Executive Summary

Overview of the disease and treatment options

Breast cancer is the most common cancer amongst women in the UK. Approximately 20% of breast cancers are HER2 positive, with approximately 50% of these HER2 positive breast cancers also having hormone receptor positive (known as co-positive) disease.

Patients with co-positive breast cancer have a poor prognosis on endocrine treatment alone due to crosstalk between the oestrogen and HER2 receptors, resulting in aggressive disease. The most clinically effective treatment option for this patient population is trastuzumab in combination with chemotherapy, the only regime demonstrating statistically significant improvement in time to progression and overall survival. If patients are unintended for chemotherapy, anti-HER2 therapy and an aromatase inhibitor is a clinically suitable option e.g. trastuzumab in combination with an aromatase inhibitor.

As the vast majority of patients with co-positive metastatic disease will be intended/suitable for chemotherapy it is anticipated that population covered by the resultant guidance of this MTA will be extremely small (around 50 patients per annum). Details of the derivation of this figure are provided within section 6.

Clinical effectiveness of trastuzumab with an aromatase inhibitor

The efficacy and safety of trastuzumab in combination with an aromatase inhibitor for the treatment of patients with HER2+/HR+ MBC has been evaluated in:

- One randomised, open label, controlled pivotal phase III study (BO16216 'TAnDEM' Clinical Study Report; Kaufmann et al. 2009), of trastuzumab in combination with anastrozole as first line treatment in postmenopausal patients with metastatic HER2 positive, hormone receptor positive breast cancer.
- Two supportive controlled trials, one single arm phase II (Marcom et al. 2007) and one randomised, open label, phase III (Huober et al. 2009) that assessed trastuzumab in combination with letrozole

The pivotal TAnDEM study demonstrated the combination of trastuzumab and anastrozole resulted in a significant improvement in progression free survival, time to progression and clinical benefit rate when compared to anastrozole alone. An end of study update performed in 2008, after the main phase of the study, demonstrated a median PFS of 2.9 months in the anastrozole alone arm vs. 5.8 months in the tratuzumab and anastrozole arm ($p<0.0001$) with a hazard ratio for PFS of 0.55 (95% CI 0.41 – 0.74).

The study also demonstrated a trend towards improved overall survival for patients treated with trastuzumab and anastrozole but the results were complicated by the fact that 70% of patients from the anastrozole only arm crossed over after progression to receive a trastuzumab containing regime and there was a significant imbalance in the

use of 2nd line chemotherapy across the arms (31% in the anastrozole arm compared to only 8% in the trasutuzmab/anastrozole arm).

A post-hoc rank preserving structural failure time (RPSFT, Robins and Tsiatis 1991) statistical model was utilized to account for the confounding influence of this 70% cross-over upon OS estimates without violating randomization. This analysis demonstrates that once this cross-over is accounted for the Tandem OS HR reduces to 0.727 (0.508, 1.041) and the median OS advantage for anastrozole/trastuzumab over anastrozole alone is 6.54 months (a median OS of 28.52 for trastuzumab/anastrozole compared to 21.98 months for anastrozole). Furthermore as the RPSFT approach was not designed to counter the imbalance in 2nd line chemotherapy it is highly likely that the true OS advantage granted by trastuzumab is higher than the 6.54 months detailed above.

Once the updated data-cut, the confounding influence of the significant post-progression cross-over and the indirect comparison (described below) is considered the TAnDEM trial demonstrates that trastuzumab/anastrozole should be considered the most-efficacious treatment option for those patients in which chemotherapy cannot be tolerated (with the MTC suggesting a PFS HR of trastuzumab/anastrozole vs lapatinib/letrozole of 0.87).

The TAnDEM trial found no unexpected adverse events that had not been previously observed with trastuzumab.

Systematic review of clinical evidence

A systematic literature review was conducted to inform a meta-analysis on regimens utilised in the treatment of hormone receptor positive metastatic breast cancer that overexpresses HER2. The research question was developed based on the scope of the appraisal. Outcomes included progression-free survival (PFS), time-to-progression (TTP), overall survival (OS), response, clinical benefit, health-related quality of life and adverse events. Treatments of interest included AI monotherapy (anastrozole, letrozole and exemestane), trastuzumab plus an AI and letrozole plus an AI.

