

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

Trastuzumab for the treatment of HER2-positive metastatic gastric cancer

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

1 Guidance

- 1.1 Trastuzumab, in combination with cisplatin and capecitabine or 5-fluorouracil, is recommended as an option for the treatment of people with human epidermal growth factor receptor 2 (HER2)-positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who:
- have not received prior treatment for their metastatic disease **and**
 - have tumours expressing high levels of HER2 as defined by a positive immunohistochemistry score of 3 (IHC3 positive).
- 1.2 People who are currently receiving treatment with trastuzumab for HER2-positive metastatic gastric cancer who do not meet the criteria in 1.1 should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

2 The technology

- 2.1 Trastuzumab (Herceptin, Roche Products) is a recombinant humanised IgG1 monoclonal antibody directed against HER2. Trastuzumab in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of patients with HER2-

positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anticancer treatment for their metastatic disease. Trastuzumab is approved for use only in patients with metastatic gastric cancer whose tumours have HER2 overexpression as defined by immunohistochemistry (IHC)2 positive and a confirmatory fluorescence in situ hybridisation (FISH) positive result, or IHC3 positive, as determined by an accurate and validated assay. On 6 August 2010, the marketing authorisation for trastuzumab was revised to include silver in situ hybridisation (SISH) testing as another method for confirming HER2 overexpression. Because of the timing of the revision, SISH testing was not considered in this appraisal. For further details see the summary of product characteristics.

- 2.2 Trastuzumab is associated with cardiotoxicity. The summary of product characteristics states that all patients should have baseline cardiac assessment before starting treatment. Cardiac function should be further monitored during treatment (for example, every 12 weeks). The summary of product characteristics also states that caution should be taken in treating people with symptomatic heart failure, a history of hypertension, or documented coronary artery disease. For full details of side effects and contraindications, see the summary of product characteristics.
- 2.3 Trastuzumab is administered at an initial loading dose of 8 mg/kg body weight. The recommended maintenance dose at 3-weekly intervals is 6 mg/kg body weight, beginning 3 weeks after the loading dose. It is given as an intravenous infusion over 90 minutes. If the initial loading dose is well tolerated, the subsequent doses can be administered as 30-minute infusions. As long as treatment is tolerated, it can be given until disease progression.

- 2.4 The net price of a 150-mg vial of trastuzumab is £407.40 (excluding VAT; 'British national formulary' [BNF] edition 59). For a patient weighing 62 kg, four vials are required for the first loading dose and three vials for each subsequent dose. Assuming that excess trastuzumab is wasted, the drug cost of eight infusions of trastuzumab (the median number of infusions in the regulatory trial) is £10,185. Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of trastuzumab and a review of this submission by the Evidence Review Group (ERG; appendix B).

- 3.1 The manufacturer's decision problem compared trastuzumab plus cisplatin and either capecitabine or 5-fluorouracil with:

- epirubicin plus cisplatin and either capecitabine or 5-fluorouracil and
- epirubicin plus oxaliplatin and capecitabine.

The choice of comparators was based on the results of a survey of commonly used treatments for gastric cancer in England and Wales. Outcomes were overall survival, progression-free survival, response rate, adverse effects of treatment and health-related quality of life. In the economic evaluation, the incremental cost per quality-adjusted life year (QALY) was presented. A lifetime horizon was used, and costs were considered from the NHS perspective.

Clinical effectiveness

- 3.2 The manufacturer identified one phase III randomised controlled trial (ToGA) evaluating the efficacy of trastuzumab plus cisplatin and a fluoropyrimidine (that is, capecitabine or 5-fluorouracil) in

people with inoperable locally advanced or recurrent and/or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction. People in the trial had tumours with high levels of HER2 protein (see section 3.4), and had received no prior treatment for their advanced or metastatic disease.

3.3 The trial randomised 594 people to receive either chemotherapy (n = 296) or trastuzumab plus chemotherapy (n = 298). The chemotherapy group in the ToGA trial received intravenous cisplatin (80 mg/m²) on day one of each cycle with either oral capecitabine (1000 mg/m²) twice daily for 14 days, or an intravenous infusion of 5-fluorouracil (800 mg/m²) on days one to five of each of the six 3-weekly cycles. In addition to six 3-weekly cycles of chemotherapy, the treatment group received trastuzumab (8 mg/kg loading dose on day one, followed by 6 mg/kg intravenous infusion every 3 weeks) until disease progression. In both groups the choice of fluoropyrimidine was at the discretion of the investigator; 87% received capecitabine and 13% received 5-fluorouracil.

3.4 People whose tumours were classed as HER2 positive were included in the ToGA trial. IHC and FISH tests were done at the same time (parallel testing) according to the trial protocol. At the time of randomisation, tumours that were IHC3 positive, or those that tested FISH positive were defined as HER2 positive. Changes in the understanding of HER2 testing during the ToGA trial resulted in HER2 positive being defined as tumours that were IHC2 positive and FISH positive, or IHC3 positive. From the full population of 594 in the ToGA trial, 446 people (75%) had tumours that met this narrower definition. The European marketing authorisation was granted for this population (referred to as the EMA subgroup). Of this subgroup, 218 people received treatment with chemotherapy

alone and 228 people received treatment with trastuzumab plus chemotherapy.

