NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

Lapatinib for the treatment of women with previously treated advanced or metastatic breast cancer

This guidance was developed using the single technology appraisal (STA) process.

1 Guidance

1.1 Lapatinib, in combination with capecitabine, is not recommended for the treatment of women with HER2-expressing, advanced or metastatic breast cancer that has progressed following treatment with anthracyclines, taxanes, and trastuzumab in the metastatic setting, except in the context of clinical trials.

1.2 Women who are currently receiving lapatinib should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

2 The technology

2.1 Lapatinib (Tyverb, GlaxoSmithKline) is an inhibitor of the intracellular tyrosine kinase domains of ErbB1 (EGFR) and ErbB2 (HER2) receptors. Lapatinib, in combination with capecitabine, has a marketing authorisation for the treatment of patients with advanced or metastatic breast cancer whose tumours overexpress ErbB2 (HER2). Patients should have progressive disease following prior therapy which must include anthracyclines, taxanes and therapy with trastuzumab in the metastatic setting. The marketing

authorisation was granted on the condition that the manufacturer performed and submitted an updated analysis of survival data for study EGF100151 (now completed) and conducted a phase III randomised, controlled clinical study to evaluate the incidence of brain metastases as the site of relapse with a lapatinib-containing therapy compared with an appropriate trastuzumab-containing therapy. Lapatinib is administered orally. The recommended dosage of lapatinib is 1250 mg per day to be taken continually. The recommended dosage of capecitabine, when taken with lapatinib, is 2000 mg/m^2 per day taken on days 1–14 of a 21-day cycle.

2.2 The summary of product characteristics (SPC) states that lapatinib has been associated with decreases in left ventricular ejection fraction. Caution should be taken if lapatinib is administered to patients with conditions that could impair left ventricular function. Left ventricular ejection fraction should be evaluated in all patients before starting treatment and continue to be evaluated during treatment with lapatinib. The SPC also states that diarrhoea, including severe diarrhoea, has been reported with lapatinib treatment. It therefore recommends proactive management of diarrhoea with anti-diarrhoeal agents. The SPC further warns of toxicity to the liver and recommends that liver function should be monitored before starting treatment and monthly thereafter or as clinically indicated. Lapatinib should be discontinued if changes in liver function are severe and patients should not be re-treated. For full details of side effects and contraindications, see the SPC.

2.3 The acquisition cost for lapatinib is £11.49 per 250-mg tablet (excluding VAT; 'British national formulary' [BNF] edition 59). The cost of lapatinib treatment is £57.45 per day, or £20,969 per year. The acquisition cost for capecitabine is £0.74 per 150-mg tablet and £2.46 per 500-mg tablet. The cost of 60 x 150-mg tablets of

capecitabine is £44.47 and 120 x 500-mg tablets is £295.06 (excluding VAT; BNF edition 59). The cost of a 21-day cycle of capecitabine treatment, based on a person with a body surface area of 1.77 m^2, is £244.00 per cycle or £4238 per year. This gives a combined cost of lapatinib plus capecitabine of approximately £25,207 per year. Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee (appendix A) considered the original and revised evidence submitted by the manufacturer of lapatinib, a further submission after an appeal and a review of these submissions by the Evidence Review Group and the Decision Support Unit (ERG and DSU; appendix B).

3.1 The manufacturer's original analysis included several different comparators including capecitabine monotherapy, vinorelbine monotherapy, trastuzumab monotherapy and trastuzumab combination therapy. Although the marketing authorisation for lapatinib specifies its use after the failure of trastuzumab (a HER2-suppressing agent), the manufacturer stated that the inclusion of trastuzumab as a comparator was justified because in the absence of an alternative HER2-suppressing agent some patients continue to receive trastuzumab after their disease progresses, either alone, or in combination with cytotoxic chemotherapy. The manufacturer reported that those patients who are most likely to receive trastuzumab after the disease progresses are those in whom the drug still appears to be having some effect despite progression. The manufacturer presented the results of market research (n = 24 patients) to support including trastuzumab as a comparator. These data identified which treatments were used following progression of disease after treatment with trastuzumab. The data showed that

17% of these patients continued to receive trastuzumab with the addition of vinorelbine, 17% continued to receive trastuzumab with the addition of capecitabine, and 7% continued to receive trastuzumab as monotherapy. The other 59% of patients switched treatment to non-trastuzumab-containing regimens.

3.2 The manufacturer reported details of one randomised controlled trial (RCT). This open-label trial enrolled women with HER2-overexpressing advanced or metastatic breast cancer who had received prior therapy, which included anthracyclines, taxanes, and trastuzumab in the advanced or metastatic setting. Patients were randomised to receive treatment with lapatinib plus capecitabine or capecitabine alone. Enrolment in the trial was stopped early after a recommendation from the Independent Data Monitoring Committee because an interim analysis showed an improvement in time to progression in the lapatinib plus capecitabine group compared with the capecitabine monotherapy group. Therefore, the trial may have been underpowered to detect a statistical difference in some of the specified secondary outcomes. At the time enrolment was ended, 198 patients were enrolled in the lapatinib plus capecitabine group and 201 patients in the capecitabine monotherapy group.

3.3 The primary outcome measure was time to progression. The secondary outcomes were overall survival, progression-free survival, overall tumour response rate, clinical benefit rate and duration of response. The results reported here all relate to the analysis using data from the April 2006 cut-off date unless otherwise stated. Median time to progression was 27.1 weeks for lapatinib plus capecitabine compared with 18.6 weeks for capecitabine monotherapy (hazard ratio [HR] 0.57; 95% confidence interval [CI] 0.43 to 0.77, $p < 0.001$). Similarly, median progression-free survival was 27.1 weeks for the lapatinib plus capecitabine

group compared with 17.6 weeks for the capecitabine monotherapy group (HR 0.55; 95% CI 0.41 to 0.74, $p < 0.001$). There was no statistically significant difference in median overall survival: 67.7 weeks for lapatinib plus capecitabine and 66.6 weeks for capecitabine monotherapy (HR 0.78; 95% CI 0.55 to 1.12, $p = 0.177$).

3.4 The manufacturer provided updated overall survival data for a September 2007 cut-off from the main RCT. In both groups the median overall survival was longer when compared with the April 2006 cut-off date (see section 3.3). However, the difference between the two groups remained statistically non-significant. Median overall survival for the lapatinib plus capecitabine group for the September 2007 data was 74.0 weeks compared with 65.9 weeks for the capecitabine monotherapy group (HR 0.90; 95% CI 0.71 to 1.12, $p = 0.3$). These data may be subject to confounding because some patients in the capecitabine monotherapy group crossed over to the lapatinib plus capecitabine group during the trial. Further updated survival data were submitted by the manufacturer with a new cut-off date of October 2008 (see section 3.20).

3.5 Diarrhoea was more common in the lapatinib plus capecitabine group compared with the capecitabine monotherapy group (affecting 65% and 40% of women in the two treatment groups respectively). Palmar-plantar erythrodysaesthesia, a well-recognised side effect of capecitabine treatment, was also a common adverse event in the RCT, reported by 53% of women in the lapatinib plus capecitabine group and 51% in the capecitabine monotherapy group. In addition, seven (4%) women in the lapatinib plus capecitabine group and two (1%) women in the capecitabine monotherapy group experienced a decreased left ventricular

ejection fraction; five of the seven women receiving combination therapy were asymptomatic. For other commonly reported adverse events (rash, vomiting, nausea and fatigue), the incidences were similar in both treatment groups. The European Medicines Agency's (EMEA) scientific discussion showed that 24% of patients in the lapatinib plus capecitabine group and 23% in the capecitabine monotherapy group stopped treatment because of adverse events.

