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'

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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 disease[6] 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 aramotase inhibitor; the only approved European Medicines Agency (EMA) indication[8] 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 1[10] and phase 2[11] 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 2009[1]

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: • 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: • 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

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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 tumo?r$ 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*