- 3.5 At baseline, characteristics in the ToGA trial were balanced between the treatment groups. These characteristics included sex, age, weight, region, and type of tumour (that is, intestinal, diffuse or mixed tumour types). A high proportion of people in the ToGA trial were male (76%) and 55% were from Asian countries. Almost all people had metastatic gastric cancer (97%), and accordingly the marketing authorisation was granted for the metastatic disease only.
- 3.6 The primary outcome in the ToGA trial was overall survival. The trial was terminated early in accordance with a revised stopping rule recommended by the Independent Data Monitoring Committee. At the time of the clinical cut-off, the median duration of survival follow-up was 18.6 months in the trastuzumab plus chemotherapy group and 17.1 months in the chemotherapy alone group. The hazard ratio for overall survival in the EMA subgroup was 0.65 (95% confidence interval [CI] 0.51 to 0.83) corresponding to a median survival for the trastuzumab plus chemotherapy group of 16 months compared with 11.8 months for the chemotherapy alone group (4.2 month improvement in survival). A median survival of 13.8 months was reported for the total trial population receiving trastuzumab plus chemotherapy compared with 11.1 months in the chemotherapy alone group (2.7 month improvement in survival).
- 3.7 The manufacturer reported the results for secondary outcomes including progression-free survival and overall response rate. For the EMA subgroup the hazard ratio for progression-free survival was 0.64 (95% CI 0.51 to 0.79), corresponding to a median progression-free survival for the trastuzumab plus chemotherapy group of 7.6 months compared with 5.5 months for the

chemotherapy alone group (a 2.1-month improvement in progression-free survival). Results for overall response rate were reported for the total trial population only, and demonstrated a statistically significantly higher overall response rate in the trastuzumab plus chemotherapy group (47.3%) compared with the chemotherapy alone group (34.5%), odds ratio 1.70 (95% CI 1.22 to 2.38, $p = 0.002$).

- 3.8 Quality of life was assessed in the ToGA trial as a secondary objective using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 (global health status, functioning and symptoms) and QLQ-STO22 (containing 22 items associated with dysphagia, pain, reflux, eating restrictions, anxiety, dry mouth, body image and hair loss). Both treatment groups in the trial showed improvements in quality of life over the course of treatment. A statistical analysis of differences in quality of life between the treatment groups was not presented. Additionally, EQ-5D data were collected at baseline and every 3 weeks until disease progression.
- 3.9 In both groups, 68% of people had grade 3 or 4 adverse events. The most frequent were disorders of the blood and lymphatic system, gastrointestinal disorders, and metabolism and nutritional disorders. More people treated with trastuzumab plus chemotherapy had asymptomatic reductions in left ventricular ejection fraction; however, the difference in symptomatic cardiac events was not statistically significant.

Cost effectiveness

- 3.10 The manufacturer developed a Markov economic model to assess the cost effectiveness of trastuzumab plus chemotherapy to treat people with HER2-positive metastatic gastric cancer. The model had three distinct health states: progression-free survival, disease

progression and death. The model had a cycle length of 1 month and an 8-year time horizon (considered to be a lifetime horizon). Both costs and benefits were discounted at a rate of 3.5%. One-way sensitivity analyses were undertaken on utility values, survival analysis, unit costs and various resource use assumptions. Probabilistic sensitivity analysis was also undertaken to explore parameter uncertainty in the model.

3.11 The treatment regimens included in the manufacturer's economic evaluation were:

- trastuzumab plus cisplatin and capecitabine
- trastuzumab plus cisplatin and 5-fluorouracil
- epirubicin plus cisplatin and capecitabine
- epirubicin plus cisplatin and 5-fluorouracil
- epirubicin plus oxaliplatin and capecitabine.

3.12 The clinical estimates (transition probabilities) in the model were derived from the overall survival and progression-free survival estimates from the trastuzumab plus chemotherapy group in the ToGA trial (EMA subgroup).

3.13 The manufacturer's literature search for comparator data did not find trials in which triple regimens including epirubicin were directly compared with triple regimens including trastuzumab. However, four studies were identified that evaluated one of the regimens of interest:

- Tobe (1992) and Kim (2001), which compared epirubicin plus cisplatin and 5-fluorouracil with cisplatin and 5-fluorouracil
- Yun (2010), which compared epirubicin plus cisplatin and capecitabine with cisplatin and capecitabine

- REAL-2 (2008), which compared the non-inferiority of capecitabine with 5-fluorouracil in triple chemotherapy regimens including epirubicin.

Additionally, a meta-analysis was identified (Wagner 2006) evaluating the efficacy of a triple regimen including an anthracycline (epirubicin) compared with a regimen that did not include an anthracycline. However, the results of this analysis were not used in the economic model because the largest trial assessed a comparison between epirubicin, cisplatin and 5-fluorouracil and cisplatin and 5-fluorouracil plus mitomycin (Ross 2002), and the other trials were presented in abstract form (Kim) or only included a small population with more severe disease (Tobe).