3.6 The manufacturer's original submission included an economic model. The model compared lapatinib plus capecitabine versus: capecitabine monotherapy, vinorelbine monotherapy, trastuzumab in combination with vinorelbine or capecitabine, and trastuzumab monotherapy. The economic model used clinical-effectiveness data for lapatinib and capecitabine from the RCT. A further systematic review carried out by the manufacturer did not identify any studies comparing lapatinib plus capecitabine against trastuzumab-containing regimens. However, the review did identify non-comparative data for trastuzumab-containing regimens. Therefore, the manufacturer pooled median time-to-progression data from eight non-RCTs of trastuzumab-containing regimens, and this was assumed to be equivalent to median progression-free survival for the trastuzumab-containing regimens. Similarly, the manufacturer's systematic review did not identify studies of vinorelbine clinical effectiveness. The manufacturer assumed that the clinical effectiveness of vinorelbine was identical to that of capecitabine, as obtained from the control group of the RCT.

3.7 The manufacturer subsequently provided an updated analysis including clinical-effectiveness data for trastuzumab. The original pooled estimate of time-to-progression data from eight studies was updated with four newly available studies, including one RCT of

trastuzumab plus capecitabine compared with capecitabine monotherapy. The updated pooled estimate of median time to progression was 27 weeks (95% CI 23.3 to 31.1) with a HR of 0.70 (95% CI 0.61 to 0.81). In addition to the pooled estimate, the manufacturer also provided data separately for the RCT of trastuzumab plus capecitabine compared with capecitabine monotherapy. The median time to progression for trastuzumab plus capecitabine was 8.2 months (95% CI 7.3 to 11.2) compared with 5.6 months (95% CI 4.2 to 6.3) for capecitabine monotherapy (HR 0.69; p = 0.034). The median overall survival for trastuzumab plus capecitabine was 25.5 months (95% CI 19.0 to 30.7) compared with 20.4 months (95% CI 17.8 to 24.7) for capecitabine monotherapy (HR 0.76; p = 0.26).

3.8 The principal determinant of patients' health-related quality of life in the model was assumed to be disease progression. In the main RCT, the pre-progression health-related utility value (0.69) was obtained using the EQ-5D in all patients, regardless of treatment group. The value following disease progression included in the model (0.47) was based on a separate study. Quality-adjusted life years (QALYs) were estimated by applying these values to the mean progression-free and post-progression survival durations for each regimen considered. The manufacturer's model assumed that health utilities did not differ according to treatments received and did not explicitly include the impact of treatment-related adverse events on quality of life.

3.9 The cost-effectiveness model distinguished between the cost of care incurred while patients were free from disease progression (and receiving active treatment) and the cost of care after disease progression. These costs included drug acquisition costs, hospital resources for chemotherapy administration, pharmacy costs,

diagnostic and laboratory costs and other related costs. The base-case economic analysis was based on a price of £11.00 per tablet of lapatinib. The model also included relative dose adjustment factors to account for differences between planned dose and actual dose prescribed in the main RCT, and to account for differences between independent and investigator-led analyses of progression-free survival. The costs of trastuzumab were based on an assumption that treatment would be administered as a weekly infusion as stated in the SPC and that all excess trastuzumab would be wasted.

3.10 The base-case analysis showed that when lapatinib plus capecitabine was compared with capecitabine monotherapy, the QALY gain was 0.171 at an incremental cost of £13,873, giving an incremental cost-effectiveness ratio (ICER) of £81,251 per QALY gained. When compared with vinorelbine monotherapy, the QALY gain was 0.171 at an incremental cost of £11,584, giving an ICER of £67,847 per QALY gained. The model suggested that lapatinib plus capecitabine dominated trastuzumab-containing regimens (that is, it was both more effective and less costly).

3.11 The manufacturer presented a range of sensitivity analyses for the comparisons with trastuzumab-containing regimens. When wastage was excluded in the analysis for all medicines, the ICER for lapatinib plus capecitabine changed from being dominant to £1650 per QALY gained in comparison with trastuzumab plus capecitabine, and to £6772 per QALY gained in comparison with trastuzumab monotherapy. In addition, when it was assumed that trastuzumab was administered 3-weekly rather than weekly as in the base case, the ICER for lapatinib plus capecitabine changed from being dominant to £20,248 per QALY gained in comparison with trastuzumab plus capecitabine, and to £27,532 per QALY

gained compared with trastuzumab monotherapy. When the progression-free survival for trastuzumab-containing regimens was assumed to be equal to that of capecitabine, the ICER for lapatinib plus capecitabine changed from being dominant to £1428 per QALY gained compared with trastuzumab plus capecitabine, and to £7099 per QALY gained in comparison with trastuzumab monotherapy. A similar trend was seen when the costs of adverse events associated with lapatinib were included in the analysis.

3.12 The ERG reported that, although the evidence from the main RCT was of reasonable methodological quality, this was the only evidence on the clinical effectiveness of lapatinib used in the cost-effectiveness analysis. The ERG noted that in the original submission, there was a lack of appropriate RCT data about the clinical effectiveness of trastuzumab to enable the calculation of an adjusted indirect comparison. The ERG stated that the unadjusted indirect comparison method used resulted in uncertainty in the cost-effectiveness estimates comparing lapatinib plus capecitabine with trastuzumab-containing regimens. It also noted that the clinical effectiveness of vinorelbine was based on an assumption of equivalence with capecitabine rather than empirical data. The ERG highlighted that the manufacturer's market research analysis to determine current service provision for patients with advanced or metastatic breast cancer had limitations in terms of details of data collection and characteristics of respondents and non-respondents.

3.13 The ERG conducted an exploratory analysis of the cumulative impact of the assumptions listed below on the cost-effectiveness modelling in the manufacturer's submission:

- Administering trastuzumab every 3 weeks, rather than weekly.
- Changing the cost for administering trastuzumab from £207 per infusion used in the manufacturer's submission to £117 per infusion based on a published assessment report for a previous appraisal ('Trastuzumab for the adjuvant treatment of early-stage HER-2 positive breast cancer', NICE technology appraisal guidance 107).
- Basing the mean HR for progression-free survival with trastuzumab-containing regimens on the minimum estimate of median time to progression from the pooled studies.
- Including the distributions of body surface area and weight used to estimate drug use from the main clinical trial.

The ERG's results showed that, when these assumptions were considered cumulatively, the ICER for lapatinib plus capecitabine changed from being dominant to up to £37,336 per QALY gained when compared with trastuzumab-containing regimens.

Further evidence provided by the manufacturer in July 2008

3.14 The manufacturer presented updated results of the market research data (described in section 3.1). The updated data included 98 patients. It reported that following disease progression on treatment with trastuzumab, 21% of patients had continued to receive trastuzumab with the addition of capecitabine, 20% continued to receive trastuzumab with the addition of vinorelbine, 2% continued to receive trastuzumab alone and 11% had continued to receive trastuzumab with the addition of other treatments. Data showed that 46% of patients had switched

treatment to non-trastuzumab-containing regimens, most frequently capecitabine monotherapy (32%). The manufacturer also provided data from an alternative survey of clinical oncologists (n = 92), which provided a comparable estimate that approximately 48% of patients switched treatment to non-trastuzumab-containing regimens.

