Nat Genet* 2002;**31**:33–6.
5. Hannah L, Crosby T, MacBeth F, editors. *Practical clinical oncology*. 1st edn. Cambridge: Cambridge University Press; 2008.
6. Endogenous Hormones Breast Cancer Collaborative Group. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. *J Natl Cancer Inst* 2002;**94**:606–16.
7. Cassidy J, Bissett D, Spence R, Payne M, editors. *Oxford handbook of oncology*. 2nd edn. Oxford: Oxford: Oxford University Press; 2006.
8. American Joint Committee on Cancer. *AJCC cancer staging manual*. 7th edn. Chicago, IL: Springer; 2009.
9. International Union Against Cancer. *TNM classification of malignant tumours*. 7th edn. New York, NY: Wiley-Liss; 2009.
10. Dowsett M, Cuzick J, Ingle J, Coates A, Forbes J, Bliss J, *et al*. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. *J Clin Oncol* 2010;**28**:509–18.
11. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;**365**:1687–717.
12. Cancer Research UK. *Predicted improvements in breast cancer survival cancer research UK*. 2010. URL: www.cancerhelp.org.uk/about-cancer/cancer-questions/predicted-improvements-in-breast-cancer-survival (accessed 6 September 2010).
13. Andreopoulou E, Hortobagyi GN. Prognostic factors in metastatic breast cancer: successes and challenges toward individualized therapy. *J Clin Oncol* 2008;**26**:3660–2.
14. Cold S, Jensen NV, Brincker H, Rose C. The influence of chemotherapy on survival after recurrence in breast-cancer – a population-based study of patients treated in the 1950s, 1960s and 1970s. *Eur J Cancer* 1993;**29**:1146–52.
15. National Institute for Health and Clinical Excellence (NICE). *Guidance on the use of trastuzumab for the treatment of advanced breast cancer*. NICE technology appraisal guidance. No.34. 2002. URL: www.nice.org.uk/nicemedia/pdf/TA107guidance.pdf (accessed 26 January 2010).
16. Cancer Research UK. *Breast cancer – UK incidence statistics*. 2010. URL: <http://info.cancerresearchuk.org/cancerstats/types/breast/incidence/> (accessed 18 August 2011).

17. Quinn M, Cooper N, Rowan S. *Cancer atlas of the United Kingdom and Ireland 1991–2000*. 2005. URL: www.statistics.gov.uk/downloads/theme_health/caUKI91_00/Preliminary_pages.pdf (accessed 14 July 2010).
18. Woods LM, Rachet B, Coleman MP. Origins of socio-economic inequalities in cancer survival: a review. *Ann Oncol* 2006;**17**:5–19.
19. GlaxoSmithKline. *Manufacturer submission to the National Institute for Health and Clinical Excellence by GlaxoSmithKline UK. Multiple technology appraisal of lapatinib (Tyverb[®]) for the treatment of HR+ HER2+ metastatic breast cancer*. Date 7 June 2010.
20. Roche. *Trastuzumab in combination with aromatase inhibitors for the 1st line treatment of metastatic hormone receptor positive breast cancer which over-expressed HER2*. Roche submission to the National Institute for Health and Clinical Excellence. Date 7 June 2010.
21. Dybdal N, Leiberman G, Anderson S, McCune B, Bajamonde A, Cohen R, *et al*. Determination of HER2 gene amplification by fluorescence in situ hybridization and concordance with the clinical trials immunohistochemical assay in women with metastatic breast cancer evaluated for treatment with trastuzumab. *Breast Cancer Res Treat* 2005;**93**:3–11.
22. Turner J, Kelly B, Swanson C, Allison R, Wetzig N. Psychosocial impact of newly diagnosed advanced breast cancer. *Psychooncology* 2005;**14**:396–407.
23. National Institute for Health and Clinical Excellence (NICE). *Advanced breast cancer: diagnosis and treatment*. NICE clinical guideline. No. 81. 2009. URL: www.nice.org.uk/Guidance/CG81 (accessed 26 January 2010).
24. Quinlan E, Thomas-Maclean R, Hack T, Kwan W, Miedema B, Tatemichi S, *et al*. The impact of breast cancer among Canadian women: disability and productivity. *Work* 2009;**34**:285–96.
25. Yoo GJ, Levine EG, Aviv C, Ewing C, Au A. Older women, breast cancer, and social support. *Support Care Cancer* 2010;**18**:1521–30.
26. Montazeri A, Vahdaninia M, Harirchi I, Ebrahimi M, Khaleghi F, Jarvandi S. Quality of life in patients with breast cancer before and after diagnosis: an eighteen months follow-up study. *BMC Cancer* 2008;**8**:330.
27. Kedrin D, Wyckoff J, Boimel PJ, Coniglio SJ, Hynes NE, Arteaga CL, *et al*. ERBB1 and ERBB2 have distinct functions in tumor cell invasion and. *Clin Cancer Res* 2009;**15**:3733–9.
28. British Medical Association and Royal Pharmaceutical Society of Great Britain. *British national formulary*. No. 59, March 2010. London: BMA and RPS; 2010.
29. European Medicines Agency (EMA). *Committee for medicinal products for human use post-authorisation summary of positive opinion for tyverb*. 2010. URL: www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion/human/000795/WC500074419.pdf (accessed 24 November 2010).
30. European Medicines Agency (EMA). *Committee for medicinal products for human use summary of positive opinion for tyverb*. 2008. URL: www.ema.europa.eu/pdfs/human/opinion/Tyverb_38267507en.pdf (accessed 26 January 2010).
31. Pharmaceutical Field. *Further indication for tyverb approved*. 2010. URL: www.pharmafield.co.uk/news/2010/06/further-indication-for-tyverb-approved (accessed 14 July 2010).
32. Jones AL, Barlow M, Barrett-Lee PJ, Canney PA, Gilmour IM, Robb SD, *et al*. Management of cardiac health in trastuzumab-treated patients with breast cancer: updated United Kingdom National Cancer Research Institute recommendations for monitoring. *Br J Cancer* 2009;**100**:684–92.

33. European Medicines Agency (EMA). *Committee for medicinal products for human use post- authorisation summary of positive opinion for herceptin*. 2009. URL: www.ema.europa.eu/pdfs/human/opinion/Herceptin_82246709en.pdf (accessed 26 January 2010).
34. National Institute for Health and Clinical Excellence (NICE). *Hormonal therapies for the adjuvant treatment of early oestrogen-receptor-positive breast cancer*. Technology appraisal No. TA112. 2006. URL: www.nice.org.uk/TA112 (accessed 26 January 2010).
35. Lavelle K, Todd C, Moran A, Howell A, Bundred N, Campbell M. Non-standard management of breast cancer increases with age in the UK: a population based cohort of women greater than or equal to 65 years. *Br J Cancer* 2007;**96**:1197–203.
36. Wyld L, Garg DK, Kumar ID, Brown H, Reed MWR. Stage and treatment variation with age in postmenopausal women with breast cancer: compliance with guidelines. *Br J Cancer* 2004;**90**:1486–91.
37. Ladva S. *Continued use of trastuzumab following disease progression in metastatic breast cancer*. London: New Drugs Group; 2010.
38. Centre for Reviews and Dissemination (CRD). *CRD's guidance for undertaking reviews in healthcare: systematic reviews*. 3rd edn. York: CRD, University of York; 2008.
39. Egger M, Smith GD, Altman DG. *Systematic reviews in health care – meta-analysis in context*. London: BMJ books; 2001.
40. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med* 2004;**23**:3105–24.
41. Langer B. *Phase II/III randomized study of anastrozole with or without trastuzumab (herceptin) in postmenopausal women with hormone-receptor positive HER2-overexpressing metastatic breast cancer*. *Physician Data Query (PDQ)*. 2001. URL: www.mrw.interscience.wiley.com/cochrane/clcentral/articles/021/CN-00362021/frame.html (accessed 30 June 2010).
42. Piccart-Gebhart MJ, Coleman RE. *Phase III randomized study of trastuzumab (herceptin) in women with HER2-positive primary breast cancer*. *Physician Data Query (PDQ)*. 2002. URL: www.mrw.interscience.wiley.com/cochrane/clcentral/articles/007/CN-00404007/frame.html (accessed 30 June 2010).
43. Stein S. *Phase III randomized study of letrozole with or without GW572016 in postmenopausal women with stage IIIB or IV breast cancer*. *Physician Data Query (PDQ)*. 2004: URL: www.mrw.interscience.wiley.com/cochrane/clcentral/articles/289/CN-00548289/frame.html (accessed 30 June 2010).
44. Novartis. *Study of the efficacy and safety of letrozole combined with trastuzumab in patients with metastatic breast cancer*. *Physician Data Query (PDQ)*. 2006. URL: www.mrw.interscience.wiley.com/cochrane/clcentral/articles/302/CN-00614302/frame.html (accessed 30 June 2010).
45. Morris P, Modi S. Trastuzumab-refractory HER2-positive metastatic breast cancer – use of tanespimycin, a novel Hsp90 inhibitor. *Am J Pediatr Hematol Oncol* 2008;**7**.
46. Maung K, O'Shaughnessy JA. Inhibition of ErbB1 and ErbB2 by lapatinib ditosylate, a dual kinase inhibitor: promising activity in pretreated advanced breast cancer. *Clin Breast Cancer* 2004;**4**:398–400.
47. Ranganathan A, Moore Z, O'Shaughnessy JA. Trastuzumab prolongs progression-free survival in patients with hormone-sensitive and HER2-overexpressing metastatic breast cancer. *Clin Breast Cancer* 2007;**7**:450–1.