3.14 The manufacturer explored the possibility of conducting a network meta-analysis between the three comparator triple regimens used in UK clinical practice (that is, epirubicin plus cisplatin and capecitabine, epirubicin plus cisplatin and 5-fluorouracil, and epirubicin plus oxaliplatin and capecitabine) and the chemotherapy comparator group from the ToGA trial, to obtain the comparator effectiveness data for the model. However, the manufacturer concluded that the results of a network meta-analysis would not produce reliable or meaningful results because the only study to evaluate epirubicin plus cisplatin and capecitabine compared with cisplatin and capecitabine (Yun) did not report the primary outcome of the ToGA trial (overall survival). Additionally, the studies that compared cisplatin and 5-fluorouracil with epirubicin plus cisplatin and 5-fluorouracil (Tobe and Kim) did not have comparable patient populations. Therefore, the manufacturer presented a narrative summary of the results from the Yun, Tobe, Kim and REAL-2 trials.

3.15 For epirubicin plus cisplatin and capecitabine, the manufacturer concluded that the estimates of overall survival and progression-

free survival could be assumed to be equivalent to those from the chemotherapy comparator group in the ToGA trial. This was because the Yun study showed no evidence of a significant difference (hazard ratio of progression-free survival for epirubicin plus cisplatin and capecitabine compared with cisplatin and capecitabine 0.96, 95% CI 0.58 to 1.57). The dose of cisplatin in the ToGA trial was also considered to be higher than it would be in UK clinical practice when added to a triple regimen including epirubicin, and that the two regimens could therefore be regarded as equivalent.

- 3.16 For epirubicin, cisplatin and 5-fluorouracil the manufacturer concluded that the estimates of progression-free survival could be assumed to be equivalent to those from the chemotherapy comparator group in the ToGA trial. The evidence to support this conclusion came from the study by Tobe (hazard ratio of overall survival for epirubicin plus cisplatin and 5-fluorouracil compared with cisplatin and 5-fluorouracil 0.57, 95% CI 0.27 to 1.2) and the study by Kim (hazard ratio of overall survival for epirubicin plus cisplatin and 5-fluorouracil compared with cisplatin and 5-fluorouracil 0.83, 95% CI 0.42 to 1.61). Additionally, the manufacturer used an overall survival benefit of capecitabine over 5-fluorouracil (hazard ratio 1.15) from a meta-analysis (Okines 2009).
- 3.17 For the third comparator regimen (epirubicin plus oxaliplatin and capecitabine), the manufacturer concluded that it could be considered equivalent to epirubicin plus cisplatin and capecitabine in effectiveness. This was based on the REAL-2 trial. The manufacturer stated that the results of this study indicated that oxaliplatin was as effective as cisplatin (hazard ratio of overall survival for oxaliplatin arms compared with cisplatin arms 0.92,

95% CI 0.80 to 1.10). Overall survival and progression-free survival estimates for epirubicin plus oxaliplatin and capecitabine were therefore considered equivalent to those for epirubicin plus cisplatin and capecitabine.

- 3.18 Health-related quality of life was estimated for progression-free survival and progressive disease health states. A utility value for the progression-free survival health state was calculated using results from the EQ-5D data collected at baseline and then every 3 weeks until progression in the ToGA trial. The manufacturer estimated a baseline utility value of 0.7292, which increased daily by 0.000142 during progression-free survival. For the progressive disease health state, an estimate from the literature was used because EQ-5D data were not collected after disease progression in the ToGA trial. The utility value of 0.577 for progressive disease was taken from 'Sunitinib for the treatment of gastrointestinal stromal tumours' (NICE technology appraisal guidance 179). Utility values associated with adverse events were not included in the model.
- 3.19 The model included costs for HER2 testing, drug acquisition, drug administration, monitoring during progression-free survival, treating adverse events, care costs in progression-free survival after chemotherapy treatment was stopped, and supportive care costs after progression of disease. The cost of HER2 testing was based on a sequential testing strategy in which only people who tested IHC2 positive received a FISH test. Total drug costs included an amount for wastage based on an assumption that 80% of centres using trastuzumab to treat gastric cancer would also use it to treat breast cancer and would share vials, thereby implying no wastage. Cardiac monitoring was assumed to be done using a multiple-gated acquisition scan or an echocardiogram and to take place once

every cycle for people treated with epirubicin and once every 3 months for people treated with trastuzumab, in accordance with the summaries of product characteristics. The costs of grade 3 or 4 adverse events with an incidence of at least 5% in any of the treatment groups were included.

- 3.20 The model suggested that trastuzumab plus cisplatin and capecitabine compared with epirubicin plus cisplatin and capecitabine, and compared with epirubicin plus oxaliplatin and capecitabine, produced a mean gain of 4.8 months of life for both comparisons. Trastuzumab plus cisplatin and 5-fluorouracil compared with epirubicin plus cisplatin and 5-fluorouracil produced a mean gain of 4.3 months of life. In the manufacturer's incremental cost-effectiveness analysis of all five regimens, epirubicin plus cisplatin and 5-fluorouracil, and epirubicin plus oxaliplatin and capecitabine, were both less effective and more expensive than the other regimens (that is, they were dominated). Additionally, although the total cost of the trastuzumab plus cisplatin and 5-fluorouracil regimen was lower than that of trastuzumab plus cisplatin and capecitabine, it was also less effective and had a higher incremental cost-effectiveness ratio (ICER) than trastuzumab, cisplatin and capecitabine (that is, it was extendedly dominated). For the two remaining regimens, trastuzumab plus cisplatin and capecitabine had an additional cost of £13,064 and produced an additional 0.25 QALYs over epirubicin plus cisplatin and capecitabine. The ICER was £51,927 per QALY gained. The manufacturer examined other scenarios in a probabilistic sensitivity analysis. Distributions were applied to utility values, unit costs, monthly supportive care costs, adverse event probabilities, survival curves, parametric parameters, and progression-free survival monthly Kaplan-Maier estimates. This resulted in ICERs that ranged from £37,180 to £95,238 per QALY gained. The probability

that trastuzumab plus cisplatin and capecitabine was cost effective at £30,000 was 0%.