3.15 The manufacturer provided a revised base-case economic analysis using updated median overall survival data for lapatinib plus capecitabine and updated progression-free survival and overall survival data for trastuzumab plus capecitabine from the trastuzumab RCT. In the revised analyses, it was assumed that 15% of trastuzumab was wasted and that trastuzumab was administered once every 3 weeks in 88% of the patients receiving treatment. The 15% trastuzumab wastage was based on the results of market research commissioned by the manufacturer of lapatinib involving 24 oncology pharmacists from 17 cancer networks. This research showed that on average, respondents estimated that on average 15% of trastuzumab is wasted because of factors such as unfinished vials (range 5 to 60%). In addition, respondents from the same market research suggested that on average 11.6% of patients treated with trastuzumab have it administered weekly with the remainder (88.4%) having it administered every 3 weeks. The updated analysis also used the actual list price of £11.49 per lapatinib tablet.

3.16 The revised base-case analysis showed that when lapatinib plus capecitabine was compared with capecitabine monotherapy, the incremental QALY gain was 0.15 at an incremental cost of £14,015, giving an ICER of £93,825 per QALY gained. When compared with vinorelbine monotherapy, the incremental QALY gain was 0.15 at an incremental cost of £11,726, giving an ICER of £78,503 per

QALY gained. When compared with trastuzumab monotherapy, the incremental QALY gain was 0.26 at an incremental cost of £638, giving an ICER of £24,227 per QALY gained. When compared with trastuzumab plus capecitabine, the incremental QALY gain for lapatinib plus capecitabine was 0.03 at an incremental cost of −£1075 meaning that it was dominant. When compared with trastuzumab plus vinorelbine, assuming the same incremental QALY gain of 0.03 at an incremental cost of −£3583, lapatinib plus capecitabine was dominant.

3.17 The manufacturer also presented an economic analysis that compared lapatinib plus capecitabine with a 'blended comparator'. This analysis was carried out in recognition of the uncertainties in identifying a subgroup of patients who would be likely to have trastuzumab combination therapies in clinical practice. The blended comparator consisted of a weighted average of both the costs and QALYs of the three main treatment options: capecitabine monotherapy (estimated to be provided in 44% of patients), and trastuzumab in combination with either capecitabine (provided in 29% of patients) or vinorelbine (provided in 27% of patients). The proportions used were based on the results of the updated market research (described in section 3.14) with further adjustments made to re-allocate treatment regimens not included in the decision problem. The QALY gain for lapatinib plus capecitabine compared with the blended comparator was 0.080 at an incremental cost of £4887, giving an ICER of £60,730 per QALY gained.

3.18 The manufacturer further provided details of a proposed patient access scheme in which the acquisition costs of lapatinib for patients who met the criteria for treatment were paid by the manufacturer for up to 12 weeks. For those patients whose disease responded to lapatinib therapy, the NHS would pay for the costs of

continued treatment with lapatinib beyond 12 weeks. Criteria for continuation of therapy beyond 12 weeks would be determined by the patient's clinician, based on reduction in size of lesion, presence of stable disease or improvement in other response criteria such as symptoms. The manufacturer reported that the scheme would continue until NICE updated the technology appraisal guidance on lapatinib.

3.19 Incorporating the patient access scheme into the economic model reduced the ICER for lapatinib plus capecitabine in comparison with the blended comparator from £60,730 to £16,384 per QALY gained. Against the individual comparators, the ICER for lapatinib plus capecitabine compared with capecitabine alone was reduced from £93,825 to £69,932 per QALY gained and against vinorelbine was reduced from £78,503 to £54,610 per QALY gained. Lapatinib plus capecitabine dominated trastuzumab combination regimens.

Further evidence provided by the manufacturer after an appeal

3.20 After the June 2009 appeal hearing, the manufacturer provided a further submission with overall survival data from the main RCT with a cut-off date of October 2008. In addition, the manufacturer submitted analyses that used different methods to adjust for the impact of patients crossing over from the capecitabine group to the lapatinib plus capecitabine group, and for differing baseline prognostic factors between the groups.

3.21 The unadjusted clinical-effectiveness data showed a difference in median overall survival for lapatinib plus capecitabine in comparison with capecitabine monotherapy of 2.4 months (HR 0.87, 95% CI 0.71 to 1.08) favouring the lapatinib plus capecitabine group. A Kaplan–Meier analysis that excluded all patients who crossed over suggested a statistically significant

median overall survival benefit in the lapatinib plus capecitabine group of 4.3 months (HR 0.78, 95% CI 0.62 to 0.97, p = 0.023). If patients were censored at the point they crossed groups, the Kaplan–Meier analysis suggested a median overall survival benefit for lapatinib plus capecitabine of 2.9 months (HR 0.82, 95% CI 0.66 to 1.02). The manufacturer also submitted analyses that considered crossover as a time-dependent covariate using Cox regression analysis and a Weibull survival model. With no adjustment for baseline prognostic factors, the model reported a median overall survival benefit for lapatinib plus capecitabine compared with capecitabine alone of 2.7 months (95% CI 0.1 to 6.0). With adjustment for baseline prognostic factors this changed to 3.3 months (95% CI 0.6 to 6.8).

3.22 The manufacturer provided results for a series of exploratory post-hoc subgroup analyses from the main RCT based on the number of previous treatment regimens received. These data were presented as supporting the benefits observed for lapatinib in the main RCT. For people who had had fewer than three previous treatment regimens the median overall survival in the lapatinib plus capecitabine and capecitabine alone groups was 87.3 and 55.1 weeks respectively (HR 0.51, 95% CI 0.30 to 0.86). For people who had three or more previous regimens the median overall survival was 71.4 and 66.6 weeks respectively (HR 0.95, 95% CI 0.76 to 1.21). For people who had only one prior trastuzumab-containing regimen in the metastatic setting the median overall survival in the lapatinib plus capecitabine and capecitabine alone groups was 71.4 and 56.6 weeks respectively (HR 0.79, 95% CI 0.60 to 1.03). For people who had more than one prior trastuzumab-containing regimen in the metastatic setting the median overall survival was 77.1 and 80.9 weeks respectively (HR 1.09, 95% CI 0.74 to 1.60).

3.23 The manufacturer provided additional supporting evidence from the Lapatinib Expanded Access Programme (LEAP); a single-arm open-label trial of lapatinib plus capecitabine for the treatment of HER2-overexpressing advanced or metastatic breast cancer. Results from 4283 patients, including 356 patients from the UK, reported median progression-free survival of 21 weeks and median overall survival of 40 weeks. Results suggested that previous use of capecitabine may have affected the treatment effect of lapatinib plus capecitabine. Patients who had not previously received capecitabine had a median progression-free survival and overall survival of 24 and 42 weeks respectively. Similar results were reported for the UK cohort. Further data were provided (academic in confidence) for a subset of the UK population (n = 162) who had been enrolled in one of five lead recruiting centres.