48. Johnston S, Arteaga C. Lapatinib (tykerb) plus letrozole (femara) or letrozole alone for postmenopausal hormone receptor-positive metastatic breast cancer. *P and T* 2009;**34**:102.
49. Johnston S, Pippen J Jr, Pivot X, Lichinitser M, Sadeghi S, Dieras V, *et al.* Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor – positive metastatic breast cancer. *J Clin Oncol* 2009;**27**:5538–46.
50. Kaufman B, Mackey JR, Clemens MR, Bapsy PP, Vaid A, Wardley A, *et al.* Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. *J Clin Oncol* 2009;**27**:5529–37.
51. Schwarzberg LS, Franco SX, Florance A, O'Rourke L, Maltzman J, Johnston SRD. Lapatinib plus letrozole as first-line therapy for HER-2+ hormone receptor-positive metastatic breast cancer. *Oncologist* 2010;**15**:122–9.
52. Huober J, Fasching P, Paepke S, Kubista E, Barsoum M, Wallwiener D, *et al.* Letrozole in combination with trastuzumab is superior to letrozole monotherapy as first line treatment in patients with hormone-receptor-positive, HER2-positive metastatic breast cancer (MBC) – results of the eLEcTRA Trial. *Cancer Res* 2009;**69**:4094.
53. Gomez HL, Doval DC, Chavez MA, Ang PC-S, Aziz Z, Nag S, *et al.* Efficacy and safety of lapatinib as first-line therapy for ErbB2-amplified locally advanced or metastatic breast cancer. *J Clin Oncol* 2008;**26**:2999–3005.
54. Cameron D, Casey M, Press M, Lindquist D, Pienkowski T, Romieu C, *et al.* A phase III randomized 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;**112**:533–43.
55. Food and Drug Administration. *Guidance for industry: clinical trial endpoints for the approval of cancer drugs and biologics*. 2007. URL: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf (accessed 22 July 2010).
56. Committee for Medicinal Products for Human Use. *Guideline on the evaluation of anticancer medicinal products in man*. 2005. URL: www.tga.gov.au/docs/pdf/euguide/ewp/020595enrev3.pdf (accessed 22 July 2010).
57. Fleming TR, Rothmann MD, Lu HL. Issues in using progression-free survival when evaluating oncology products. *J Clin Oncol* 2009;**27**:2874–80.
58. Saad ED, Katz A. Progression-free survival and time to progression as primary end points in advanced breast cancer: often used, sometimes loosely defined. *Ann Oncol* 2009;**20**:460–4.
59. Sherif B, Sherrill B, Amonkar M, Wu Y, Maltzman J, O'Rourke L, *et al.* Lapatinib plus letrozole compared with letrozole alone as first-line therapy in hormone receptor-positive HER2+ metastatic breast cancer (MBC): a quality-of-life (QOL) analysis. *J Clin Oncol* 2009;**27**:abstr 1039.
60. Robins JM, Tsiatis AA. Correcting for non-compliance in randomized trials using rank preserving structural failure time models. *Comm Stat Theor* 1991;**20**:2609–31.
61. Mark SD, Robins JM. A method for the analysis of randomized trials with compliance information: an application to the multiple risk factor intervention trial. *Control Clin Trials* 1993;**14**:79–97.

62. Morden JP, Lambert PC, Latimer N, Abrams KR, Wailoo AJ. *Assessing methods for dealing with treatment switching in randomised controlled trials*. University of Leicester. 2010. URL: www.le.ac.uk/hs/kra1/2010_BS01.pdf (accessed 17 August 2010).
63. National Institute for Health and Clinical Excellence (NICE). *Final appraisal determination: sunitinib for the treatment of gastrointestinal stromal tumours*. 2009. URL: www.nice.org.uk/nicemedia/live/11817/43174/43174.pdf (accessed 17 August 2010).
64. National Institute for Health and Clinical Excellence (NICE). *Final appraisal determination: everolimus for the second-line treatment of advanced renal cell carcinoma*. 2010. URL: <http://guidance.nice.org.uk/TA/WaveCRS1/48> (accessed 17 August 2010).
65. Robins J, Finkelstein D. Correcting for noncompliance and dependent censoring in an AIDS clinical trial with inverse probability of censoring weighted (IPCW) log-rank tests. *Biometrics* 2000;**56**:779–88.
66. Branson M, Whitehead J. Estimating a treatment effect in survival studies in which patients switch treatment. *Stat Med* 2002;**21**:2449–63.
67. Walker A, White I, Babiker A. Parametric randomization-based methods for correcting for treatment changes in the assessment of the causal effect of treatment. *Stat Med* 2004;**23**:571–90.
68. Bonnetterre J, Thürlimann B, Robertson JF, Krzakowski M, Mauriac L, Koralewski P, *et al*. Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the tamoxifen or arimidex randomized group efficacy and tolerability study. *J Clin Oncol* 2000;**18**:3748–57.
69. Nabholz JM, Buzdar A, Pollak M, Harwin W, Burton G, Mangalik A, *et al*. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. *J Clin Oncol* 2000;**18**:3758–67.
70. Buzdar AU, Jones SE, Vogel CL, Wolter J, Plourde P, Webster A. A phase III trial comparing anastrozole (1 and 10 milligrams), a potent and selective aromatase inhibitor, with megestrol acetate in postmenopausal women with advanced breast carcinoma. Arimidex Study Group. *Cancer* 1997;**79**:730–9.
71. Jonat W, Howell A, Blomqvist C, Eiermann W, Winblad G, Tyrrell C, *et al*. A randomised trial comparing two doses of the new selective aromatase inhibitor anastrozole (Arimidex) with megestrol acetate in postmenopausal patients with advanced breast cancer. *Eur J Cancer* 1996;**32**:404–12.
72. Parmar M, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med* 1998;**17**:2815–34.
73. Bucher H, Guyatt G, Griffith L, Walter S. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol* 1997;**50**:683–91.
74. Sutton AJ, Higgins JPT. *Recent developments in meta-analysis*. Oxford: John Wiley & Sons, Ltd; 2008. pp. 625–50.
75. Puhan M, Bachmann L, Kleijnen J, ter Riet G, Kessels A. Inhaled drugs to reduce exacerbations in patients with chronic obstructive pulmonary disease: a network meta-analysis. *BMC Med* 2009;**7**:2.
76. Mouridsen HT. Letrozole in advanced breast cancer: the PO25 trial. *Breast Cancer Res Treat* 2007;**105**:19–29.

77. Buzdar A, Douma J, Davidson N, Elledge R, Morgan M, Smith R, *et al.* Phase III, multicenter, double-blind, randomized study of letrozole, an aromatase inhibitor, for advanced breast cancer versus megestrol acetate. *J Clin Oncol* 2001;**19**:3357–66.
78. Dombernowsky P, Smith I, Falkson G, Leonard R, Panasci L, Bellmunt J, *et al.* Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double-blind randomized trial showing a dose effect and improved efficacy and tolerability compared with megestrol acetate. *J Clin Oncol* 1998;**16**:453–61.
79. Kaufmann M, Bajetta E, Dirix LY, Fein LE, Jones SE, Cervek J, *et al.* Exemestane improves survival compared with megestrol acetate in postmenopausal patients with advanced breast cancer who have failed on tamoxifen. Results of a double-blind randomised phase III trial. *Eur J Cancer* 2000;**36**:S86–7.
80. Mouridsen H, Sun Y, Gershanovich M, Perez-Carrion R, Becquart D, Chaudri-Ross HA, *et al.* Superiority of letrozole to tamoxifen in the first-line treatment of advanced breast cancer: evidence from metastatic subgroups and a test of functional ability. *Oncologist* 2004;**9**:489–96.
81. Paridaens R, Dirix L, Beex L, Nooij M, Cufer T, Lohrisch C, *et al.* Promising results with exemestane in the first-line treatment of metastatic breast cancer: a randomized phase II EORTC trial with a tamoxifen control. *Clin Breast Cancer* 2000;**1**:S19–21.
82. Rose C, Vtoraya O, Pluzanska A, Davidson N, Gershanovich M, Thomas R, *et al.* An open randomised trial of second-line endocrine therapy in advanced breast cancer. Comparison of the aromatase inhibitors letrozole and anastrozole. *Eur J Cancer* 2003;**39**:2318–27.
83. Campos SM, Guastalla JP, Subar M, Abreu P, Winer EP, Cameron DA. A comparative study of exemestane versus anastrozole in patients with postmenopausal breast cancer with visceral metastases. *Clin Breast Cancer* 2009;**9**:39–44.
84. Howell A, Robertson JF, Quaresma Albano J, Aschermannova A, Mauriac L, Kleeberg UR, *et al.* Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. *J Clin Oncol* 2002;**20**:3396–403.
85. Osborne CK, Pippin J, Jones SE, Parker LM, Ellis M, Come S, *et al.* Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: results of a North American trial. *J Clin Oncol* 2002;**20**:3386–95.
86. Robertson JF, Llombart-Cussac A, Rolski J, Feltl D, Dewar J, Macpherson E, *et al.* Activity of fulvestrant 500 mg versus anastrozole 1 mg as first-line treatment for advanced breast cancer: results from the FIRST study. *J Clin Oncol* 2009;**27**:4530–5.
87. Paridaens RJ, Dirix LY, Beex LV, Nooij M, Cameron DA, Cufer T, *et al.* Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women: the European Organisation for Research and Treatment of Cancer Breast Cancer Cooperative Group. *J Clin Oncol* 2008;**26**:4883–90.
88. Chernozemsky I, Kalinov K, Tzekov H, Racheva M, Hristova S, Tomova A, *et al.* Randomized phase III trial of exemestane or tamoxifen in first-line hormonal treatment of postmenopausal women with metastatic breast cancer. *Breast Cancer Res Treat* 2007;**106**:S119.
89. Mauriac L, Romieu G, Bines J. Activity of fulvestrant versus exemestane in advanced breast cancer patients with or without visceral metastases: data from the EFECT trial. *Breast Cancer Res Treat* 2009;**117**:69–75.

90. Kaufmann M, Bajetta E, Dirix LY, Fein LE, Jones SE, Zilembo N, *et al.* Exemestane is superior to megestrol acetate after tamoxifen failure in postmenopausal women with advanced breast cancer: results of a phase III randomized double-blind trial. *J Clin Oncol* 2000;**18**:1399–411.
91. Hind D, Ward S, De Nigris E, Simpson E, Carroll C, Wyld L. Hormonal therapies for early breast cancer: systematic review and economic evaluation. *Health Technol Assess* 2007;**11**(26).
92. Dranitsaris G, Leung P, Mather J, Oza A. Cost utility analysis of second line hormonal therapy in advanced breast cancer: a comparison of two aromatase inhibitors to megestrol acetate. *Anticancer Drugs* 2000;**11**:591–601.
93. Dranitsaris G, Verma S, Trudeau M. Cost utility analysis of first-line hormonal therapy in advanced breast cancer. *Am J Clin Oncol* 2003;**26**:289–96.
94. Marchetti M, Caruggi M, Colombo G. Cost utility and budget impact of third-generation aromatase inhibitors for advanced breast cancer: a literature based model analysis of cost in the Italian national health service. *Clin Ther* 2004;**26**:1546–61.
95. Verma S, Rodchi A. Economic evaluation of antiaromatase agents in the second line treatment of metastatic breast cancer. *Support Care Cancer* 2003;**11**:728–34.
96. Hastings V, Amonkar M, Lykopoulos K, Diaz J, Johnston S. *Indirect comparison of the cost-effectiveness of letrozole plus lapatinib (LET+LAP) versus anastrozole plus trastuzumab (ANA + TZ) as first-line treatment for postmenopausal women with HER2+ and HR+ metastatic breast cancer (MBC) from the U.K. national health service (NHS) perspective.* ASCO 2010, abstract no. 1035. Poster presented in Chicago, IL, USA, June 2010.
97. National Institute for Health and Clinical Excellence (NICE). *Guide to the methods of technology appraisal.* London: National Institute for Health and Clinical Excellence; 2008. URL: www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf (accessed 26 January 2010).
98. Curtis L. *Unit costs of health and social care 2008.* Kent: Personal Social Services Research Unit, University of Kent; 2008. URL: www.pssru.ac.uk/uc/uc2008contents.htm (accessed 25 August 2010).
99. Department of Health. *NHS reference costs 2008–2009.* 2010. URL: www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_111591 (accessed 25 August 2010).
100. Remak E, Brazil L. Cost of managing women presenting with stage IV breast cancer in the United Kingdom. *Br J Cancer* 2004;**91**:77–83.
101. Cella DF, Tulskey DS, Gray G, Sarafian B, Linn E, Bonomi A, *et al.* The functional assessment of cancer therapy scale: development and validation of the general measure. *J Clin Oncol* 1993;**11**:570–9.
102. Dobrez D, Cella D, Pickard S, Lai J-S, Nickolov A. Estimation of patient preference-based utility weights from the functional assessment of cancer therapy-general. *Value Health* 2007;**10**:266–72.
103. Delea TE *et al.* Patient preference-based utility weights from the Functional Assessment of Cancer Therapy-general (FACT-G) in women with hormone receptor positive metastatic breast cancer receiving letrozole plus lapatinib or letrozole alone. *Value Health* 2010;**3**:43 Abstract PCN0105.
104. Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. *Br J Cancer* 2006;**95**:683–90.