- 3.21 The manufacturer also presented the results of pair-wise comparisons between trastuzumab plus cisplatin and 5-fluorouracil and epirubicin plus cisplatin and 5-fluorouracil, and between trastuzumab plus cisplatin and capecitabine and epirubicin plus oxaliplatin and capecitabine. The ICERs for these comparisons were £50,838 and £40,711 per QALY gained respectively.

Evidence review group comments

- 3.22 The ERG stated that the manufacturer identified the only trial evaluating trastuzumab in the treatment of HER2-positive metastatic gastric cancer (the ToGA trial). This trial was a well-conducted phase III randomised controlled trial with appropriate validity assessment. The ERG considered that the ToGA trial demonstrated improved overall survival of people treated with trastuzumab when added to cisplatin plus either capecitabine or 5-fluorouracil. The economic model was considered appropriate for the decision problem and the general approach employed by the manufacturer to estimate lifetime cost effectiveness met the requirements of the NICE reference case.
- 3.23 The ERG identified some small errors in the manufacturer's model related to inconsistent assumptions about adverse events, distributions of survival data and resource use. Correcting these errors reduced the ICER from £51,927 per QALY gained to £49,005 per QALY gained. This ICER represented an additional cost of £12,332 and an additional 0.251 QALYs from treatment with trastuzumab plus cisplatin and capecitabine over epirubicin plus cisplatin and capecitabine.

3.24 The ERG highlighted the following main areas of concern in the manufacturer's submission:

- The relevance of the trial data to a UK population.
- The comparator data considered for network meta-analysis.
- The relative effectiveness estimates of comparators in the model.
- The utility values applied during progression-free survival.
- The frequency of cardiac monitoring with trastuzumab and epirubicin.
- The use of parallel and sequential HER2 testing strategies.

3.25 The ERG stated that the efficacy of standard triple regimens in people with HER2-positive gastric cancer was unknown. It was assumed that the HER2-positive population is equivalent to a mixed-HER2 population containing an unknown proportion of HER2-positive people. The ERG noted that the trial population in the ToGA trial was substantially younger than the UK population of people with gastric cancer, of whom only 17% die before the age of 65. The population of the ToGA trial also differed substantially from the UK clinical population, in that over 50% of people in the trial were from Asian countries.

3.26 The ERG considered that the most relevant comparators in the context of current clinical practice were epirubicin plus cisplatin and capecitabine, epirubicin plus cisplatin and 5-fluorouracil, epirubicin plus oxaliplatin and capecitabine, and epirubicin plus oxaliplatin and 5-fluorouracil. However, it stated that epirubicin plus oxaliplatin and capecitabine was likely to be used more often in routine clinical practice in England and Wales than the 6% suggested in the manufacturer's submission. Following clarification by the manufacturer, the ERG concluded that all relevant trials had been

identified for inclusion in a possible network meta-analysis to establish a link between the triple regimens with the chemotherapy comparator group of the ToGA trial. The ERG considered that the manufacturer's decision not to attempt a network meta-analysis using these trials was justified, mainly because of differences in the trial populations.

3.27 The ERG stated that the manufacturer's assumption of no difference in effect between the chemotherapy comparator regimen in the ToGA trial and the comparator regimens in the economic evaluation largely rested on the critique of the meta-analysis by Wagner. This study found a benefit for triple regimens including an anthracycline over regimens that did not include an anthracycline. The ERG stated that the manufacturer's decision to exclude the meta-analysis on the basis that it contained a trial that had only been published in abstract form (Kim) and a trial with a small population of people with more severe disease (Tobe) was inconsistent with the decision to include these studies individually. As a result of dismissing the meta-analysis, the small phase II Kim, Tobe and Yun trials were used as evidence of no effect between double and triple regimens, and the ERG stated that these were underpowered to detect a statistically significant benefit of treatment. The ERG therefore considered that the manufacturer's assumption of no difference in effectiveness between the chemotherapy comparator group in the ToGA trial and triple regimens including epirubicin was not justified. The ERG noted that the balance of evidence suggested that there may be an advantage in adding epirubicin to a double regimen.

3.28 The ERG explored the effect on the ICER using the hazard ratio from the Yun study (0.96), which indicated a small benefit of adding epirubicin to a double regimen. When applied to progression-free

survival only, the ICER increased from the revised base case of £49,005 per QALY gained to £49,754 per QALY gained. When applied to progression-free survival and overall survival, the ICER increased from £49,005 per QALY gained to £52,709 per QALY gained.