3.24 The manufacturer provided a further revised economic evaluation that included the most recent survival data from the main RCT using a cut-off date of October 2008, with costs updated to 2008, and including grade 3 and 4 adverse event costs. The revised ICER for lapatinib plus capecitabine compared with capecitabine alone was £86,736 per QALY gained. When overall survival was adjusted to consider crossover as a time-dependent covariate, taking into account baseline prognostic factors, the ICER was £77,996 per QALY gained. With the addition of the patient access scheme the ICER was £59,441 per QALY gained. When it was assumed that the additional life years gained from lapatinib treatment were experienced at the age-adjusted average utility value for the population (0.85) the ICER was reduced to £45,524 per QALY gained (also including the patient access scheme).

3.25 The manufacturer also provided an economic analysis, including the patient access scheme, of two subgroups:

- people who had had fewer than three previous treatment regimens
- people who had only one prior trastuzumab-containing regimen in the metastatic setting.

The ICER for the first group was £46,169 per QALY gained. The ICER for the second group was £56,406 per QALY gained. When it was assumed that the additional life years gained from lapatinib treatment were experienced at the same utility (0.85) as a healthy individual the ICERs were reduced to £32,440 and £44,688 per QALY gained respectively.

Evaluation of July 2008 data and economic analysis by the DSU

3.26 The DSU evaluated the additional clinical-effectiveness data and the updated economic analysis from the manufacturer. The DSU was asked to comment on the use of trastuzumab after progression of disease and the appropriateness of the indirect comparison methodology used by the manufacturer to compare lapatinib plus capecitabine with trastuzumab-containing regimens. In addition, the DSU was asked to provide a critique of the methodology used to obtain the blended comparator proposed by the manufacturer and to establish that the model had been updated appropriately.

3.27 The DSU noted that the updated lapatinib clinical-effectiveness data were for overall survival and that time-to-progression data were not provided. The DSU reported that the same methodological limitations applied to the updated pooled estimate of trastuzumab efficacy as had applied to the original pooled estimate (see section 3.12). The DSU also noted that the RCT comparing trastuzumab plus capecitabine with capecitabine

monotherapy reported results for overall survival and time to progression that favoured trastuzumab. However, the DSU stated that neither lapatinib nor trastuzumab had demonstrated a statistically significant increase in overall survival. The DSU commented that although the HR for time to progression for trastuzumab-containing regimens compared with lapatinib in combination with capecitabine derived from pooling non-RCT data was similar to that derived from the trastuzumab plus capecitabine trial, both methods were associated with methodological limitations because neither maintained randomisation.

3.28 The DSU stated that the updated assumptions in the economic analysis were implemented as described by the manufacturer. The DSU provided analyses that explored the sensitivity of the ICERs to the assumptions about trastuzumab wastage and administration. These showed that if the wastage was 10% rather than 15%, then lapatinib plus capecitabine would still dominate trastuzumab combination therapies, but the incremental costs would be reduced. For example, the incremental cost of trastuzumab plus capecitabine compared with lapatinib plus capecitabine would be reduced from £1075 to £478. Alternatively, if 92% of patients had trastuzumab administered every 3 weeks rather than 88%, then the incremental cost for trastuzumab plus capecitabine compared with lapatinib plus capecitabine would be reduced from £1075 to £952.

3.29 The DSU commented that the blended comparator assumed that all the comparator treatments were used in routine practice and that it would be appropriate for each of them to be displaced from NHS practice. The DSU provided analyses that explored how the ICERs changed if the proportion of trastuzumab use changed using a variety of market research estimates provided by the manufacturers of lapatinib and trastuzumab. Using estimates from

the manufacturer of lapatinib, if trastuzumab was used to treat 49% of patients rather than 56%, then the ICER for lapatinib plus capecitabine compared with the blended comparator increased from £60,730 to £67,050 per QALY gained. If trastuzumab was used to treat 12% of patients, as suggested by the manufacturer of trastuzumab, the ICER increased further to £89,545 per QALY gained. The DSU also explored how the ICERs would change when the patient access scheme was applied. The DSU showed that when the proportion of women continuing trastuzumab-containing regimens after disease progression was estimated to be 56% (as in the manufacturer base case), the ICER for lapatinib plus capecitabine compared with the blended comparator was £16,387 per QALY gained. When the estimate was 54%, the ICER was £19,108 per QALY gained. An estimate of 49% gave an ICER of £26,993 per QALY gained, and an estimate of 12% gave an ICER of £63,034 per QALY gained.

3.30 The DSU commented that a more appropriate approach to economic analysis in the context of the NICE 'Guide to the methods of technology appraisal' and general economic literature would have been to consider all treatment options in a single incremental analysis comparing each successive alternative from the least costly to the most costly. Using this methodology and the data provided by the manufacturer of lapatinib, the DSU estimated that the most cost-effective treatment option was capecitabine monotherapy. Vinorelbine monotherapy was dominated by capecitabine, that is, it had greater costs and the same QALYs. The ICER for lapatinib plus capecitabine compared with capecitabine monotherapy was £93,825 per QALY gained. Trastuzumab monotherapy compared with capecitabine monotherapy gave an ICER of £108,748 per QALY gained. Trastuzumab combination regimens were dominated by

trastuzumab monotherapy. The ICER for lapatinib plus capecitabine compared with trastuzumab monotherapy was £24,227 per QALY gained. The DSU also carried out a probabilistic sensitivity analysis to determine the probability of each treatment being cost effective across a range of thresholds. The analysis showed that capecitabine monotherapy is likely to be the most cost-effective treatment option up to a threshold of approximately £80,000 per QALY gained.

DSU evaluation of the evidence provided by the manufacturer after the appeal

3.31 The DSU evaluated the additional clinical-effectiveness data and the updated economic analysis from the manufacturer. The DSU was asked to comment on the accuracy of the changes to the model, the methods used to adjust for crossover and baseline prognostic variables, and the subgroup analyses. After clarification with the manufacturer, the DSU considered that the changes to the model had been made appropriately. The DSU considered that the methods used to adjust for crossover may have led to biased estimates that could have exaggerated the size of the relative treatment effect. It identified a number of alternative methods that it considered may have been more appropriate. The manufacturer clarified that it had used a similar method to adjust for crossover and baseline prognostic factors in the subgroup analyses. The DSU considered that it may not have been appropriate to use the same baseline prognostic factors in the subgroups as the main analysis. It commented that the subgroup analyses in the model had used higher median overall survival than had been reported in the manufacturer's submission.

3.32 Full details of all the evidence are in the manufacturer's submissions, the manufacturer's response to the appraisal

consultation documents (ACDs), the ERG reports and DSU reports, which are available from www.nice.org.uk/TAxxx

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of lapatinib in combination with capecitabine, having considered evidence on the nature of the condition and the value placed on the benefits of lapatinib plus capecitabine by women with advanced or metastatic breast cancer, those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources.

4.2 The Committee considered current clinical practice in the treatment of advanced or metastatic breast cancer following disease progression after treatment with anthracycline-based regimens, taxanes and trastuzumab. The Committee noted inconsistency in the evidence provided, which suggested a range of estimates of continued trastuzumab use after disease progression, from approximately 10 to 50% of patients. The Committee was aware of comments from the ERG that there was uncertainty in the market research data as set out in section 3.12. The Committee heard from clinical specialists that continued provision of trastuzumab after disease progression varied considerably in England and Wales, but that they considered the higher estimates to be more appropriate. The Committee concluded that there is no agreed standard treatment for patients whose disease progresses after treatment with trastuzumab, but that this could include capecitabine-, vinorelbine- and trastuzumab-containing regimens.