105. Oxford Outcomes. *Utility measurement study for patients with metastatic breast cancer treated with Tyverb*. Draft Report. 7 October 2009.
106. Doyle S, Lloyd A, Walker M. Health state utility scores in advanced non-small cell lung cancer. *Lung Cancer* 2009;**62**:374–80.
107. Ward S, Pilgrim H, Hind D. Trastuzumab for the treatment of primary breast cancer in HER2-positive women: a single technology appraisal. *Health Technol Assess* 2009;**13** (Suppl. 1):1–6.
108. Curtis L. *Unit costs of health and social care 2009*. Personal Social Services Research Unit, University of Kent; 2010. URL: www.pssru.ac.uk/uc/uc2009contents.htm (accessed 25 August 2010).
109. Cooper N, Abrams K, Sutton A, Turner D, Lambert P. A bayesian approach to markov modelling in cost effectiveness analyses: application to taxane use in advanced breast cancer. *J Roy Statistical Society* 2003;**166**:389–405.
110. Regional Drugs and Therapeutics Centre. *The use of bevacizumab in the management of metastatic breast cancer*. 2007. URL: www.nyrdtc.nhs.uk/docs/eva/Bevacizumab%20MBC%20RDTC%20FINAL.pdf (accessed 25 August 2010).
111. National Institute for Health and Clinical Excellence (NICE). *Lapatinib for the treatment of previously treated women with advanced, metastatic or recurrent breast cancer (final scope)*. 2007. URL: <http://guidance.nice.org.uk/nicemedia/live/11731/35243/35243.pdf> (accessed 25 August 2010).
112. Dolan P, Gudex C, Kind P, Williams A. The time trade-off method: results from a general population survey. *Health Econ* 1996;**5**:141–54.
113. Swain L. *OPCS-4.5 chemotherapy regimens list & guidance for clinical coders version 2.0 dated 10th March 2010*. 2010. URL: www.wales.nhs.uk/sites3/Documents/920/chemoreglistandguideopcs45v2.pdf (accessed 25 August 2010).
114. GlaxoSmithKline. *A study to compare the safety and efficacy of an aromatase inhibitor in combination with lapatinib, trastuzumab or both for the treatment of hormone receptor positive, HER2+ metastatic breast cancer*. URL: <http://clinicaltrials.gov/ct2/show/NCT01160211> (accessed 24 November 2010).

Appendix 1

Literature search strategies

MEDLINE 1950 to April week 4 2010

Searches	Search terms	Results
1	(lapatinib or tykerb or tyverb or lapatinib ditosylate).af.	456
2	(trastuzumab or herceptin).af.	340
3	(letrozole or femara or anastrozole or arimidex or exemestane or aromasin).af.	2106
4	exp Aromatase Inhibitors/	4804
5	aromatase inhibitor\$.tw.	3518
6	1 or 2	3627
7	3 or 5	4323
8	6 and 7	121
9	exp Breast Neoplasms/	172,296
10	(breast\$adj5 (neoplasm\$or cancer\$or tumor?\$or carcinoma\$or adenocarcinoma\$or sarcoma\$or dcis or ductal or infiltrat\$or intraductal\$or lobular or medullary)).mp.	203,286
11	9 or 10	203,391
12	8 and 11	115

EMBASE 1980 to week 18 2010

Searches	Search terms	Results
1	(lapatinib or tykerb or tyverb or lapatinib ditosylate).af.	2435
2	(trastuzumab or herceptin).af.	10,741
3	(letrozole or femara or anastrozole or arimidex or exemestane or aromasin).af.	5962
4	Aromatase Inhibitors.mp. or exp aromatase inhibitor/	11,914
5	1 or 2	11,728
6	3 or 4	11,959
7	5 and 6	1472
8	(breast\$adj5 (neoplasm\$or cancer\$or tumor?\$or carcinoma\$or adenocarcinoma\$or sarcoma\$or dcis or ductal or infiltrat\$or intraductal\$or lobular or medullary)).mp.	195,921
9	exp breast cancer/	167,175
10	8 or 9	197,019
11	7 and 10	1378
12	limit 11 to (human and english language)	1195

The Cochrane Library Issue 4, 2010

Searches	Search terms	Results
1	(lapatinib or tykerb or tyverb or lapatinib ditosylate or trastuzumab or herceptin or letrozole or femara or anastrozole or arimidex or exemestane or aromasin or aromatase inhibitor*)	1196
2	MeSH descriptor Breast Neoplasms explode all trees	6865
3	(breast cancer* or breast neoplasm* or breast tumor* or breast tumour* or breast carcinoma*)	14,097
4	(#2 OR #3)	14,097
5	(#1 AND #4)	932
Search Results by each database in The Cochrane Library		Results
Cochrane Database of Systematic Reviews (CDSR)		24
Database of Abstracts of Reviews of Effects (DARE)		26
Cochrane Central Register of Controlled Trials (CENTRAL)		757
Cochrane Methodology Register (CMR)		11
Health Technology Assessment Database		34
NHS Economic Evaluation Database (NHS EED)		79

MeSH, medical subject heading.

The search strategy for The Cochrane Library is broader than MEDLINE or EMBASE, combining all the drug-related free-text words with breast cancer [both using medical subject heading (MeSH) Breast Neoplasms and free-text words] to identify relevant reviews and particularly economic evaluations in the area.

All databases

Total number of results from all databases: 2228.

After electronic removal of duplicates: 2202.

After manual removal of duplicates: 2069.

Appendix 2

Tables of excluded studies with rationale

Excluded studies from clinical review

The following citations were excluded by the AG at screening stage 2.

Study	Reason for exclusion
Langer 2001 ⁴¹	Data Physicians Query apparently relating to the TAnDEM ⁵⁰ trial
Maung and O'Shaughnessy 2004 ⁴⁶	LAP monotherapy, not LAP + AI
Morris and Modi 2008 ⁴⁵	TRA + tanespimycin, not TRA + AI
Novartis 2006 ⁴⁴	Data Physicians Query apparently relating to the eLEcTRA ⁵² trial
Piccart-Gebhart and Coleman 2002 ⁴²	Data Physicians Query apparently relating to the TAnDEM ⁵⁰ trial
Ranganathan <i>et al.</i> 2007 ⁴⁷	News article reporting on conference presentation for the TAnDEM ⁵⁰ trial
Stein 2004 ⁴³	Data Physicians Query apparently relating to the EGF30008 ⁴⁹ trial

Studies included in the indirect comparisons analyses performed by the manufacturers

The following studies were included in the GlaxoSmithKline¹⁹ and/or Roche²⁰ submissions, but excluded by the AG.

Study	Submission(s) included in	Reason for exclusion
TARGET (outside North America) ⁶⁸	GlaxoSmithKline ¹⁹ and Roche ²⁰	ANA vs TAM, not HER2+
PO25 ⁷⁶	GlaxoSmithKline ¹⁹ and Roche ²⁰	LET vs TAM, not limited to first-line, not HER2+
TARGET (North America) ⁶⁹	GlaxoSmithKline ¹⁹ and Roche ²⁰	ANA vs TAM, not HER2+
Rose <i>et al.</i> 2003 ⁸²	Roche ²⁰	ANA vs LET, second-line, not HER2+
Campos <i>et al.</i> 2009 ⁸³	Roche ²⁰	ANA vs EXE, not limited to first-line, not HER2+
020 ⁸⁴	Roche ²⁰	ANA vs fulvestrant (Faslodex [®] , AstraZeneca) not limited to first-line, not HER2+
021 ⁸⁵	Roche ²⁰	ANA vs fulvestrant, not limited to first-line, not HER2+
FIRST ⁸⁶	Roche ²⁰	ANA vs fulvestrant, HER2 status not clear
Jonat <i>et al.</i> 1996 ⁷¹	Roche ²⁰	ANA vs megestrol acetate, not clear if first-line, not HER2+
Buzdar <i>et al.</i> 1997 ⁷⁰	Roche ²⁰	ANA vs megestrol acetate, not limited to first-line, not HER2+
Dombernowsky <i>et al.</i> 1998 ⁷⁸	Roche ²⁰	LET vs megestrol acetate, second-line, not HER2+
Buzdar <i>et al.</i> 2001 ⁷⁷	Roche ²⁰	LET vs megestrol acetate, not limited to first-line, not HER2+
EORTC ⁸⁷	Roche ²⁰	EXE vs TAM, not HER2+
Chernozemsky <i>et al.</i> 2007 ⁸⁸	Roche ²⁰	EXE vs TAM, not HER2+
EFFECT ⁸⁹	Roche ²⁰	EXE vs fulvestrant, not clear if first-line, not HER2+
Kaufmann <i>et al.</i> 2000 ⁹⁰	Roche ²⁰	EXE vs megestrol acetate, not clear if first-line, not HER2+

Appendix 3

Final protocol

Date: 23/02/2010

1. Title of the project:

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

2. TAR team and 'lead'

Liverpool Reviews and Implementation Group (LRiG)
University of Liverpool
Room B05
Whelan Building
The Quadrangle
Brownlow Hill
Liverpool
L69 3GB
Tel: +44 (0) 151 794 5682/8116
Fax: +44 (0) 151 794 5821
Email: LRiG@liv.ac.uk

Lead: Nigel Fleeman (Research Fellow)
Tel: +44 (0) 151 795 5458
Email: Nigel.Fleeman@liverpool.ac.uk

3. Plain English Summary

Breast cancer is the most common cancer affecting women in the UK. Some breast cancers have higher than normal levels of receptors for oestrogen and/or progesterone (hormone receptor positive). Tumours that have receptors to oestrogen and progesterone hormones are more likely to respond to hormonal therapies (i.e. drugs or treatments that block the effects of hormones, or lower the levels of oestrogen and progesterone) and patients with such tumours tend to have a better prognosis. Some breast cancers also have proteins called human epidermal growth factor 2 (HER2). Tumours that are HER2-positive tend to grow more quickly than other types of breast cancer and patients with such tumours tend to have a worse prognosis and reduced overall survival. Up to a third of women with metastatic breast cancer (i.e. cancer which has spread to other parts of the body) have higher levels of HER2 and around half of all these are also hormone receptor positive. Currently the only therapy available for patients with metastatic breast cancer is palliative treatment.