- 3.29 The ERG also explored the effect of the manufacturer's assumption of no difference between triple regimens including oxaliplatin and triple regimens including cisplatin. From the REAL-2 trial, a hazard ratio for overall survival and progression-free survival (0.87) was derived that suggested a benefit of oxaliplatin regimens over cisplatin regimens. As a result, the cisplatin regimen no longer dominated the oxaliplatin regimen in the incremental analysis, which increased the ICER for trastuzumab plus cisplatin and capecitabine. When applied to overall survival alone, the ICER increased from £49,005 per QALY gained to £50,745 per QALY gained. When applied to overall survival and progression-free survival, the ICER increased from £49,005 per QALY gained to £54,114 per QALY gained.
- 3.30 The ERG stated that the manufacturer's base-case approach was relatively optimistic because utility values were assumed to increase by 0.000142 for each day in progression-free survival. The ERG suggested that it would be more appropriate to apply a small decrease in utility values over time to reflect the change in utility over time for an equivalent group of people from UK general population norms for EQ-5D. The ERG calculated this utility decrement to be 0.003502 per year. The ERG explored the impact of applying this assumption to the corrected manufacturer's base case and reported an increase from £49,005 per QALY gained to £51,309 per QALY gained.

- 3.31 The ERG highlighted the manufacturer's base-case assumption that cardiac monitoring took place once every cycle with epirubicin and once every 3 months with trastuzumab. Although the summary of product characteristics for epirubicin recommends an echocardiogram before and after each treatment cycle, the ERG's clinical advisers considered that, in the UK, cardiac monitoring is not done this often. The ERG carried out an exploratory analysis assuming that cardiac monitoring was carried out at the same frequency for epirubicin as for trastuzumab. This resulted in the ICER increasing from the corrected base-case estimate of £49,005 per QALY gained to £50,816 per QALY gained.
- 3.32 The ERG raised a number of issues relating to HER2 testing in the manufacturer's base case. These included the potential costs of repeat tests needed because of test failures and that the effectiveness estimates in the model were derived from the ToGA trial, which used a parallel testing strategy rather than a sequential testing strategy. The ERG also noted the estimate that 17.8% of people with metastatic gastric cancer whose tumours are HER2-positive came from the full trial population; however, in the UK subgroup of people in the ToGA trial, this was 26%. To explore the impact of variations in the HER2-positive rate, the ERG undertook an exploratory analysis in which the HER2 rate was varied between 5% and 30%, indicating the lower and upper limits which it considered reasonable. The resulting ICERs from this analysis ranged from £52,866 per QALY gained for the lower assumption of 5% to £48,395 per QALY gained for the higher assumption of 30%.
- 3.33 To consider the combined potential impact of some of the uncertainties raised, the ERG undertook two alternative exploratory analyses in which the following key assumptions were considered to be equally plausible:

- The hazard ratio of epirubicin plus oxaliplatin and capecitabine compared with epirubicin plus cisplatin and capecitabine was changed to 0.87.
- The hazard ratio of epirubicin plus cisplatin and capecitabine compared with cisplatin and capecitabine was changed to 0.96 for progression-free survival and overall survival (indicating a survival benefit for epirubicin plus cisplatin and capecitabine compared with cisplatin and capecitabine alone).
- Utility values during progression-free survival were changed to incorporate an expected decrease in utility in line with the general population over time.
- The frequency of cardiac monitoring for epirubicin was changed to be the same as trastuzumab.

The ERG presented the results of these exploratory analyses separately for sequential and parallel HER2 testing strategies. In both analyses, epirubicin plus cisplatin and capecitabine was no longer the dominant comparator regimen and the relevant comparator for trastuzumab plus cisplatin and capecitabine was epirubicin plus oxaliplatin and capecitabine. When trastuzumab plus cisplatin and capecitabine was compared with epirubicin plus oxaliplatin and capecitabine, the QALY gain was 0.149 at an incremental cost of £9,987, giving an ICER of £66,982 per QALY gained using a sequential testing strategy. When a parallel testing strategy was assumed, the QALY gain was the same, however, the incremental costs increased to £10,681, giving an ICER of £71,637 per QALY gained.

3.34 Finally, the ERG undertook a separate exploratory analysis in which the hazard ratio was 0.77 (indicating a survival benefit) for epirubicin plus cisplatin and capecitabine, and epirubicin plus oxaliplatin and capecitabine, compared with cisplatin and

capecitabine alone. This estimate of effectiveness was inferred from the Wagner meta-analysis in which a triple regimen including an anthracycline therapy had been compared with a regimen without an anthracycline. When applied to overall survival only, the QALY gain was approximately 0.13 at an incremental cost of £10,993, giving an ICER of £84,373 per QALY gained. When applied to overall survival and progression-free survival, the QALY gain was approximately 0.13 at an incremental cost of £11,226, giving an ICER of £99,797 per QALY gained.

Additional data provided by the manufacturer

3.35 The manufacturer's response to the appraisal consultation document (ACD) included an alternative base-case analysis and a new economic analysis for a subgroup of people from the ToGA trial who were IHC3 positive.