The search was conducted in MEDLINE, MEDLINE-IN-PROCESS, EMBASE, Cochrane Central Register of Controlled Trials, Web of Science proceedings and BIOSIS. A hand search was also performed. The search retrieved 3,320 unique citations. The screening was undertaken to exclude irrelevant publications based on the study design, population, treatment and outcomes.

As initial searches revealed a paucity of evidence in the co-positive population of interest the population selection criteria was expanded to incorporate all hormone receptor positive patients. The completed search revealed only three trials in the co-positive population (Tandem, EGF30008 and Electra) without a common AI comparator to link the network. In the expanded population (i.e. not limited to HER2+) a total of eighty-eight publications were reviewed in full-text and 36 publications were included in the tabular report

The systematic review undertaken found no evidence base capable of robustly linking all the regimens of interest in the population of interest. Whilst head to head RCTs of trastuzumab + AI and lapatinib + AI were found in the co-positive population, no evidence was available to link the different AIs. In the broader non-HER2+ limited population a network capable of linking the regimens of interest was established.

Network Meta-Analysis

As the systematic review uncovered no network capable of informing the decision problem of interest in the first line co-positive mBC population it was determined that some sort of assumption founded on the results in the mixed HER2 status population network was necessary in order to inform the indirect comparisons required. In order to ensure that any assumption made was well founded within the evidence base available a network meta-analysis was conducted with the objective of determining whether it was appropriate to assume that the AIs hold a 'class effect' (as suggested by clinicial experts and as found in the only head to head trial of anastrozole and letrozole (Rose 2003, a 2nd line mBC study)) in the mixed HER2 status population and to determine point estimates of the relative efficacy of the AIs in the mixed HER2 status population if the assumption of class effect did not hold.

Trials including the treatments of interest (AIs, lapatinib + AI and trastuzumab + AI) and any treatment, which could be used to link the network of evidence were selected. Megestrol acetate and tamoxifen were identified as comparators linking the network. The primary outcome of interest was progression-free survival, defined as the time from randomisation to death for any reason and the secondary outcome was overall survival. The hazard ratio was selected as the common statistic to conduct the meta-analysis. Fifteen studies were eligible for the meta-analysis, seven were used for the progression-free survival analysis and twelve were included in the secondary analysis of overall survival.

The base case analysis indicated that there was no significant difference in progression-free survival across the three aromatase inhibitors administered alone: the hazard ratios comparing the AIs varied from 0.92 for letrozole vs. anastrozole (95%CrI: [0.60;1.36]) to 0.97 for letrozole vs. exemestane and exemestane vs. anastrozole (corresponding 95%CrI: [0.58;1.53] and [0.74;1.24] respectively). In the analysis where the AIs were not considered to exude a class effect and instead are treated independently, the hazard ratio of trastuzumab in combination with anastrozole versus lapatinib in combination with letrozole was estimated at 0.87 (95% CrI,[0.48;1.55]) and was not statistically significant. However, trastuzumab in combination with anastrozole was associated with a probability of best efficacy of 68% suggesting a higher probability of better efficacy than lapatinib in combination with letrozole. Similarly, the base case analysis of overall survival treating AIs as single agents indicated no significant differences between the treatments of interest.

Due to the specificity of the target population, no trial was found with the exception of the combination therapy trials that focused on this patients population. Therefore, extensive sensitivity analyses were conducted to assess the potential impact of studies and outcomes selection on the results.

The network meta-analysis conducted has several limitations, including the use of a HER2-mixed population, 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.

The study confirmed that anastrozole, letrozole and exemestane seem to hold a 'class effect' with respect to progression-free survival and overall survival in the mixed HER2 status population. All results should be treated with extreme caution when applied to the co-positive population as there is no evidence base capable of informing this analysis in the population specified by the decision problem. Furthermore as understanding of HER2 was not fully developed at the period when most of the evidence base identified was formed 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.

Cost Effectiveness analysis

Introduction

A cost-utility analysis was conducted in order to inform the decision problem set in the final scope. NICE's Guide to Methods was followed throughout. The following regimens were compared:

- Trastuzumab in combination with anastrozole
- Lapatinib in combination with letrozole
- Letrozole monotherapy
- Anastrozole monotherapy

As no evidence comparing the PFS and OS of trastuzumab in combination with letrozole, trastuzumab in combination with exemestane, lapatinib in combination with anastrozole or lapatinib in combination with exemestane was found in the systematic review conducted these regimens could not be incorporated into the economic evaluation undertaken (despite both biologics holding licenses or CHMP positive opinion on use in combination with any AI).