The aim of this review is to assess the clinical and cost effectiveness of lapatinib and trastuzumab, in combination with an aromatase inhibitor (e.g. anastrozole or letrozole), in the first-line treatment of metastatic hormone receptor positive breast cancer which over-expresses HER2. Evidence for clinical

evidence will be derived from a systematic review of randomised controlled trials. The evidence for cost effectiveness will be derived from clinical trial evidence as well as published economic evaluations, modelling studies and other data sources. Cost effectiveness will be expressed in terms of incremental cost per quality adjusted life years. Costs will be considered from an NHS and Personal Social Services perspective.

4. Decision problem

Purpose of the decision to be made

Breast cancer is the most common cancer affecting women in the UK, accounting for nearly one in three of all cancers in women.¹ In England and Wales, around 40,000 new cases were diagnosed in 2006,² and there were nearly 11,000 deaths due to breast cancer in 2007.³ It has been estimated that approximately 550,000 women are alive in the UK who have had a diagnosis of breast cancer; these figures were derived from diagnoses up to the end of 2004 applied to the population in 2008.⁴ In the UK, this equates to more than 2% of the total female population and nearly 12% of the female population aged 65 years and older.²

Of new cases of breast cancer, a small proportion are diagnosed in the advanced stages, when the tumour has spread significantly within the breast (i.e. advanced breast cancer) or to other organs of the body (i.e. metastatic breast cancer).⁵ Many breast cancers are stimulated to grow and change by the naturally occurring female sex hormones, oestrogen and progesterone; these tumours consist of cells that express receptors for oestrogen and/or progesterone (hormone receptor positive). It has been estimated that around 30% of women with earlier stages of breast cancer will eventually be diagnosed with metastatic disease⁶ and the prevalence is thought to be high because some women live with the disease for many years.⁷

The prognosis of metastatic breast cancer depends on age, extent of disease, oestrogen receptor status and previous chemotherapy treatment. A significant number of women who have been previously treated with curative intent also subsequently develop metastases.⁵ There is also evidence that the over-expression of ErbB2, a protein commonly referred to as human epidermal growth factor 2 (HER2), is an important prognostic factor, indicating a more aggressive form of the disease with a more rapid progression and shortened survival time. In women with metastatic breast cancer, up to 30% of women have tumours which over-express HER2, of which approximately 50%¹ have been reported to also express hormone receptors.

Thus at the onset of metastases, the disease is largely incurable and the aim of treatments for these patients is to palliate symptoms, prolong survival and maintain a good quality of life (QoL) with

minimal adverse events (AEs). Choice of treatment depends on previous therapy, oestrogen receptor status, HER2 status and the extent of the disease. Tumours that have receptors to oestrogen and progesterone hormones are more likely to respond to hormonal therapies (such as an aromatase inhibitor) and patients with such tumours tend to have a better prognosis. In contrast, patients with HER2-positive tumours have a worse prognosis and reduced overall survival (OS).

The remit of this appraisal is to review the clinical and cost effectiveness evidence base for lapatinib and trastuzumab in combination with an aromatase inhibitor within their licensed indications for the first-line treatment of metastatic hormone receptor positive breast cancer which over-expresses ErbB2 (HER2) receptor. Evidence for clinical effectiveness will be derived from randomised controlled trials (RCTs). The cost effectiveness of treatments will be expressed in terms of incremental cost per quality adjusted life year (QALY). The time horizon for estimating clinical and cost effectiveness will be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.

Interventions

Lapatinib (Tyverb/Tykerb, GlaxoSmithKline) is an oral therapy which inhibits the tyrosine kinase components of the ErbB2 receptor, and a second receptor, ErbB1 (also commonly known as EGFR1), which have been implicated in the growth of various tumour types. Stimulation of ErbB1 and ErbB2 is associated with cell proliferation, and with multiple processes involved in tumour progression, invasion and metastasis.¹ Trastuzumab (Herceptin, Roche Products) is a recombinant humanised IgG1 monoclonal antibody directed against HER2. Trastuzumab is administered by intravenous infusion.¹ It is indicated for the treatment of metastatic gastric cancer, early breast cancer and metastatic breast cancer.¹

Lapatinib is not currently licensed for use with an aromatase inhibitor; the only approved European Medicines Agency (EMA) indication⁸ is for the treatment of patients with advanced or metastatic breast cancer in combination with capecitabine for patients with advanced or metastatic breast cancer whose tumours over-express ErbB2 (HER2) and who have received prior therapy including anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting. Trastuzumab is licensed for a number of different uses,⁹ including the treatment of patients with HER2-positive metastatic breast cancer as monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone receptor positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments. It is also licensed in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not

suitable and in combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease. Of specific interest to this appraisal, trastuzumab is indicated in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive metastatic breast cancer, not previously treated with trastuzumab.

Place of the interventions in the treatment pathway

In accordance with the NICE guideline for advanced breast cancer,⁵ postmenopausal women with metastatic hormone receptor positive breast cancer which over-expresses HER2 are likely to receive chemotherapy or an aromatase inhibitor as first-line treatment. The choice of treatment largely depends on whether the disease is imminently life-threatening or requires early relief of symptoms because of significant visceral organ involvement. For patients who have been treated with chemotherapy as their first-line treatment, NICE recommends patients receive endocrine therapy (such as an aromatase inhibitor) following the completion of chemotherapy. Commonly trastuzumab is given in combination with chemotherapy for this patient population. NICE has not made any recommendations about combining either lapatinib or trastuzumab with aromatase inhibitors (for any patient population). However, recent phase 1¹⁰ and phase 2¹¹ trials have suggested that there may be a role for lapatinib and/or trastuzumab in combination with an aromatase inhibitor for the first-line treatment of these patients. As already noted, trastuzumab in combination with an aromatase inhibitor has been licensed for the treatment of postmenopausal patients with hormone-receptor positive metastatic breast cancer, not previously treated with trastuzumab.⁹

Relevant comparators

Lapatinib in combination with an aromatase inhibitor will be compared to trastuzumab in combination with an aromatase inhibitor. Both interventions will also be compared to any aromatase inhibitor.

Population and relevant subgroups

The population of interest to the current appraisal is postmenopausal women with hormone receptor positive (i.e. oestrogen receptor and/or progesterone receptor positive) metastatic breast cancer which over-expresses HER2 who have not previously received treatment for metastatic disease and for whom treatment with an aromatase inhibitor is suitable. If the evidence allows, the review will also consider a subgroup of patients based on disease characteristics such as tumour burden, number of metastatic sites and disease free interval (length of time prior to onset of metastatic disease).

Key factors to be addressed

NICE has stated that guidance will only be issued in accordance with the European marketing authorisations for lapatinib and trastuzumab.¹ Of the two interventions being considered in this review, only trastuzumab is currently approved for use with an aromatase inhibitor in the UK.⁹

5. Report methods for the synthesis of clinical effectiveness

Search strategy

Randomised controlled trials will be identified by searching major electronic medical databases including MEDLINE, EMBASE and the Cochrane Library. Information on studies in progress, unpublished research or research reported in the grey literature will be sought by searching a range of relevant databases including National Research Register and Controlled Clinical Trials. In addition, bibliographies of previous reviews and retrieved articles will be searched for further studies. A sample of the search strategy to be used for MEDLINE is presented in Appendix 1.

Further attempts to identify studies will be made by contacting clinical experts and examining the reference lists of all retrieved articles. The submissions provided by manufacturers will be assessed for unpublished data. Citation searches of key articles will be undertaken.

A database of published and unpublished literature will be assembled from systematic searches of electronic sources, hand searching, contacting manufacturers and consultation with experts in the field. The database will be held in the Endnote X2 software package.

Inclusion and exclusion

The inclusion criteria specified in Table 1 will be applied to all studies after screening.

Table 1 Inclusion criteria (clinical effectiveness) based on the decision problem issued by NICE 2009¹

Study design	Randomised controlled trials
Population(s)	Postmenopausal women with HER2-positive metastatic breast cancer which is oestrogen receptor and/or progesterone receptor positive, who have not previously received treatment for metastatic disease and for whom treatment with an aromatase inhibitor is suitable. The following broad subgroups will be considered if data permits: <ul style="list-style-type: none"> • patients based on disease characteristics such as tumour burden • number of metastatic sites • disease free interval (length of time prior to onset of metastatic disease)
Intervention(s)	Lapatinib (Tyverb/Tykerb) in combination with an aromatase inhibitor; Trastuzumab (Herceptin) in combination with an aromatase inhibitor.
Comparators	The two interventions should be compared with each other; The interventions should also be compared with aromatase inhibitors*
Outcomes	The outcome measures to be considered include: <ul style="list-style-type: none"> • overall survival • progression free survival • time to progression • response rate • adverse effects of treatment • clinical benefit rate • health-related quality of life.

* The licensed aromatase inhibitors for first line use are letrozole (Femara) and anastrozole (Arimidex). Exemestane (Aromasin) is currently only licensed for second-line therapy but may still be considered a comparator if in routine use

Two reviewers will independently screen all titles and abstracts of papers identified in the initial search. Discrepancies will be resolved by discussion with involvement of a third reviewer where necessary. If time constraints allow, where a study is found which meets all the inclusion criteria apart from the relevant outcomes, attempts will be made to collect this information from authors. Where studies do not meet the inclusion criteria they will be excluded.

Data extraction strategy

Using a standardised data extraction form (see Appendix 2), data will be extracted by one reviewer and independently checked for accuracy by a second reviewer. Disagreement will be resolved through consensus and if necessary a third reviewer will be consulted. If time constraints allow, attempts will be made to contact authors for missing data. Data from multiple publications will be extracted and reported as a single study.