3.36 The manufacturer's alternative base case incorporated three of the four parameter changes in the ERG's exploratory analysis (see section 3.33). These were:

- a hazard ratio of 0.87 for epirubicin plus oxaliplatin and capecitabine compared with epirubicin plus cisplatin and capecitabine
- a hazard ratio of 0.96 for overall survival for epirubicin plus cisplatin and capecitabine compared with cisplatin plus capecitabine
- the same frequency of cardiac monitoring for epirubicin as trastuzumab.

The decrement in utility values during progression-free survival in the ERG's exploratory analysis was not incorporated. The manufacturer included the estimate of increasing utility values during progression-free survival used in its original base-case analysis. The ICER for trastuzumab plus cisplatin and capecitabine

in comparison with epirubicin plus oxaliplatin and capecitabine was £62,829 per QALY gained. The other treatments in the analysis were either dominated or extendedly dominated. A probabilistic sensitivity analysis for the same comparison produced an ICER with a mean value of £67,786 per QALY gained.

- 3.37 A new economic analysis based on a subgroup of people who tested IHC3 positive (that is, people with very high levels of HER2) was provided by the manufacturer. The analysis included 279 people, of whom 144 received treatment with trastuzumab plus cisplatin and either capecitabine or 5-fluorouracil, and 135 received treatment with cisplatin plus either capecitabine or 5-fluorouracil.
- 3.38 The clinical evidence submitted for the IHC3-positive subgroup included an analysis of overall survival. Analyses of progression-free survival and time to progression were provided as commercial-in-confidence. The hazard ratio of overall survival for the trastuzumab plus chemotherapy group compared with the chemotherapy alone group was 0.57 (95% CI 0.41 to 0.79), corresponding to a median survival for the trastuzumab plus chemotherapy group of 18 months compared with 12.4 months for the chemotherapy alone group (5.6 month improvement in survival). The manufacturer also provided an adjusted hazard ratio to account for an imbalance in baseline characteristics between the treatment groups in the IHC3-positive subgroup. The adjusted hazard ratio of overall survival for the trastuzumab plus chemotherapy group compared with the chemotherapy alone group was 0.51 (95% CI 0.36 to 0.72).
- 3.39 The manufacturer presented the results of an economic analysis for the IHC3-positive subgroup using the adjusted hazard ratio. The modelled mean overall survival for trastuzumab plus cisplatin and capecitabine was 7.4 months when compared with epirubicin plus

cisplatin and capecitabine, and 6.2 months when compared with epirubicin plus oxaliplatin and capecitabine. The incremental analysis of all interventions resulted in an ICER of £42,969 per QALY gained for trastuzumab plus cisplatin and capecitabine compared with epirubicin plus cisplatin and capecitabine. This represented incremental costs of £16,654 and 0.388 incremental QALYs gained. All other treatment regimens were either dominated or extendedly dominated. A probabilistic sensitivity analysis produced a mean ICER of £43,970 per QALY gained.

ERG comments on the manufacturer's additional data

- 3.40 The ERG commented that the manufacturer's alternative base-case analysis allowed the quality of life during progression-free survival to rise above that of the general population. It considered that this was not a plausible assumption. Therefore the ERG re-ran the analyses presented by the manufacturer using a ceiling utility value equal to general population utility value estimates. The results were presented separately for deterministic and probabilistic analyses. The incremental analysis of all interventions resulted in an ICER of £63,081 per QALY (deterministic) and £71,463 per QALY gained (probabilistic) for trastuzumab plus cisplatin and capecitabine compared with epirubicin plus oxaliplatin and capecitabine. All other regimens were either dominated or extendedly dominated.
- 3.41 The ICERs calculated by the ERG for the IHC3-positive subgroup were presented separately using the manufacturer's adjusted hazard ratio (stratified analysis, see section 3.39) and the unadjusted hazard ratio (unstratified analysis). The incremental analysis of all interventions using the stratified hazard ratio resulted in an ICER of £43,206 per QALY gained (deterministic) and £44,490 per QALY gained (probabilistic) for trastuzumab plus

cisplatin and capecitabine compared with epirubicin plus cisplatin and capecitabine. When the unstratified hazard ratio was used, the optimal comparator treatment in the incremental analysis changed depending on whether a deterministic or probabilistic analysis was used. In the deterministic analysis, the ICER was £49,970 per QALY gained for trastuzumab plus cisplatin and capecitabine compared with epirubicin plus cisplatin and capecitabine. For the probabilistic analysis, the ICER was £51,934 per QALY gained for trastuzumab plus cisplatin and capecitabine compared with epirubicin plus oxaliplatin and capecitabine.

- 3.42 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from www.nice.org.uk/guidance/TAXXX

4 Consideration of the evidence

- 4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of trastuzumab when given in combination with cisplatin and either capecitabine or 5-fluorouracil, having considered evidence on the nature of metastatic gastric cancer and the value placed on the benefits of trastuzumab by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

Clinical effectiveness

- 4.2 The Committee discussed current clinical practice in the UK. It noted comments from consultation that no treatment options for metastatic gastric cancer currently target HER2 overexpression, and that trastuzumab offers a new option for this patient group. The Committee heard from clinical specialists that current clinical practice in the UK is normally a triple regimen that includes an

anthracycline, a platinum agent, and a fluoropyrimidine. It understood that epirubicin, cisplatin and capecitabine are the standard anthracycline, platinum agent and fluoropyrimidine therapies used. It also understood that oxaliplatin is sometimes used in place of cisplatin and that 5-fluorouracil is sometimes used in place of capecitabine. The Committee considered this in the context of the comparator regimen given in the ToGA trial, which was a double regimen including a platinum agent and a fluoropyrimidine, but not an anthracycline. The Committee discussed the fact that double regimens were not often used in UK clinical practice, and concluded that the comparator in the ToGA trial did not represent current practice in the UK.