Methods

Given the paucity of evidence capable of linking the AIs of interest in the co-positive mBC population in the base-case analysis it was assumed that the AIs hold a class effect in terms of PFS and OS. This assumption is supported by clinical expert opinion and the network meta-analysis conducted in the mixed HER2 status population and was therefore assumed to hold in the exclusively HER2+ population of interest in this appraisal. The uncertainty surrounding this assumption was explored extensively in sensitivity analysis.

An area under the curve model founded on the latest (28th April 2008) data-cut from the Tandem trial was created in Excel©. 3 health states (progression free survival, progressed disease and death) were simulated within the model. All indirect comparisons were implemented under the assumption of proportional hazards with the anastrozole PFS and OS curves forming the baseline to generate the simultaneous comparison of those regimens not featured in Tandem (i.e. letrozole monotherapy and lapatinib/letrozole combination therapy). As 70% of anastrozole patients in Tandem

crossed-over to receive trastuzumab post-progression a rank preserving structural failure time (RPSFT) model was utilised (Robins and Tsiatis, 1991) in order to account for this cross-over. This approach had been implemented and accepted in two previous NICE appraisal (sunitinib in GIST and everolimus in aRCC). As there was also a significant imbalance in post-progression chemotherapy between the two arms of Tandem (with 31% receiving 2nd line chemotherapy in the anastrozole arm compared to only 8% in the trastuzumab arm) the relative OS efficacy used in the base-case model is likely an under-estimate of the true OS efficacy of trastuzumab (and so the base-case ICERs vs trastuzumab can be regarded as conservative).

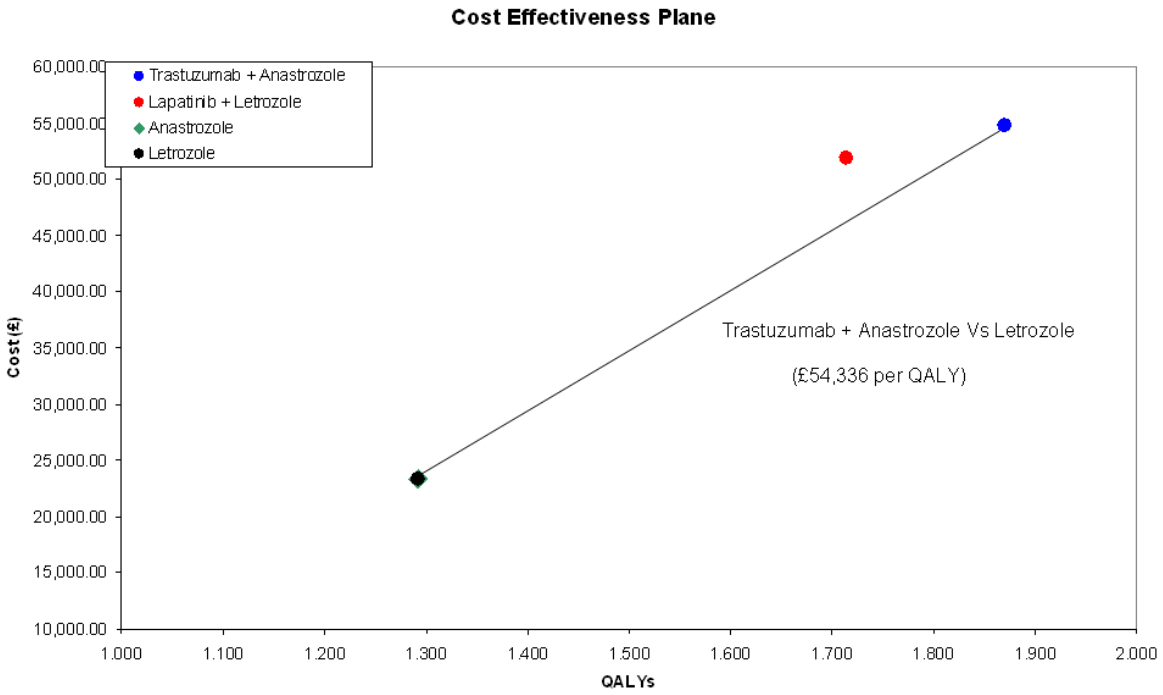
Health state utilities used were those utilised in the development of NICE CG81 (advanced breast cancer guidelines). Costs came from recent NICE appraisals, NHS reference costs 2008/2009, BNF 59 and PSSRU 2008/2009. Resource use figures were derived from NICE CG81 and expert opinion.