Quality assessment strategy

The quality of the individual clinical-effectiveness studies will be assessed by one reviewer, and independently checked for agreement by a second. Disagreements will be resolved through consensus and if necessary a third reviewer will be consulted. The quality of the clinical-effectiveness studies will be assessed according to criteria based on the CRD's guidance for undertaking reviews in healthcare.¹²

Methods of analysis/synthesis

The results of the data extraction and quality assessment for each study will be presented in structured tables and as a narrative summary. The possible effects of study quality on the effectiveness data and review findings will be discussed. Studies will be grouped according to the comparator used. All summary statistics will be extracted for each outcome and where possible, data will be pooled using a standard meta-analysis.¹³ Heterogeneity between the studies will be assessed using the I^2 test.¹⁴ Both fixed and random effects results will be presented as forest plots. Where a direct comparison between lapatinib in combination with an aromatase inhibitor and trastuzumab in combination with an aromatase inhibitor is not possible, if sufficient data allows, an indirect comparisons analysis will be conducted.¹⁵

6. Report methods for synthesising evidence of cost effectiveness

The literature review of economic evidence will include the quality assessment of published cost-minimisation, cost effectiveness, cost-utility and cost-benefit analyses. Economic model(s) included in the manufacturer submission(s) will be critiqued as appropriate.

If appropriate data are available, an economic model will be developed to estimate the cost effectiveness of lapatinib and trastuzumab in combination with an aromatase inhibitor for first-line treatment of hormone receptor positive metastatic breast cancer which over-expresses HER2.

The likely budget impact that would arise for the NHS in England and Wales will also be estimated. This budget impact will take account of available information on current and anticipated patient numbers and service configuration for the treatment of this condition.

Search strategy

The search strategies detailed in section 5 will be adapted accordingly to identify economic evaluations for inclusion in the cost effectiveness literature review. At the same time, the search strategy will be used to identify economic evaluations and other information sources which may include data that can be used to populate a de novo economic model where appropriate. Other searching activities, including electronic searching of online health economics journals and contacting experts in the field will also be undertaken. Full details of the search process will be presented in the final report.

Inclusion and exclusion

Only full economic evaluations that compare two or more options and consider both costs and consequences (including cost effectiveness, cost-utility and cost-benefit analyses) will be included in the review of published literature. In addition, any economic models included in the manufacturer submission(s) will be included as appropriate. The following outcomes will be examined:

- Incremental cost per life year gained (LYG)
- Incremental cost per QALY

Data extraction strategy

Data will be extracted by one reviewer and independently checked for accuracy by a second reviewer. Disagreement will be resolved through consensus and, if necessary, a third reviewer will be consulted. If time constraints allow, attempts will be made to contact authors for missing data. Data from multiple publications will be extracted and reported as a single study.

Quality assessment strategy

The quality of the individual cost effectiveness studies/models will be assessed by one reviewer, and independently checked for agreement by a second. Disagreements will be resolved through consensus and, if necessary, a third reviewer will be consulted. The quality of the cost effectiveness

studies/models will be assessed according to the guidelines for authors and peer reviewers of economic submissions to the BMJ.¹⁶

Methods for estimating costs, benefits and cost effectiveness ratios

Cost data

The primary perspective for the analysis of cost information will be the NHS and Personal Social Services. Cost data will therefore focus on the marginal direct health service costs associated with the interventions. The relevant time horizon of analysis will be a patient's lifetime in order to reflect the chronic nature of the disease.

Quantities of resources used will be identified from consultation with experts, primary data from relevant sources and the reviewed literature. Unit cost data will be extracted from the literature (e.g. Personal Social Services Research Unit) or obtained from other relevant sources (drug price lists, NHS reference costs and Chartered Institute of Public Finance and Accounting cost databases).

Where appropriate, costs will be discounted at 3.5% per annum, the rate recommended in NICE guidance to manufacturers and sponsors of submissions.¹⁷

Assessment of benefits

A balance sheet will be constructed to list benefits and costs arising from alternative treatment options. The Assessment Group (AG) anticipates that the main measures of benefit will be increased QALYs.

Where appropriate, effectiveness and other measures of benefit will be discounted at 3.5%, the rate recommended in NICE guidance to manufacturers and sponsors of submissions.¹⁷

Modelling

The ability of the AG to construct an economic model will depend on the data available. Where modelling is appropriate, a summary description of the model and a critical appraisal of key structures, assumptions, resources, data and sensitivity analysis (see below) will be presented. In addition, the AG will provide an assessment of the model's strengths and weaknesses and discuss the implications of using different assumptions in the model. Reasons for any major discrepancies between the results obtained from the AG model and the manufacturer model(s) will be explored.

The time horizon will be a patient's lifetime in order to reflect the chronic nature of the disease. Both costs and QALYs will be discounted at 3.5% as recommended by NICE.¹⁷

A formal combination of costs and benefits will also be performed, although the type of economic evaluation will only be chosen in light of the variations in outcome identified from the clinical-effectiveness review evidence.

If data are available, the results will be presented as incremental cost per QALY ratios for each alternative considered. If sufficient data are not available to construct these measures with reasonable precision, incremental cost effectiveness analysis or cost-minimisation analysis will be undertaken. Any failure to meet the reference case will be clearly specified and justified, and the likely implications will, as far as possible, be quantified.

Sensitivity analysis

If appropriate, sensitivity analysis will be applied to the AG model in order to assess the robustness of the results to realistic variations in the levels of the underlying parameter values and key assumptions. Where the overall results are sensitive to a particular variable, the sensitivity analysis will explore the exact nature of the impact of variations.

Imprecision in the principal model cost effectiveness results with respect to key parameter values will be assessed by use of techniques compatible with the modelling methodology deemed appropriate to the research question and to the potential impact on decision making for specific comparisons (e.g. multi-way sensitivity analysis, cost effectiveness acceptability curves etc).

7. Handling the manufacturer submission(s)

All data submitted by the drug manufacturers received prior to 14/06/2010 and meeting the set inclusion criteria will be considered for inclusion in the review. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review, they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluation included in the manufacturer submission(s), provided it complies with NICE's advice on presentation, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model. If the AG judges that the existing economic evidence is not robust, then further work will be undertaken, either by adapting what already exists or developing a *de-novo model*.

Any 'commercial in confidence' data taken from a manufacturer submission, and specified as confidential in the check list, will be highlighted in blue and underlined in the assessment report (followed by an indication of the relevant manufacturer name, e.g. in brackets). Any 'academic in confidence' information will be highlighted in yellow and underlined in the assessment report.

8. Competing interests of authors

None

References

1. National Institute for Health and Clinical Excellence (NICE). Final scope for the proposed appraisal of lapatinib and trastuzumab in combination with an aromatase inhibitor for the first line treatment of hormone receptor positive metastatic breast cancer which over expresses HER2. January 2010.
2. Cancer Research UK. Breast cancer - UK incidence statistics. [cited 25/01/2010]; Available from: <http://info.cancerresearchuk.org/cancerstats/types/breast/incidence/>.
3. Cancer Research UK. Breast cancer - UK mortality statistics. [cited 25/01/2010]; Available from: <http://info.cancerresearchuk.org/cancerstats/types/breast/mortality/index.htm>.
4. Maddams JMH, Devane C. Cancer Prevalence in the UK 2008. London: Thames Cancer Registry and Macmillan Cancer Support; 2008.
5. National Institute for Health and Clinical Excellence (NICE). Advanced breast cancer: diagnosis and treatment. NICE clinical guideline 81. 2009 [cited 26/01/2010]; Available from: <http://www.nice.org.uk/Guidance/CG81>.
6. MBC Advocacy Working Group. Metastatic breast cancer patients: addressing their unmet needs. Community Oncology. 2008; 5(12):645-9.
7. Stebbing J, Slater S, Slevin M. Breast cancer (metastatic). 2007 [cited 26/01/2010]; Available from: http://clinicalevidence.bmj.com/ceweb/conditions/woh/0811/0811_background.jsp.
8. European Medicines Agency (EMA). Committee for Medicinal Products for Human use summary of positive opinion for Tyverb. 2008 [cited 26/01/2010]; Available from: http://www.ema.europa.eu/pdfs/human/opinion/Tyverb_38267507en.pdf.
9. European Medicines Agency (EMA). Committee for Medicinal Products for Human use post-authorisation summary of positive opinion for Herceptin. 2009 [cited 26/01/2010]; Available from: http://www.ema.europa.eu/pdfs/human/opinion/Herceptin_82246709en.pdf.
10. Chu I, Blackwell K, Chen S, Slingerland J. The dual ErbB1/ErbB2 inhibitor, lapatinib (GW572016), cooperates with tamoxifen to inhibit both cell proliferation- and estrogen-dependent gene expression in antiestrogen-resistant breast cancer. Cancer Res. 2005; 65(1):18-25.
11. Marcom PK, Isaacs C, Harris L, Wong ZW, Kommarreddy A, Novielli N, *et al*. The combination of letrozole and trastuzumab as first or second-line biological therapy produces durable responses in a subset of HER2-positive and ER positive advanced breast cancers. Breast Cancer Res Treat. 2007; 102(1):43-9.
12. Centre for Reviews and Dissemination (CRD). CRD's guidance for undertaking reviews in healthcare: Systematic Reviews (3rd Edition). York: CRD, University of York 2008.
13. Egger M, Smith GD, Altman DG. Systematic reviews in health care – Meta-analysis in context: BMJ books; 2001.
14. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analysis. British Medical Journal. 2003; 327:557-60.
15. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med. 2004; 23(20):3105-24.
16. Drummond M, Jefferson T. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ. 1996; 313(7052):275-83.
17. National Institute for Health and Clinical Excellence (NICE). Guide to the methods of technology appraisal. London: NICE 2008.