- 4.3 The Committee considered whether the population in the ToGA trial could be considered representative of the population of people with HER2-positive metastatic gastric cancer in England in Wales. It noted that most of the people in the trial were from Asia. The Committee acknowledged subgroup analyses that appeared to confirm a similar overall survival benefit for the group of European people in the trial.
- 4.4 The Committee discussed the clinical effectiveness of the trastuzumab regimens presented in the ToGA trial. It noted that, compared with cisplatin plus either capecitabine or 5-fluorouracil, trastuzumab plus cisplatin and either capecitabine or 5-fluorouracil provided a 4.2 month gain in overall survival and a 2.1 month gain in progression-free survival. The Committee concluded that the ToGA trial demonstrated trastuzumab plus cisplatin and capecitabine or 5-fluorouracil offers clinical benefit.
- 4.5 The Committee discussed the likely clinical effectiveness of the current UK triple regimens, that is, when epirubicin is added to cisplatin and fluoropyrimidine. It heard from clinical specialists that

adding epirubicin to cisplatin and a fluoropyrimidine provides sufficient additional benefit to be standard practice. However, clinical specialists underlined that this treatment regimen had not been subject to rigorous evaluation. The Committee discussed the evidence identified by the manufacturer and the ERG, recognising that none of the studies were completed in a HER2-positive population. The Committee acknowledged the lack of ideal evidence for this comparison. However, it considered, based on the evidence and the views of the clinical specialists, that epirubicin provided some additional benefit when added to a cisplatin and fluoropyrimidine combination.

- 4.6 The Committee discussed whether the results of the ToGA trial could be applied to the comparison between a trastuzumab plus chemotherapy regimen and an epirubicin plus chemotherapy regimen. It noted that the ToGA trial had used a higher dose of cisplatin than would be used as part of a triple regimen in UK clinical practice, and recognised the manufacturer's view that adding epirubicin to high-dose cisplatin would offer less benefit than adding it to lower-dose cisplatin. The Committee also noted comments from consultation that dose intensity was an important factor in chemotherapy and that reduced doses over a longer number of cycles could not be considered equivalent to higher doses over a shorter number of cycles. However, based on clinical specialist opinion, the Committee was not persuaded that the outcomes for the chemotherapy comparator group in the ToGA trial were representative of the outcomes of triple regimens in UK clinical practice. It did, however, accept that trastuzumab plus cisplatin and either capecitabine or 5-fluorouracil was likely to offer a survival benefit over treatment with epirubicin plus cisplatin and either capecitabine or 5-fluorouracil.

- 4.7 The Committee then discussed the range of possible estimates submitted for the clinical effectiveness of the triple regimens over the double regimens. It first considered the hazard ratio for progression-free survival of 0.96 for epirubicin plus cisplatin and capecitabine compared with cisplatin plus capecitabine from the Yun study. The Committee heard from the ERG that it had chosen to use this estimate in its revised base-case analysis because it was taken from a study that compared cisplatin plus capecitabine with epirubicin plus cisplatin and capecitabine. In the absence of any evidence specifically for the HER2-positive group, it considered that this study best represented the decision problem in the appraisal.
- 4.8 The Committee also considered the hazard ratio for overall survival of 0.77 (indicating a more favourable benefit of treatment with epirubicin) from the Wagner meta-analysis. It discussed concerns raised by the ERG that this study was not directly applicable to the estimates of effectiveness of the regimens including capecitabine, because two of the studies used 5-fluorouracil regimens and the third study compared two triple therapies. The Committee heard from clinical specialists that they considered that the meta-analysis may have overestimated the survival benefit of adding epirubicin to cisplatin and a fluoropyrimidine. It further noted comments from consultees that the quality of the studies in the meta-analysis was poor. The evidence from the largest study (Ross) was from an unplanned subgroup, which provided a greater estimate of the effect of epirubicin than the full population. The Committee further noted comments from consultees that the low doses of cisplatin in the studies did not reflect the higher dose used in the ToGA trial. The Committee concluded that the survival benefit of a triple regimen including epirubicin compared with that of a double regimen without epirubicin was unlikely to be represented by a

hazard ratio of 0.77, and that the estimate would be closer to 0.96. However, this was associated with considerable uncertainty.

4.9 The Committee discussed the clinical effectiveness of trastuzumab for the IHC3-positive subgroup, who in clinical practice would not require a confirmatory FISH test. It noted the efficacy in the trial was greater for the subgroup than for the whole population. The Committee discussed the biological plausibility of greater benefit in the IHC3-positive subgroup and considered that greater effectiveness may be experienced with higher levels of HER2. The Committee concluded it was an appropriate subgroup and discussed the clinical evidence. It noted that the hazard ratio of overall survival for the trastuzumab plus chemotherapy group compared with the chemotherapy alone group was 0.57, corresponding to a median survival for the trastuzumab plus chemotherapy group of 18 months compared with 12.4 months for the chemotherapy alone group (a 5.6 month gain in survival). The Committee concluded that trastuzumab plus cisplatin and capecitabine or 5-fluorouracil is clinically effective in the IHC3-positive subgroup.