4.3 The Committee noted that the decision problem from the manufacturer included trastuzumab-containing regimens. The

Committee accepted that the continued use of trastuzumab after disease progression was not currently licensed, but was mindful of comments from clinical specialists that it was being used in clinical practice. The Committee recognised that the NICE 'Guide to the methods of technology appraisal' allows unlicensed comparators to be considered in appraisals if they are in clinical use in the NHS. The Committee was persuaded by the evidence of trastuzumab usage from consultees (described in section 4.2) and the testimony from clinical specialists that it should allow consideration of the clinical- and cost-effectiveness analyses that included trastuzumab as a comparator.

4.4 The Committee considered the evidence for the clinical effectiveness of trastuzumab-containing regimens following progression of disease in the advanced or metastatic settings. The Committee noted the availability of clinical-effectiveness data from an RCT in which trastuzumab was continued after disease progression, as well as an updated review of the trastuzumab clinical-effectiveness evidence provided by the manufacturer of lapatinib. The Committee heard from clinical specialists that evidence for the effect of continuing trastuzumab treatment after disease progression was increasing, but its effectiveness remained uncertain. The Committee noted that 'Advanced breast cancer: diagnosis and treatment' (NICE clinical guideline 81) recommends that treatment with trastuzumab should be discontinued at the time of disease progression outside the central nervous system. The clinical guideline further recommends that trastuzumab should not be discontinued if disease progression is only within the central nervous system. The Committee heard that no cost-effectiveness analysis was carried out on the continued use of trastuzumab if disease progression is only within the central nervous system during the development of NICE clinical guideline 81. The decision

was based on clinical opinion about when trastuzumab should be considered to have failed. The Committee was persuaded that data from the RCT investigating the continuation of trastuzumab after disease progression suggested that this may be of benefit, but considered that there remained considerable uncertainty about the size of the benefit.

4.5 The Committee discussed the clinical effectiveness of lapatinib plus capecitabine presented in the main RCT. It noted that lapatinib plus capecitabine was associated with improved time to progression, progression-free survival and other secondary outcomes compared with capecitabine monotherapy. The Committee considered the manufacturer's assertion that lapatinib has the potential to be beneficial to patients who have brain metastases because its smaller molecular size may allow it to cross the blood–brain barrier. The Committee heard from the manufacturer that mechanistic studies provided radiological evidence that lapatinib is able to cross the blood–brain barrier. In addition, the Committee noted that the manufacturer had provided clinical evidence from a subgroup of patients in the LEAP trial supporting the use of lapatinib for patients with brain metastases. The Committee also heard from the manufacturer that there are ongoing randomised controlled trials in patients with metastatic breast cancer with brain metastases, but full results of the studies are not expected for some time. The Committee was supportive of this ongoing research and recommended further research as a means of identifying the groups of patients who may benefit most from lapatinib.

4.6 The Committee noted that adverse events reported in the main RCT by patients in the lapatinib plus capecitabine group included diarrhoea and palmar-plantar erythrodysaesthesia. The lapatinib plus capecitabine group had a marginally higher incidence of these

adverse events than the capecitabine monotherapy group. Clinical specialists and patient experts commented that people with this stage of disease are often willing to accept side effects to have the benefits of lapatinib plus capecitabine treatment. The Committee also noted that, although the side effects were significant, they could be managed in routine clinical practice.

4.7 The Committee agreed that the evidence to show that lapatinib plus capecitabine had fewer side effects than trastuzumab was limited. The Committee also discussed the potential for cardiotoxicity associated with lapatinib treatment and noted the results in the main RCT. The Committee considered the manufacturer's suggestion in its original submission that lapatinib was less cardiotoxic than trastuzumab. The Committee was not persuaded that, in the situation of limited life expectancy associated with advanced or metastatic breast cancer, this would necessarily influence the choice of treatments. This was supported by the clinical specialists and patient experts.

4.8 The Committee considered the evidence on the cost effectiveness of lapatinib plus capecitabine presented in the manufacturer's submission as well as the revised base-case analysis. The Committee discussed the comparisons presented in the submission, in which lapatinib plus capecitabine was compared with capecitabine monotherapy, vinorelbine monotherapy and trastuzumab-containing regimens. The Committee understood that the clinical-effectiveness data used for the comparison with capecitabine monotherapy were based on the main clinical trial. It noted that the ICER presented in the revised base-case analysis by the manufacturer for this comparison was greater than £90,000 per QALY gained. The Committee also noted the scenario when overall survival was adjusted to consider crossover as a time-dependent

covariate: taking into account baseline prognostic factors, the cost per QALY gained was approximately £78,000. The Committee concluded that this did not represent a cost-effective use of NHS resources.

4.9 The Committee noted that the comparisons with vinorelbine presented in the modelling were not based on data from RCTs and that the efficacy of vinorelbine was assumed to be the same as that of capecitabine. The Committee considered that the data supporting this comparison were subject to considerable uncertainty. It also noted that in the revised base-case analysis the results of lapatinib plus capecitabine compared with vinorelbine monotherapy gave an ICER of approximately £79,000 per QALY gained and concluded that this did not represent a cost-effective use of NHS resources.

4.10 The Committee specifically considered the estimates of cost effectiveness of lapatinib plus capecitabine compared with capecitabine and vinorelbine monotherapies that included the patient access scheme. The Committee noted that the ICERs were approximately £70,000 and £55,000 per QALY gained respectively. The Committee noted that the first of these ICERs had been revised to £59,400 per QALY gained in the manufacturer's submission after the appeal in June 2009. The Committee was mindful of the factors that inform judgements about the acceptability of a technology as an effective use of NHS resources within, and above, the £20,000–£30,000 per QALY gained range. However, it concluded that lapatinib plus capecitabine could not be judged to be a cost-effective use of NHS resources, even taking into account the proposed patient access scheme.

4.11 The Committee accepted that the economic analysis comparing lapatinib plus capecitabine with trastuzumab-containing regimens

had been revised to reflect the July 2008 clinical-effectiveness data available. The Committee recognised that two estimates had been provided: one using the RCT of continued trastuzumab use after progression and another using an updated pooled analysis of trastuzumab studies (see section 3.7). The Committee noted that both were based on an unadjusted indirect comparison to derive the comparative efficacy of lapatinib plus capecitabine with the trastuzumab-containing regimens used in the model. The Committee expressed concerns about the pooling of estimates from experimental and observational studies, and considered that the indirect estimate using trial data was more appropriate. The Committee noted that the characteristics of the patients enrolled in the two RCTs were different in terms of the extent of previous treatment. The Committee also noted that the results from the two RCTs showed that the capecitabine monotherapy arm in the trastuzumab plus capecitabine trial had better efficacy results compared with the capecitabine monotherapy arm in the lapatinib plus capecitabine trial. In the absence of head-to-head comparisons of lapatinib and trastuzumab regimens, the Committee concluded that although the indirect estimate using data from the trastuzumab RCT was associated with considerable uncertainty, it formed an appropriate basis for considering the cost-effectiveness estimates presented by the manufacturer.