9. Appendices

Appendix 1: draft search strategy for MEDLINE

- 1 (lapatinib or tykerb or tyverb or lapatinib ditosylate).af.
- 2 (trastuzumab or herceptin).af.
- 3 (letrozole or femara or anastrozole or arimidex or exemestane or aromasin).af.
- 4 exp Aromatase Inhibitors/
- 5 aromatase inhibitor\$.tw.
- 6 1 or 2
- 7 or/3-5
- 8 6 and 7
- 9 exp Breast Neoplasms/
- 10 (breast\$ adj5 (neoplasm\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or dcis or ductal or infiltrat\$ or intraductal\$ or lobular or medullary)).mp.
- 11 9 or 10
- 12 8 and 11

Appendix 2: data extraction forms

Clinical effectiveness data will be extracted and entered under the following headings:

Study details

- Author (i.e. Jones et al.)
- Year (i.e. year of publication or date of interim data collection)
- Endnote reference (endnote reference number)
- Study design (summary of study design and details of subgroup analyses [if any])
- Inclusion/exclusion criteria (summary of trial inclusion/exclusion criteria)
- Follow-up duration

Intervention details

Data for each intervention will be entered in the following format:

- Intervention (i.e. drug name[s])
- Dose(s) of intervention(s) (dose)

Participant characteristics

Data for each intervention will be entered in the following format:

- Number of participants enrolled (summary or 'not stated')
- Number of participants lost to follow up (summary or 'not stated')
- Average age (mean/median, range, standard deviation) (age)
- Disease characteristics (tumour burden, number of metastatic sites, interval between early breast cancer and the onset of metastatic breast cancer) (disease)

Outcomes: Definitions and measures

- Primary outcome (description of outcome as reported)
- Secondary outcome (description of outcome as reported)
- Adverse events (description of outcome as reported)
- Quality of life (description of outcome as reported)

Outcomes: Results

Data for all outcomes specified in the protocol will be entered in the following format:

- Outcome (description of outcome measure)
- Results for intervention (summary or 'not stated')

Economic evaluation data will be extracted as follows:

- Endnote reference (in the form of xyz, no '#')
- Primary source [database, handsearching, manufacturer submission]
- Author (i.e. Jones et al)
- Date (i.e. year of publication or date of interim data collection)
- Type of economic evaluation [cost effectiveness analysis, cost utility analysis, cost benefit analysis]
- Currency used [\$US, \$AS, £Sterling, not stated]
- Year to which costs apply (enter year or not stated)
- Perspective used (e.g. health service, hospital, third party payer, patient, unclear)
- Study population (describe the population characteristics)
- Intervention 1 (description of intervention 1)
- Intervention 2 (description of intervention 2)
- Source of effectiveness data [single study, review/synthesis of previous studies, expert opinion, not stated]
- Source of resource use data [single study, review/synthesis of previous studies, expert opinion, not stated]
- Source of unit cost data [literature, data from actual source, combination of literature and data from actual source, not stated]
- Link between cost and effectiveness data [prospective/concurrent, retrospective/disconnected...]
- Clinical outcomes measured and methods of valuation used (summary of outcomes and valuation methods used)
- Cost data handled appropriately (summary of methods used to e.g. discount, inflate)
- Modelling (summary of models used, type of model, purpose of model, components of model, key input parameters and model outputs)
- Outcome measures used in economic evaluations (summary of outcome measures used in economic evaluations e.g. incremental cost effectiveness ratio, net benefit, cost effectiveness acceptability curve)
- Statistical analysis for patient-level stochastic data (summary of analyses used)
- Appropriateness of statistical analysis (comment on appropriateness)
- Uncertainty around cost effectiveness expressed
- Appropriateness of method of dealing with uncertainty around cost effectiveness
- Sensitivity analysis (list summary of analysis)
- Appropriateness of sensitivity analysis (comment on appropriateness)
- Modelling inputs and techniques appropriate
- Author's conclusions (list as in publication)
- Implications for practice (summary of implications)
- Comments (summary of comments)

Appendix 3: details of TAR team

Details of the TAR team are provided separately – see *lapatinib+trastuzumab_details_of_TAR_team.doc*

Health Technology Assessment programme

Director,
Professor Tom Walley, CBE,
 Director, NIHR HTA programme, Professor of Clinical Pharmacology,
 University of Liverpool

Deputy Director,
Professor Hywel Williams,
 Professor of Dermato-Epidemiology,
 Centre of Evidence-Based Dermatology,
 University of Nottingham

Prioritisation Group

Members

<p>Chair, Professor Tom Walley, CBE, Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool</p> <p>Professor Imti Choonara, Professor in Child Health, Academic Division of Child Health, University of Nottingham Chair – Pharmaceuticals Panel</p> <p>Dr Bob Coates, Consultant Advisor – Disease Prevention Panel</p> <p>Dr Andrew Cook, Consultant Advisor – Intervention Procedures Panel</p> <p>Dr Peter Davidson, Director of NETSCC, Health Technology Assessment</p>	<p>Dr Nick Hicks, Consultant Adviser – Diagnostic Technologies and Screening Panel, Consultant Advisor–Psychological and Community Therapies Panel</p> <p>Ms Susan Hird, Consultant Advisor, External Devices and Physical Therapies Panel</p> <p>Professor Sallie Lamb, Director, Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick Chair – HTA Clinical Evaluation and Trials Board</p> <p>Professor Jonathan Michaels, Professor of Vascular Surgery, Sheffield Vascular Institute, University of Sheffield Chair – Interventional Procedures Panel</p>	<p>Professor Ruairidh Milne, Director – External Relations</p> <p>Dr John Pounsford, Consultant Physician, Directorate of Medical Services, North Bristol NHS Trust Chair – External Devices and Physical Therapies Panel</p> <p>Dr Vaughan Thomas, Consultant Advisor – Pharmaceuticals Panel, Clinical Lead – Clinical Evaluation Trials Prioritisation Group</p> <p>Professor Margaret Thorogood, Professor of Epidemiology, Health Sciences Research Institute, University of Warwick Chair – Disease Prevention Panel</p>	<p>Professor Lindsay Turnbull, Professor of Radiology, Centre for the MR Investigations, University of Hull Chair – Diagnostic Technologies and Screening Panel</p> <p>Professor Scott Weich, Professor of Psychiatry, Health Sciences Research Institute, University of Warwick Chair – Psychological and Community Therapies Panel</p> <p>Professor Hywel Williams, Director of Nottingham Clinical Trials Unit, Centre of Evidence-Based Dermatology, University of Nottingham Chair – HTA Commissioning Board Deputy HTA Programme Director</p>
---	---	--	--

HTA Commissioning Board

Chair,
Professor Hywel Williams,
 Professor of Dermato-Epidemiology, Centre of Evidence-Based Dermatology, University of Nottingham

Deputy Chair,
Professor Jon Deeks,
 Department of Public Health and Epidemiology, University of Birmingham

Professor Tom Walley, CBE,
 Professor of Clinical Pharmacology, Director, NIHR HTA programme, University of Liverpool

Members

<p>Professor Ann Ashburn, Professor of Rehabilitation and Head of Research, Southampton General Hospital</p> <p>Professor Peter Brocklehurst, Professor of Women's Health, Institute for Women's Health, University College London</p> <p>Professor Jenny Donovan, Professor of Social Medicine, University of Bristol</p> <p>Professor Jonathan Green, Professor and Acting Head of Department, Child and Adolescent Psychiatry, University of Manchester Medical School</p>	<p>Professor John W Gregory, Professor in Paediatric Endocrinology, Department of Child Health, Wales School of Medicine, Cardiff University</p> <p>Professor Steve Halligan, Professor of Gastrointestinal Radiology, University College Hospital, London</p> <p>Professor Freddie Hamdy, Professor of Urology, Head of Nuffield Department of Surgery, University of Oxford</p> <p>Professor Allan House, Professor of Liaison Psychiatry, University of Leeds</p>	<p>Dr Martin J Landray, Reader in Epidemiology, Honorary Consultant Physician, Clinical Trial Service Unit, University of Oxford</p> <p>Professor Stephen Morris, Professor of Health Economics, University College London, Research Department of Epidemiology and Public Health, University College London</p> <p>Professor Irwin Nazareth, Professor of Primary Care and Head of Department, Department of Primary Care and Population Sciences, University College London</p>	<p>Professor E Andrea Nelson, Professor of Wound Healing and Director of Research, School of Healthcare, University of Leeds</p> <p>Professor John David Norrie, Chair in Clinical Trials and Biostatistics, Robertson Centre for Biostatistics, University of Glasgow</p> <p>Dr Rafael Perera, Lecturer in Medical Statistics, Department of Primary Health Care, University of Oxford</p>
---	--	--	--

HTA Commissioning Board *(continued)*

Professor Barney Reeves,
Professorial Research Fellow
in Health Services Research,
Department of Clinical Science,
University of Bristol

Professor Martin Underwood,
Professor of Primary Care
Research, Warwick Medical
School, University of Warwick

Professor Marion Walker,
Professor in Stroke Rehabilitation,
Associate Director UK Stroke
Research Network, University of
Nottingham

Dr Duncan Young,
Senior Clinical Lecturer and
Consultant, Nuffield Department
of Anaesthetics, University of
Oxford

Observers

Dr Tom Foulks,
Medical Research Council

Dr Kay Pattison,
Senior NIHR Programme
Manager, Department of Health

HTA Clinical Evaluation and Trials Board

Chair,

Professor Sallie Lamb,
Director,
Warwick Clinical Trials Unit,
Warwick Medical School,
University of Warwick and Professor of
Rehabilitation,
Nuffield Department of Orthopaedic,
Rheumatology and Musculoskeletal Sciences,
University of Oxford

Deputy Chair,

Professor Jenny Hewison,
Professor of the Psychology of Health Care,
Leeds Institute of Health Sciences,
University of Leeds

Programme Director,

Professor Tom Walley, CBE,
Director, NIHR HTA programme, Professor of
Clinical Pharmacology, University of Liverpool

Members

Professor Keith Abrams,
Professor of Medical Statistics,
Department of Health Sciences,
University of Leicester

Dr Jennifer Burr,
Director, Centre for Healthcare
Randomised trials (CHART),
University of Aberdeen

Professor Paul Jones,
Professor of Respiratory Medicine,
Department of Cardiac and
Vascular Science, St George's
Hospital Medical School,
University of London

Professor Jonathan Sterne,
Professor of Medical Statistics
and Epidemiology, Department
of Social Medicine, University of
Bristol

Professor Martin Bland,
Professor of Health Statistics,
Department of Health Sciences,
University of York

Professor Linda Davies,
Professor of Health Economics,
Health Sciences Research Group,
University of Manchester

Professor Khalid Khan,
Professor of Women's Health and
Clinical Epidemiology, Barts and
the London School of Medicine,
Queen Mary, University of London

Mr Andy Vail,
Senior Lecturer, Health Sciences
Research Group, University of
Manchester

Professor Jane Blazeby,
Professor of Surgery and
Consultant Upper GI Surgeon,
Department of Social Medicine,
University of Bristol

Professor Simon Gilbody,
Prof of Psych Medicine and Health
Services Research, Department of
Health Sciences, University of York

Professor Richard J McManus,
Professor of Primary Care
Cardiovascular Research, Primary
Care Clinical Sciences Building,
University of Birmingham

Professor Clare Wilkinson,
Professor of General Practice and
Director of Research North Wales
Clinical School, Department of
Primary Care and Public Health,
Cardiff University

Professor Julia M Brown,
Director, Clinical Trials Research
Unit, University of Leeds

Professor Steven Goodacre,
Professor and Consultant in
Emergency Medicine, School of
Health and Related Research,
University of Sheffield

Professor Helen Rodgers,
Professor of Stroke Care, Institute
for Ageing and Health, Newcastle
University

Dr Ian B Wilkinson,
Senior Lecturer and Honorary
Consultant, Clinical Pharmacology
Unit, Department of Medicine,
University of Cambridge

Professor Alistair Burns,
Professor of Old Age Psychiatry,
Psychiatry Research Group, School
of Community-Based Medicine,
The University of Manchester &
National Clinical Director for
Dementia, Department of Health