Expert health economic, statistical and clinical validation was sought throughout the development of the evaluation undertaken.

Results

The regimens compared were simultaneously assessed for dominance and extended dominance and those regimens on the efficiency frontier defined. In the base case anastrozole was dominated by letrozole (i.e. is slightly more costly yet no more effective) and lapatinib/letrozole was extendedly dominated by a combination of letrozole and trastuzumab/anastrozole (even when the Lapatinib PAS proposed in the ongoing STA of Lapatinib in 2nd line mBC was implemented within the model). Two regimens made up the efficiency frontier; Trastuzumab/Anastrozole and anastrozole monotherapy. The ICER for this comparison was £54,336 (an extra 0.58 QALYs at an incremental cost of £31,421).

The cost-effectiveness plane below demonstrates the base-case results.



Deterministic and probabilistic sensitivity analysis was conducted to evaluate the strength of the cost-effectiveness estimates produced to plausible variation in uncertain parameters. Key areas of uncertainty included the relative efficacy of the AIs in the HER2+ population, the appropriate utility values for use in this population and the OS efficacy of trastuzumab due to the confounding influence of the 70% cross-over observed in Tandem and the significant imbalance in 2nd line chemotherapy use between the two trial arms.

When a modest detriment (HR=1.1) was applied to the RPSFT adjusted anastrozole OS baseline to account for the likely over-estimation of anastrozole OS caused by the 2nd line chemotherapy imbalance the base case ICER fell to £49,246 per QALY. Roche are currently investigating possible statistical techniques to quantitatively account for this chemotherapy imbalance and hope to provide further analyses in the future.

When the utility values utilised by Hastings et al 2010 (a poster on the cost-effectiveness of lapatinib/letrozole compared to trastuzumab/anastrozole in the treatment of co-posiiive mBC published at ASCO in Chicago on 5th June 2010) were uitlised the base-case ICER comparing trastuzumab/anastrozole to letrozole alone fell to £44,497. Once these utility values were combined with a modest 1.1 HR detriment to the anastrozole OS curve (for the reasons detailed previously) the base case ICER fell to £40,096.

End of Life Criteria

The Tandem trial demonstrated that despite 70% cross-over and a significant imbalance in 2nd line chemotherapy trastuzumab produced a median OS gain of 4.6 months over

anastrozole therapy. When the RPSFT approach was used this gain rose to 6.54 months and given the confounding influence of the 2nd line chemotherapy imbalance the true OS gain of this comparison is likely to be higher.

The prognosis of patients with HER2+ metastatic breast cancer is notoriously poor if not treated with a HER2 targeted therapy such as trastuzumab. Despite the confounding detailed above the median OS of anastrozole patients in Tandem was only 23.9 months. This fell to 21.98 months when the RPSFT approach was implemented and fell further to 11.3 months if those patients who crossed over were censored from the analysis. All the likely median OS of patients treated with anastrozole first line for co-positive mBC is likely somewhere between the RPSFT estimate and the censored approach (due to the 2nd line chemotherapy imbalance not accounted for in the RPSFT analysis).

Trastuzumab is a targeted therapy that only works in HER2+ positive patients. It currently has indications in metastatic gastric cancer and metastatic and early breast cancer within this subgroup. Across all the indications 7,158 patients are eligible to receive trastuzumab each year (2,333 from mBC, 4,319 from eBC and 506 from mGC). Of these only 50 mBC patients each year are estimated to be in the population under appraisal in this MTA (as the vast majority of patients are eligible for trastuzumab plus chemotherapy and those that are unsuitable/unintended for chemotherapy are most likely also unsuitable for trastuzumab).

Given that trastuzumab in combination with an aromatase inhibitor appears to fulfil the criteria established in NICE's supplementary end of life guidance Roche respectfully request that the committee consider trastuzumab's eligibility under this guidance when establishing their decision.

Resource Implications

The eligible patient population under consideration in this appraisal is approximately 50 patients per year, as noted above. It is anticipated that positive NICE guidance for trastuzumab in combination with an aromatase inhibitor will have a budget impact of £0.63 million in 2011 rising to £1.61 million in 2013.