4.12 The Committee next considered the cost effectiveness of lapatinib plus capecitabine compared with trastuzumab-containing regimens presented by the manufacturer. The Committee noted that in the manufacturer's revised base-case analysis the assumptions about trastuzumab wastage and administration had been updated, so that 15% of trastuzumab was wasted instead of all excess trastuzumab, and 88% of patients had trastuzumab administered once every 3 weeks, instead of once a week for all patients. The Committee

heard from clinical specialists that they considered that an assumption of 15% trastuzumab wastage could still be an overestimate, because arrangements were usually made to treat patients in groups on the same day and therefore vial use was optimised. The Committee also heard that administration of trastuzumab once every 3 weeks was standard clinical practice. The Committee noted that the ICERs were very sensitive to changes in these assumptions and that if the level of trastuzumab wastage was assumed to be 10% rather than 15% the cost savings associated with lapatinib treatment compared with trastuzumab would be reduced from £1075 to £478. Slightly increasing the number of patients receiving trastuzumab every 3 weeks from 88% to 92% reduced the cost savings associated with lapatinib treatment compared with trastuzumab from £1705 to £952. The Committee concluded that although the manufacturer's base-case analysis suggested that lapatinib plus capecitabine dominated trastuzumab-containing regimens, the differences in costs and modelled benefits were small. The Committee considered that under these circumstances the final ICERs were potentially subject to considerable variation on the basis of small changes in the assumptions made. In addition, the Committee concluded that based on the testimony from clinical specialists about trastuzumab wastage and administration, the differences in cost may be even smaller than those in the revised base-case analysis.

4.13 The Committee examined the incremental analysis to evaluate cost effectiveness provided by the DSU (which used the data submitted by the manufacturer of lapatinib) comparing the cost and effect of each technology successively from the least costly to the most costly. The Committee noted that in this analysis capecitabine monotherapy represented the most cost-effective use of NHS resources, and had the highest probability of being cost effective up

to a willingness-to-pay threshold of approximately £80,000 per QALY gained. The Committee noted that the ICER for lapatinib plus capecitabine in comparison with trastuzumab monotherapy was approximately £24,000 per QALY gained, but that this did not take into account the comparison of trastuzumab monotherapy with capecitabine for which the ICER was approximately £109,000 per QALY gained. The Committee further noted that the DSU report suggested that, using the data from the manufacturer of lapatinib, the ICER for trastuzumab plus capecitabine versus capecitabine alone would be higher (approximately £122,000 per QALY gained) than that of trastuzumab monotherapy compared with capecitabine. The Committee considered that, although the analysis presented by the manufacturer suggested that lapatinib plus capecitabine compared with trastuzumab-containing regimens was cost effective in the base case, the incremental analysis demonstrated that it was based on a comparison of capecitabine with trastuzumab that was not cost effective. The Committee was mindful that there was uncertainty about the effectiveness of trastuzumab-containing regimens, but considered that even if future evidence on the effectiveness of trastuzumab plus capecitabine demonstrated that it was more cost effective than had been assumed, this would only increase the ICERs for lapatinib plus capecitabine in comparison. Therefore, the Committee concluded that the results of the manufacturer's cost-effectiveness analysis in this situation were unsupportable, and the Committee could not, on this basis, recommend lapatinib plus capecitabine as a cost-effective use of NHS resources.

4.14 The Committee next examined the economic analysis from the manufacturer that used a blended comparator, which weighted the costs and QALYs of the lapatinib comparators (that is, capecitabine-, vinorelbine- and trastuzumab-containing regimens)

to produce a single ICER of approximately £61,000 per QALY gained for lapatinib plus capecitabine in comparison with all comparators included in the economic analyses. The Committee noted that the analysis was performed because the manufacturer recognised that at present it was difficult to identify a group of patients who in clinical practice would be likely to continue treatment with trastuzumab after progression of disease. The Committee noted that the blended comparator assumed that all comparators were in routine use and that it was appropriate for lapatinib to displace each of the comparators. The Committee was not persuaded that it was appropriate to combine independent treatments to produce a single estimate of cost effectiveness or that the economic analyses that compared lapatinib plus capecitabine with a blended comparator were appropriate. Specifically the Committee was not persuaded that it was acceptable to include treatments in the blended comparator approach which, when considered individually, were not cost effective. Therefore, the Committee did not consider that the cost-effectiveness analyses using a blended comparator could form the basis of a decision on the appropriate use of NHS resources.

4.15 The Committee noted that the proposed patient access scheme (see section 3.18) had been applied to the blended comparator. The Committee was aware that the manufacturer proposed to pay for the costs of lapatinib for the first 12 weeks of treatment for all people eligible for treatment as part of the scheme. The Committee recognised that the patient access scheme reduced the ICER, using the blended comparator, from approximately £61,000 per QALY gained to approximately £16,000 per QALY gained. The Committee did not consider that applying the patient access scheme to the blended comparator was appropriate because of its views on the acceptability of the blended comparator as an

appropriate basis for making recommendations about the cost effectiveness of lapatinib as detailed in section 4.14.

4.16 The Committee specifically discussed whether lapatinib should be considered as an option for those people for whom NICE clinical guideline 81 recommends not to discontinue trastuzumab after disease progression, namely those whose disease progresses only in the central nervous system. The Committee noted comments from consultees that they considered that, in this situation, lapatinib and trastuzumab had similar clinical effectiveness but that lapatinib had potentially lower costs. The Committee considered that this decision problem reflected a scenario of not discontinuing trastuzumab or switching to lapatinib. The Committee was mindful of consultee comments and also evidence from the manufacturer representatives (see section 4.5) but did not consider that clinical- or cost-effectiveness evidence had been presented that reflected this scenario. The Committee concluded that lapatinib could not be recommended in the subgroup of patients with disease progression only in the central nervous system, but that the use of lapatinib in the context of clinical trials should be supported.

4.17 The Committee considered the wider benefits that may be associated with lapatinib. These included providing a range of technologies for the treatment of advanced or metastatic breast cancer and the fact that lapatinib is taken orally, potentially reducing time spent in hospital and the burden of hospital attendance. The Committee also noted comments made by consultees that there was an unmet need for women with advanced or metastatic breast cancer because of the few treatment options at this stage of the treatment pathway. The Committee was mindful of the innovative nature of lapatinib; it is a small molecule with a novel mechanism of action and the potential to cross the blood–brain

barrier, unlike monoclonal antibodies. The Committee also recognised the importance of patient choice. However, it considered that lapatinib could not be recommended in the light of the current evidence on its cost effectiveness. The Committee was not persuaded that the potential additional benefits associated with molecular innovation or the importance of patient choice, which might not have been fully captured by the estimates of health-related quality of life, were sufficient to influence its decision that lapatinib was not an appropriate use of NHS resources.

4.18 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- 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.
- The treatment is licensed or otherwise indicated for small patient populations.

In addition, when taking these into account the Committee must be persuaded that the estimates of the extension to life are robust and the assumptions used in the reference case economic modelling are plausible, objective and robust.

4.19 The Committee considered the criteria that needed to be met to consider lapatinib as a life-extending, end-of-life treatment. First, the Committee considered the life expectancy of patients with

advanced or metastatic breast cancer. It understood that the main RCT reported a median overall survival for patients receiving capecitabine monotherapy of approximately 15 months (64.7 weeks). Other studies also suggested survival below 24 months even in cohorts of patients who were treated with lapatinib. Therefore, the Committee was persuaded that lapatinib met the criterion of short life expectancy.

4.20 The Committee considered the size of the patient population. It is estimated that approximately 2000 patients with HER2-overexpressing metastatic breast cancer per year receive second- or third-line chemotherapy and therefore may be offered treatment with lapatinib. The Committee was satisfied that lapatinib met the criterion of small patient population.