Professor Dyfrig Hughes,
Professor of Pharmacoeconomics,
Centre for Economics and Policy
in Health, Institute of Medical
and Social Care Research, Bangor
University

Professor Ken Stein,
Professor of Public Health,
Peninsula Technology Assessment
Group, Peninsula College
of Medicine and Dentistry,
Universities of Exeter and
Plymouth

Observers

Ms Kate Law,
Director of Clinical Trials,
Cancer Research UK

Dr Morven Roberts,
Clinical Trials Manager, Health
Services and Public Health
Services Board, Medical Research
Council

Diagnostic Technologies and Screening Panel

Members

<p>Chair, Professor Lindsay Wilson Turnbull, Scientific Director of the Centre for Magnetic Resonance Investigations and YCR Professor of Radiology, Hull Royal Infirmary</p> <p>Professor Judith E Adams, Consultant Radiologist, Manchester Royal Infirmary, Central Manchester & Manchester Children's University Hospitals NHS Trust, and Professor of Diagnostic Radiology, University of Manchester</p> <p>Mr Angus S Arunkalaivanan, Honorary Senior Lecturer, University of Birmingham and Consultant Urogynaecologist and Obstetrician, City Hospital, Birmingham</p> <p>Dr Diana Baralle, Consultant and Senior Lecturer in Clinical Genetics, University of Southampton</p>	<p>Dr Stephanie Dancer, Consultant Microbiologist, Hairmyres Hospital, East Kilbride</p> <p>Dr Diane Eccles, Professor of Cancer Genetics, Wessex Clinical Genetics Service, Princess Anne Hospital</p> <p>Dr Trevor Friedman, Consultant Liaison Psychiatrist, Brandon Unit, Leicester General Hospital</p> <p>Dr Ron Gray, Consultant, National Perinatal Epidemiology Unit, Institute of Health Sciences, University of Oxford</p> <p>Professor Paul D Griffiths, Professor of Radiology, Academic Unit of Radiology, University of Sheffield</p> <p>Mr Martin Hooper, Public contributor</p>	<p>Professor Anthony Robert Kendrick, Associate Dean for Clinical Research and Professor of Primary Medical Care, University of Southampton</p> <p>Dr Nicola Lennard, Senior Medical Officer, MHRA</p> <p>Dr Anne Mackie, Director of Programmes, UK National Screening Committee, London</p> <p>Mr David Mathew, Public contributor</p> <p>Dr Michael Millar, Consultant Senior Lecturer in Microbiology, Department of Pathology & Microbiology, Barts and The London NHS Trust, Royal London Hospital</p> <p>Mrs Una Rennard, Public contributor</p>	<p>Dr Stuart Smellie, Consultant in Clinical Pathology, Bishop Auckland General Hospital</p> <p>Ms Jane Smith, Consultant Ultrasound Practitioner, Leeds Teaching Hospital NHS Trust, Leeds</p> <p>Dr Allison Streetly, Programme Director, NHS Sickle Cell and Thalassaemia Screening Programme, King's College School of Medicine</p> <p>Dr Matthew Thompson, Senior Clinical Scientist and GP, Department of Primary Health Care, University of Oxford</p> <p>Dr Alan J Williams, Consultant Physician, General and Respiratory Medicine, The Royal Bournemouth Hospital</p>
--	--	---	---

Observers

<p>Dr Tim Elliott, Team Leader, Cancer Screening, Department of Health</p> <p>Dr Joanna Jenkinson, Board Secretary, Neurosciences and Mental Health Board (NMHB), Medical Research Council</p>	<p>Professor Julietta Patnick, Director, NHS Cancer Screening Programme, Sheffield</p> <p>Dr Kay Pattison, Senior NIHR Programme Manager, Department of Health</p>	<p>Professor Tom Walley, CBE, Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool</p>	<p>Dr Ursula Wells, Principal Research Officer, Policy Research Programme, Department of Health</p>
--	--	---	---

Disease Prevention Panel

Members

<p>Chair, Professor Margaret Thorogood, Professor of Epidemiology, University of Warwick Medical School, Coventry</p> <p>Dr Robert Cook, Clinical Programmes Director, Bazian Ltd, London</p> <p>Dr Colin Greaves, Senior Research Fellow, Peninsula Medical School (Primary Care)</p> <p>Mr Michael Head, Public contributor</p>	<p>Professor Cathy Jackson, Professor of Primary Care Medicine, Bute Medical School, University of St Andrews</p> <p>Dr Russell Jago, Senior Lecturer in Exercise, Nutrition and Health, Centre for Sport, Exercise and Health, University of Bristol</p> <p>Dr Julie Mytton, Consultant in Child Public Health, NHS Bristol</p>	<p>Professor Irwin Nazareth, Professor of Primary Care and Director, Department of Primary Care and Population Sciences, University College London</p> <p>Dr Richard Richards, Assistant Director of Public Health, Derbyshire County Primary Care Trust</p> <p>Professor Ian Roberts, Professor of Epidemiology and Public Health, London School of Hygiene & Tropical Medicine</p>	<p>Dr Kenneth Robertson, Consultant Paediatrician, Royal Hospital for Sick Children, Glasgow</p> <p>Dr Catherine Swann, Associate Director, Centre for Public Health Excellence, NICE</p> <p>Mrs Jean Thurston, Public contributor</p> <p>Professor David Weller, Head, School of Clinical Science and Community Health, University of Edinburgh</p>
---	--	--	--

Observers

<p>Ms Christine McGuire, Research & Development, Department of Health</p>	<p>Dr Kay Pattison, Senior NIHR Programme Manager, Department of Health</p>	<p>Professor Tom Walley, CBE, Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool</p>
---	---	---

External Devices and Physical Therapies Panel

Members

Chair, Dr John Pounsford, Consultant Physician North Bristol NHS Trust	Dr Dawn Carnes, Senior Research Fellow, Barts and the London School of Medicine and Dentistry	Dr Shaheen Hamdy, Clinical Senior Lecturer and Consultant Physician, University of Manchester	Mr Jim Reece, Public contributor
Deputy Chair, Professor E Andrea Nelson, Reader in Wound Healing and Director of Research, University of Leeds	Dr Emma Clark, Clinician Scientist Fellow & Cons. Rheumatologist, University of Bristol	Professor Christine Norton, Professor of Clinical Nursing Innovation, Bucks New University and Imperial College Healthcare NHS Trust	Professor Maria Stokes, Professor of Neuromusculoskeletal Rehabilitation, University of Southampton
Professor Bipin Bhakta, Charterhouse Professor in Rehabilitation Medicine, University of Leeds	Mrs Anthea De Barton-Watson, Public contributor	Dr Lorraine Pinnigton, Associate Professor in Rehabilitation, University of Nottingham	Dr Pippa Tyrrell, Senior Lecturer/Consultant, Salford Royal Foundation Hospitals' Trust and University of Manchester
Mrs Penny Calder, Public contributor	Professor Nadine Foster, Professor of Musculoskeletal Health in Primary Care Arthritis Research, Keele University	Dr Kate Radford, Senior Lecturer (Research), University of Central Lancashire	Dr Nefyn Williams, Clinical Senior Lecturer, Cardiff University

Observers

Dr Kay Pattison, Senior NIHR Programme Manager, Department of Health	Dr Morven Roberts, Clinical Trials Manager, Health Services and Public Health Services Board, Medical Research Council	Professor Tom Walley, CBE, Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool	Dr Ursula Wells, Principal Research Officer, Policy Research Programme, Department of Health
---	---	---	---

Interventional Procedures Panel

Members

Chair, Professor Jonathan Michaels, Professor of Vascular Surgery, University of Sheffield	Mr Seumas Eckford, Consultant in Obstetrics & Gynaecology, North Devon District Hospital	Dr Fiona Lecky, Senior Lecturer/Honorary Consultant in Emergency Medicine, University of Manchester/Salford Royal Hospitals NHS Foundation Trust	Professor Jon Moss, Consultant Interventional Radiologist, North Glasgow Hospitals University NHS Trust
Deputy Chair, Mr Michael Thomas, Consultant Colorectal Surgeon, Bristol Royal Infirmary	Professor Sam Eljamel, Consultant Neurosurgeon, Ninewells Hospital and Medical School, Dundee	Dr Nadim Malik, Consultant Cardiologist/Honorary Lecturer, University of Manchester	Dr Simon Padley, Consultant Radiologist, Chelsea & Westminster Hospital
Mrs Isabel Boyer, Public contributor	Dr Adele Fielding, Senior Lecturer and Honorary Consultant in Haematology, University College London Medical School	Mr Hisham Mehanna, Consultant & Honorary Associate Professor, University Hospitals Coventry & Warwickshire NHS Trust	Dr Ashish Paul, Medical Director, Bedfordshire PCT
Mr Sankaran Chandra Sekharan, Consultant Surgeon, Breast Surgery, Colchester Hospital University NHS Foundation Trust	Dr Matthew Hatton, Consultant in Clinical Oncology, Sheffield Teaching Hospital Foundation Trust	Dr Jane Montgomery, Consultant in Anaesthetics and Critical Care, South Devon Healthcare NHS Foundation Trust	Dr Sarah Purdy, Consultant Senior Lecturer, University of Bristol
Professor Nicholas Clarke, Consultant Orthopaedic Surgeon, Southampton University Hospitals NHS Trust	Dr John Holden, General Practitioner, Garswood Surgery, Wigan		Dr Matthew Wilson, Consultant Anaesthetist, Sheffield Teaching Hospitals NHS Foundation Trust
Ms Leonie Cooke, Public contributor			Professor Yit Chiun Yang, Consultant Ophthalmologist, Royal Wolverhampton Hospitals NHS Trust

Observers

Dr Kay Pattison, Senior NIHR Programme Manager, Department of Health	Dr Morven Roberts, Clinical Trials Manager, Health Services and Public Health Services Board, Medical Research Council	Professor Tom Walley, CBE, Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool	Dr Ursula Wells, Principal Research Officer, Policy Research Programme, Department of Health
---	---	---	---

Pharmaceuticals Panel

Members

Chair, Professor Imti Choonara, Professor in Child Health, University of Nottingham	Dr James Gray, Consultant Microbiologist, Department of Microbiology, Birmingham Children's Hospital NHS Foundation Trust	Dr Maria Kouimtzi, Pharmacy and Informatics Director, Global Clinical Solutions, Wiley-Blackwell	Mrs Katrina Simister, Assistant Director New Medicines, National Prescribing Centre, Liverpool
Deputy Chair, Dr Yoon K Loke, Senior Lecturer in Clinical Pharmacology, University of East Anglia	Dr Jurjees Hasan, Consultant in Medical Oncology, The Christie, Manchester	Professor Femi Oyeboode, Consultant Psychiatrist and Head of Department, University of Birmingham	Professor Donald Singer, Professor of Clinical Pharmacology and Therapeutics, Clinical Sciences Research Institute, CSB, University of Warwick Medical School
Dr Martin Ashton-Key, Medical Advisor, National Commissioning Group, NHS London	Dr Carl Heneghan, Deputy Director Centre for Evidence-Based Medicine and Clinical Lecturer, Department of Primary Health Care, University of Oxford	Dr Andrew Prentice, Senior Lecturer and Consultant Obstetrician and Gynaecologist, The Rosie Hospital, University of Cambridge	Mr David Symes, Public contributor
Dr Peter Elton, Director of Public Health, Bury Primary Care Trust	Dr Dyfrig Hughes, Reader in Pharmacoeconomics and Deputy Director, Centre for Economics and Policy in Health, IMSCaR, Bangor University	Ms Amanda Roberts, Public contributor	Dr Arnold Zermansky, General Practitioner, Senior Research Fellow, Pharmacy Practice and Medicines Management Group, Leeds University
Dr Ben Goldacre, Research Fellow, Epidemiology London School of Hygiene and Tropical Medicine		Dr Gillian Shepherd, Director, Health and Clinical Excellence, Merck Serono Ltd	

Observers

Dr Kay Pattison, Senior NIHR Programme Manager, Department of Health	Dr Heike Weber, Programme Manager, Medical Research Council	Dr Ursula Wells, Principal Research Officer, Policy Research Programme, Department of Health
Mr Simon Reeve, Head of Clinical and Cost- Effectiveness, Medicines, Pharmacy and Industry Group, Department of Health	Professor Tom Walley, CBE, Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool	

Psychological and Community Therapies Panel

Members

Chair, Professor Scott Weich, Professor of Psychiatry, University of Warwick, Coventry	Mrs Val Carlill, Public contributor	Dr Jeremy J Murphy, Consultant Physician and Cardiologist, County Durham and Darlington Foundation Trust	Dr Paul Ramchandani, Senior Research Fellow/Cons. Child Psychiatrist, University of Oxford
Deputy Chair, Dr Howard Ring, Consultant & University Lecturer in Psychiatry, University of Cambridge	Dr Steve Cunningham, Consultant Respiratory Paediatrician, Lothian Health Board	Dr Richard Neal, Clinical Senior Lecturer in General Practice, Cardiff University	Dr Karen Roberts, Nurse/Consultant, Dunston Hill Hospital, Tyne and Wear
Professor Jane Barlow, Professor of Public Health in the Early Years, Health Sciences Research Institute, Warwick Medical School	Dr Anne Hesketh, Senior Clinical Lecturer in Speech and Language Therapy, University of Manchester	Mr John Needham, Public contributor	Dr Karim Saad, Consultant in Old Age Psychiatry, Coventry and Warwickshire Partnership Trust
Dr Sabyasachi Bhaumik, Consultant Psychiatrist, Leicestershire Partnership NHS Trust	Dr Peter Langdon, Senior Clinical Lecturer, School of Medicine, Health Policy and Practice, University of East Anglia	Ms Mary Nettle, Mental Health User Consultant	Dr Lesley Stockton, Lecturer, School of Health Sciences, University of Liverpool
	Dr Yann Lefeuvre, GP Partner, Burrage Road Surgery, London	Professor John Potter, Professor of Ageing and Stroke Medicine, University of East Anglia	Dr Simon Wright, GP Partner, Walkden Medical Centre, Manchester
		Dr Greta Rait, Senior Clinical Lecturer and General Practitioner, University College London	

Observers

Dr Kay Pattison, Senior NIHR Programme Manager, Department of Health	Dr Morven Roberts, Clinical Trials Manager, Health Services and Public Health Services Board, Medical Research Council	Professor Tom Walley, CBE, Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool	Dr Ursula Wells, Principal Research Officer, Policy Research Programme, Department of Health
--	--	--	---

Expert Advisory Network

Members

Professor Douglas Altman,
Professor of Statistics in Medicine,
Centre for Statistics in Medicine,
University of Oxford

Professor John Bond,
Professor of Social Gerontology
& Health Services Research,
University of Newcastle upon Tyne

Professor Andrew Bradbury,
Professor of Vascular Surgery,
Solihull Hospital, Birmingham

Mr Shaun Brogan,
Chief Executive, Ridgeway
Primary Care Group, Aylesbury

Mrs Stella Burnside OBE,
Chief Executive, Regulation and
Improvement Authority, Belfast

Ms Tracy Bury,
Project Manager, World
Confederation of Physical Therapy,
London

Professor Iain T Cameron,
Professor of Obstetrics and
Gynaecology and Head of the
School of Medicine, University of
Southampton

Professor Bruce Campbell,
Consultant Vascular & General
Surgeon, Royal Devon & Exeter
Hospital, Wonford

Dr Christine Clark,
Medical Writer and Consultant
Pharmacist, Rossendale

Professor Collette Clifford,
Professor of Nursing and Head
of Research, The Medical School,
University of Birmingham

Professor Barry Cookson,
Director, Laboratory of Hospital
Infection, Public Health
Laboratory Service, London

Dr Carl Counsell,
Clinical Senior Lecturer in
Neurology, University of Aberdeen

Professor Howard Cuckle,
Professor of Reproductive
Epidemiology, Department
of Paediatrics, Obstetrics &
Gynaecology, University of Leeds

Professor Carol Dezateaux,
Professor of Paediatric
Epidemiology, Institute of Child
Health, London

Mr John Dunning,
Consultant Cardiothoracic
Surgeon, Papworth Hospital NHS
Trust, Cambridge

Mr Jonathan Earnshaw,
Consultant Vascular Surgeon,
Gloucestershire Royal Hospital,
Gloucester

Professor Martin Eccles,
Professor of Clinical Effectiveness,
Centre for Health Services
Research, University of Newcastle
upon Tyne

Professor Pam Enderby,
Dean of Faculty of Medicine,
Institute of General Practice
and Primary Care, University of
Sheffield

Professor Gene Feder,
Professor of Primary Care
Research & Development, Centre
for Health Sciences, Barts and The
London School of Medicine and
Dentistry

Mr Leonard R Fenwick,
Chief Executive, Freeman
Hospital, Newcastle upon Tyne

Mrs Gillian Fletcher,
Antenatal Teacher and Tutor and
President, National Childbirth
Trust, Henfield

Professor Jayne Franklyn,
Professor of Medicine, University
of Birmingham

Mr Tam Fry,
Honorary Chairman, Child
Growth Foundation, London

Professor Fiona Gilbert,
Consultant Radiologist and NCRN
Member, University of Aberdeen

Professor Paul Gregg,
Professor of Orthopaedic Surgical
Science, South Tees Hospital NHS
Trust

Bec Hanley,
Co-director, TwoCan Associates,
West Sussex

Dr Maryann L Hardy,
Senior Lecturer, University of
Bradford

Mrs Sharon Hart,
Healthcare Management
Consultant, Reading

Professor Robert E Hawkins,
CRC Professor and Director of
Medical Oncology, Christie CRC
Research Centre, Christie Hospital
NHS Trust, Manchester

Professor Richard Hobbs,
Head of Department of Primary
Care & General Practice,
University of Birmingham

Professor Alan Horwich,
Dean and Section Chairman,
The Institute of Cancer Research,
London

Professor Allen Hutchinson,
Director of Public Health and
Deputy Dean of ScHARR,
University of Sheffield

Professor Peter Jones,
Professor of Psychiatry, University
of Cambridge, Cambridge

Professor Stan Kaye,
Cancer Research UK Professor of
Medical Oncology, Royal Marsden
Hospital and Institute of Cancer
Research, Surrey

Dr Duncan Keeley,
General Practitioner (Dr Burch &
Ptnrs), The Health Centre, Thame

Dr Donna Lamping,
Research Degrees Programme
Director and Reader in
Psychology, Health Services
Research Unit, London School of
Hygiene and Tropical Medicine,
London

Professor James Lindesay,
Professor of Psychiatry for the
Elderly, University of Leicester

Professor Julian Little,
Professor of Human Genome
Epidemiology, University of
Ottawa

Professor Alistaire McGuire,
Professor of Health Economics,
London School of Economics

Professor Neill McIntosh,
Edward Clark Professor of Child
Life and Health, University of
Edinburgh

Professor Rajan Madhok,
Consultant in Public Health, South
Manchester Primary Care Trust

Professor Sir Alexander Markham,
Director, Molecular Medicine
Unit, St James's University
Hospital, Leeds

Dr Peter Moore,
Freelance Science Writer, Ashtead

Dr Andrew Mortimore,
Public Health Director,
Southampton City Primary Care
Trust

Dr Sue Moss,
Associate Director, Cancer
Screening Evaluation Unit,
Institute of Cancer Research,
Sutton

Professor Miranda Mugford,
Professor of Health Economics
and Group Co-ordinator,
University of East Anglia

Professor Jim Neilson,
Head of School of Reproductive
& Developmental Medicine
and Professor of Obstetrics
and Gynaecology, University of
Liverpool

Mrs Julietta Patnick,
Director, NHS Cancer Screening
Programmes, Sheffield

Professor Robert Peveler,
Professor of Liaison Psychiatry,
Royal South Hants Hospital,
Southampton

Professor Chris Price,
Director of Clinical Research,
Bayer Diagnostics Europe, Stoke
Poges

Professor William Rosenberg,
Professor of Hepatology and
Consultant Physician, University
of Southampton

Professor Peter Sandercock,
Professor of Medical Neurology,
Department of Clinical
Neurosciences, University of
Edinburgh

Dr Philip Shackley,
Senior Lecturer in Health
Economics, Sheffield Vascular
Institute, University of Sheffield

Dr Eamonn Sheridan,
Consultant in Clinical Genetics, St
James's University Hospital, Leeds

Dr Margaret Somerville,
Director of Public Health
Learning, Peninsula Medical
School, University of Plymouth

Professor Sarah Stewart-Brown,
Professor of Public Health,
Division of Health in the
Community, University of
Warwick, Coventry

Dr Nick Summerton,
GP Appraiser and Codirector,
Research Network, Yorkshire
Clinical Consultant, Primary Care
and Public Health, University of
Oxford

Professor Ala Szczepura,
Professor of Health Service
Research, Centre for Health
Services Studies, University of
Warwick, Coventry

Dr Ross Taylor,
Senior Lecturer, University of
Aberdeen

Dr Richard Tiner,
Medical Director, Medical
Department, Association of the
British Pharmaceutical Industry

Mrs Joan Webster,
Consumer Member, Southern
Derbyshire Community Health
Council

Professor Martin Whittle,
Clinical Co-director, National
Co-ordinating Centre for Women's
and Children's Health, Lymington

Feedback

The HTA programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.