4.21 The Committee then considered the updated survival data provided by the manufacturer and the alternative analyses that adjusted for crossover and baseline prognostic factors. The Committee noted that the revised unadjusted estimate of overall median survival benefit was 2.4 months. The alternative analyses, variously adjusting for crossover and baseline prognostic factors, gave estimates in the range of 2.7 to 4.3 months. The Committee noted that where presented the confidence intervals were wide, extending down to 1 month or less. The Committee heard from the DSU that it considered that the methods used to adjust for crossover may have led to some bias in the estimates and that there were alternative methods that might be more valid and might give different estimates. The Committee was not therefore persuaded that the adjusted estimates of overall survival presented by the manufacturer led to estimates that were any more valid than the unadjusted estimate of 2.4 months, and certainly did not provide robust evidence that the extension of life provided by lapatinib was

3 months or greater. However, the Committee noted that there was a minor chance that lapatinib plus capecitabine might offer an increase in overall survival of 3 months compared with capecitabine alone. It therefore concluded that it should consider the ICERs presented by the manufacturer in light of the end-of-life considerations (see 4.23).

4.22 The Committee also considered the subgroup evidence submitted by the manufacturer (see section 3.22). It noted that the analyses were presented as exploratory and supportive of the benefits shown in the main trial population. It recognised that these analyses were unplanned and included relatively small sample sizes. The Committee considered that the results from the subgroups were inconsistent: it noted that the overall survival of patients in the capecitabine group who had had three or more prior regimens of treatment was longer than in the group that had had fewer than three regimens, but that the opposite pattern was observed in the lapatinib groups. This made it difficult to interpret the data. The Committee considered that although the subgroup data could be considered as hypothesis generating, it did not consider that these data resolved the uncertainty about the benefits of lapatinib or were sufficient to make recommendations on the use of lapatinib in these subgroups.

4.23 The Committee considered the further revised economic evaluation presented by the manufacturer. The Committee noted that the ICER in the further revised base case, including the patient access scheme, was £59,400 per QALY gained. The Committee also noted that the modelled overall survival benefit from lapatinib treatment in the further revised base case was 3.5 months. The Committee discussed the extra weight that might be considered acceptable for a potential increase in life expectancy of 3 months,

taking into account the unique and innovative aspects of lapatinib, patient need, and previous appraisals where judgements were made taking into consideration the end-of-life supplementary advice, to allow the cost-effectiveness estimates to fall within the range that is normally accepted as a cost effective use of NHS resources. The Committee concluded that the magnitude of additional weight that would need to be assigned to the QALY benefits for the base-case ICER of £59,400 per QALY gained to fall within the current threshold range was not acceptable. The Committee further concluded that the magnitude of greater weight that would need to be given to the QALYs gained in the later stages of terminal disease, using the assumption that the extended survival period is experienced at the full quality of life anticipated for a healthy person of the same age, was also not acceptable.

Reconsideration of the use of trastuzumab following progression of disease

4.24 NICE's Guidance Executive asked the Committee to reconsider whether the use of trastuzumab after progression of disease in the NHS meant that there was an opportunity to use NHS resources more efficiently by substituting this with lapatinib plus capecitabine. No new evidence was considered.

4.25 The Committee, although noting again the limitations of the data and wide geographical variation described, remained persuaded that trastuzumab treatment was being continued in patients in the NHS in England and Wales after progression of disease outside the central nervous system. Therefore, trastuzumab regimens could also be considered as relevant comparators, alongside capecitabine and vinorelbine monotherapies. The Committee noted that trastuzumab was being used after progression of disease in a variety of situations, and that this use of trastuzumab was not in

line with NICE clinical guideline 81. The Committee discussed the RCT data for trastuzumab use after progression of disease, noting that the trial data were not from a selected population specifically thought to benefit from continuing trastuzumab, whereas the manufacturer of lapatinib had suggested that patients most likely to receive trastuzumab after disease progression are those in whom trastuzumab still appears to be having some effect, despite progression. It noted that this meant that the data available were not specific to the clinical effectiveness of trastuzumab in this situation, or of lapatinib in this selected population. It noted that this was also true of populations with progression in the central nervous system alone. It also noted again that the patient populations in the lapatinib and trastuzumab trials differed, for example, in terms of previous treatments received. The Committee concluded there was considerable uncertainty about the relative treatment effect of lapatinib plus capecitabine compared with trastuzumab regimens.

4.26 The Committee recognised that the manufacturer's analysis suggested that lapatinib could be associated with fewer costs and more QALYs than trastuzumab regimens. However, these were based on small differences in costs and QALYs and assumed that a proportion of trastuzumab was wasted and that some people received trastuzumab each week rather than 3 weekly. The Committee noted that the DSU had stated that the ICERs were very sensitive to small changes in wastage and dose frequency assumptions for trastuzumab, and so were not persuaded of the stability of the manufacturer's estimates. The Committee reconsidered the incremental analysis carried out by the DSU using the manufacturer's data, noting that capecitabine monotherapy was the most cost-effective use of NHS resources, up to a willingness-to-pay threshold of £80,000 per QALY gained. The Committee confirmed its view that the incremental analysis was the

appropriate way of considering cost effectiveness. It noted that the data for lapatinib had since been updated in the context of its end-of-life deliberations, but considered that this would not affect the lapatinib ICERs sufficiently to affect its views. It noted that the ICERs for trastuzumab regimens compared with capecitabine of over £100,000 per QALY gained were dependent on the uncertain estimates of clinical effectiveness (section 4.24). The Committee was not persuaded that it was appropriate to consider lapatinib as an alternative to trastuzumab when trastuzumab had not been shown to be a cost-effective use of NHS resources and when such use was not recommended in the NICE clinical guideline. Additionally, the Committee considered that a positive recommendation for lapatinib would mean potentially displacing not only trastuzumab regimens but also capecitabine and vinorelbine monotherapies, against which lapatinib was shown not to be cost effective. The Committee did not consider that this would lead to an efficient use of NHS resources, and could lead to a less efficient use of resources in situations in which capecitabine or vinorelbine were currently being used. The Committee noted that it had not been presented with evidence that identified specific groups of people continuing trastuzumab treatment after disease progression for whom specific recommendations could be made. The Committee considered it could not make specific recommendations about these subgroups without such evidence. The Committee concluded again that lapatinib could not be recommended as an appropriate use of NHS resources.

5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS on implementing NICE technology appraisal guidance. When a NICE

technology appraisal recommends use of a drug or treatment, or other technology, the NHS must provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. The NHS is not required to fund treatments that are not recommended by NICE.

5.2 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website (www.nice.org.uk/TAXXX). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing report and costing template to estimate the savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Recommendations for further research

6.1 The Committee proposed the following research: a trial of lapatinib plus capecitabine compared with trastuzumab-containing regimens and other relevant regimens used for the treatment of breast cancer in the advanced or metastatic setting after progression of disease with trastuzumab. In this research, emphasis should be placed on identifying potential subgroups that may benefit from this treatment, such as patients with brain metastases.

7 Related NICE guidance

Published

- Advanced breast cancer: diagnosis and treatment. NICE clinical guideline 81 (2009). Available from www.nice.org.uk/CG81
- Bevacizumab for the first-line treatment of metastatic breast cancer (terminated appraisal). NICE technology appraisal guidance 147 (2008). Available from www.nice.org.uk/TA147
- Gemcitabine for the treatment of metastatic breast cancer. NICE technology appraisal guidance 116 (2007). Available from www.nice.org.uk/TA116
- Familial breast cancer: the classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care. NICE clinical guideline 41 (2006). Available from www.nice.org.uk/CG41
- Guidance on cancer services. Improving outcomes in breast cancer. NICE clinical guideline manual update (2002). Available from www.nice.org.uk/CSGBC
- Guidance on the use of trastuzumab for the treatment of advanced breast cancer. NICE technology appraisal guidance 34 (2002). Available from www.nice.org.uk/TA34

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer. NICE technology appraisal guidance (publication expected September 2010)
- Bevacizumab in combination with non-taxane chemotherapy for the first-line treatment of metastatic breast cancer. NICE technology appraisal guidance (publication expected January 2011)
- Sunitinib in combination with a taxane for the first-line treatment of advanced and/or metastatic breast cancer. NICE technology appraisal guidance (publication expected May 2011)
- Sunitinib in combination with capecitabine for the treatment of advanced and/or metastatic breast cancer. NICE technology appraisal guidance (publication expected August 2011)

8 Review of guidance

8.1 The guidance on this technology will be considered for review in May 2013. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Philip Home
Chair, Appraisal Committee
February 2010

Appendix A: Appraisal Committee members, guideline representatives and NICE project team

A Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Jane Adam (Chair of Committee – from September 2009 onwards)
Department of Diagnostic Radiology, St George's Hospital

Professor David Barnett (Chair of Committee)
Professor of Clinical Pharmacology, University of Leicester

Professor A E Ades
MRC Senior Scientist, MRC Health Services Research Collaboration, Department of Social Medicine, University of Bristol

Dr Amanda Adler

Consultant Physician, Cambridge University Hospitals Trust

Dr Tom Aslan

General Practitioner, Stockwell, London

Dr Matt Bradley

Value Demonstration Director, AstraZeneca

Elizabeth Brain

Lay Member

Dr Robin Carlisle

Deputy Director of Public Health, Rotherham PCT

David Chandler

Lay Member

Professor Karl Claxton

Professor of Health Economics, Department of Economics & Related Research, University of York

Dr Simon Dixon

Reader in Health Economics, University of Sheffield

Dr Fiona Duncan

Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool

Mr Christopher Earl

Surgical Care Practitioner, Renal Transplant Unit, Manchester Royal Infirmary

Dr Paul Ewings

Statistician, Taunton & Somerset NHS Trust, Taunton

Professor John Geddes

Professor of Epidemiological Psychiatry, University of Oxford

John Goulston

Chief Executive, Barking, Havering and Redbridge Hospitals NHS Trust

Adrian Griffin

VP Strategic Affairs, LifeScan, Johnson & Johnson

Dr Richard Harling

Director of Health Policy, Worcestershire PCT and Worcestershire County Council

Dr Rowan Hillson

Consultant Physician, Diabeticare, The Hillingdon Hospital

Professor Philip Home (Vice Chair of Committee) – Chair for this appraisal from September 2009

Professor of Diabetes Medicine, Newcastle University

Dr Vincent Kirkbride

Consultant Neonatologist, Regional Neonatal Intensive Care Unit, Sheffield

Dr Simon Maxwell

Senior Lecturer in Clinical Pharmacology and Honorary Consultant Physician, Queen's Medical Research Institute, University of Edinburgh

Dr Alec Miners

Lecturer in Health Economics, London School of Hygiene and Tropical Medicine

Dr Ann Richardson

Lay Member

Angela Schofield

Chairman, Bournemouth and Poole Teaching PCT

David Thomson

Lay Member

William Turner

Consultant Urologist, Addenbrooke's Hospital

Dr Luke Twelves

GP, Ramsey Health Centre, Cambridgeshire

Mike Spencer

General Manager, Cardiff and Vale NHS Trust – Facilities and Clinical Support Services

Professor Iain Squire

Consultant Physician, University Hospitals of Leicester

Dr James Moon

Consultant Cardiologist and Senior Lecturer, University College London Hospital (UCLH) and UCL

Dr Ian Lewin

Consultant Endocrinologist, North Devon District Hospital

Dr Norman Vetter

Reader, Department of Epidemiology, Statistics and Public Health, College of Medicine, University of Wales, Cardiff

Dr Paul Watson

Director of Commissioning, East of England Strategic Health Authority

B Guideline representative

The following individual, representing the Guideline Development Group responsible for developing the Institute's clinical guideline related to this topic, was invited to attend the meetings to observe and to contribute as an adviser to the Committee:

- Dr Nick Murray, National Collaborating Centre for Cancer

C NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

João Vieira – (from September 2009 onwards)

Technical Lead

David Chandiwana

Technical Lead

Zoe Garrett (from July 2008 onwards)

Technical Adviser

Louise Longworth

Technical Adviser

Bijal Joshi (from September 2008 onwards)

Project Manager

Eloise Saile

Project Manager

Appendix B: Sources of evidence considered by the Committee

A The Decision Support Unit (DSU) prepared the following reports for this appraisal:

- Tosh J, et al., Lapatinib for breast cancer (for use in women with previously treated advanced or metastatic breast cancer): post appeal, report by the Decision Support Unit, September 2009
- Longworth L, et al., Lapatinib for the treatment of advanced and metastatic breast cancer: a review of the response to the ACD provided by the manufacturer of Lapatinib , Addendum to report of 7 September 2008, report by the Decision Support Unit, October 2008
- Longworth L, et al., Lapatinib for the treatment of advanced and metastatic breast cancer: a review of the response to the ACD provided by the manufacturer of Lapatinib , report by the Decision Support Unit, September 2008

The Evidence Review Group (ERG) report for this appraisal was prepared by the Southampton Health Technology Assessment Centre:

- Jones J, Takeda A, Picot J et al. Lapatinib for HER2 over-expressing breast cancer, June 2007

B The following organisations accepted the invitation to participate in this appraisal. They were invited to comment on the DSU Report. Organisations listed in I and II were also invited to make written submissions. Organisations listed in I and II have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor:

- GlaxoSmithKline

II Professional/specialist and patient/carer groups:

- Breakthrough Breast Cancer
- Breast Cancer Campaign
- Breast Cancer Care
- British Association of Surgical Oncology
- Cancer Research UK
- Cancerbackup
- Macmillan Cancer Support
- National Collaborating Centre for Cancer
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians (Medical Oncology Joint Special Committee)
- Welsh Assembly Government

III Commentator organisations (did not provide written evidence and without the right of appeal):

- British National Formulary
- Department of Health, Social Services and Public Safety for Northern Ireland
- Eli Lilly and Company
- NHS Quality Improvement Scotland
- Pierre Fabre
- Roche

C The following individuals were selected from clinical specialist and patient advocate nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on lapatinib by attending the initial Committee discussion and providing written evidence to the Committee. They were invited to comment on the ACD.

- Professor Dudley Sinnett, nominated by British Association of Surgical Oncology – clinical specialist
- Dr Justin Stebbing, nominated by Royal College of Physicians – clinical specialist
- Dr Rob Stein, nominated by Royal College of Physicians – clinical specialist
- Mrs Marie Wilby, nominated by Breast Cancer Care – patient expert
- Ms Carolyn Rogers, nominated by Breast Cancer Care – patient expert

D Representatives from the following manufacturer/sponsor attended Committee Meetings. They did not fully participate in the discussion. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- GlaxoSmithKline