4.10 The Committee discussed the quality-of-life data from the ToGA trial. It noted that there were no differences in quality-of-life scores between the two treatment groups and no statistical analysis of these data. It heard from clinical specialists that treatment could bring about some improvement in quality of life, because gastric cancer has serious disease symptoms including pain, vomiting and anaemia, which chemotherapy can reduce. The clinical specialists considered that reduced symptoms outweighed the side effects of chemotherapy. The Committee was persuaded that because of the disease symptoms associated with gastric cancer it was plausible that quality of life could increase during progression-free survival.

4.11 The Committee discussed the adverse event data provided by the manufacturer. The Committee heard from clinical specialists that they considered that the adverse effects of trastuzumab are known and manageable in clinical practice because of its use in breast cancer. It further heard that epirubicin was associated with adverse effects and that providing trastuzumab as an alternative to epirubicin may have benefits. The Committee understood that trastuzumab is associated with cardiotoxicity, but noted that the incidence of cardiac failure in the trial was low and was similar in both treatment groups in the ToGA trial (two in the chemotherapy alone group and one in the trastuzumab plus chemotherapy group). It also noted commercial-in-confidence information relating to infusion-related reactions.

Cost effectiveness

4.12 The Committee considered the base-case estimates of cost effectiveness in the manufacturer's model. It noted that after consultation on the ACD the manufacturer's alternative base-case ICER of £62,800 per QALY gained was approximately £11,000 per QALY gained higher than the original base-case ICER of £51,900 per QALY gained. It further noted that the alternative base case incorporated a number of assumptions considered equally plausible by the ERG in its report. The Committee discussed the analyses of cost effectiveness and specifically considered the following assumptions:

- The most plausible estimate of comparator effectiveness.
- The frequency of cardiac monitoring for people treated with epirubicin.
- A parallel or sequential HER2 testing strategy.
- The change in utility values during progression-free survival.

- The assumption that 80% of centres would share vials of trastuzumab.

4.13 The Committee discussed the most plausible estimate of clinical effectiveness for the triple comparators. It recognised that, in the manufacturer's base-case analysis, a hazard ratio of 1.00 was used to estimate overall survival and progression-free survival of people treated with epirubicin plus cisplatin and capecitabine compared with cisplatin plus capecitabine. It noted that the ERG modified this to 0.96 in its exploratory analysis, and that this was incorporated into the manufacturer's alternative base case. It noted that when this parameter change was applied to both overall survival and progression-free survival, the ICER increased by less than £1000. The Committee also considered the estimate of the ICER using a hazard ratio of 0.77 (indicating a more favourable benefit of treatment with epirubicin) from the Wagner meta-analysis. The Committee noted that, although the effect of changing the hazard ratio to 0.96 had been relatively minor, the effect of changing the hazard ratio to 0.77 increased the ICER by up to £50,000 per QALY gained. The Committee concluded that it was appropriate to consider the ICERs that had used a hazard ratio of 0.96 (see section 4.8). However, it considered that there was considerable uncertainty in this estimate.

4.14 The Committee discussed the frequency of cardiac monitoring for people treated with epirubicin in the UK. It noted that the manufacturer's alternative base-case analysis assumed that people would have cardiac monitoring every 3 months whether they were treated with epirubicin or trastuzumab. This assumption was the same as that proposed by the ERG. The Committee heard from the clinical specialists that people on epirubicin treatment were not necessarily given cardiac monitoring this often in the UK. It heard

that in current practice people were tested before starting epirubicin treatment and this was only repeated when treatment levels made it necessary or if cardiac toxicity was suspected during treatment. The Committee therefore concluded that an alternative scenario assuming equal monitoring may still slightly overestimate the cost of the comparator strategies. However, the Committee noted that the ICER was not very sensitive to this parameter. It therefore agreed to consider the ICERs that assumed equal frequency of cardiac monitoring for trastuzumab and epirubicin.

- 4.15 The Committee discussed sequential and parallel HER2 testing. It heard from the clinical specialists that people with gastric cancer are not routinely tested for their HER2 status. However, for people with breast cancer in the UK, testing is sequential and only people with a score of IHC2 have a confirmatory FISH test. The clinical specialists considered that there were no reasons to assume a different testing strategy for metastatic gastric cancer. The Committee therefore concluded that sequential testing would be appropriate in assessing HER2 status in people with metastatic gastric cancer.
- 4.16 The Committee discussed the manufacturer's assumption of a daily increase in utility during progression-free survival that was included in both the base-case and alternative base-case analyses. It was aware that this assumption was based on data only for people in the clinical trial surviving without progression without any adjustments. The Committee discussed the ERG's alternative assumption of a very slow decrease in utility calculated from those of a similar age group based on UK general population norms for EQ-5D. It recognised comments from the clinical specialists (see section 4.10) and noted that after consultation the ERG suggested that an increase in utility may be appropriate, but not above that of

the general population. The Committee was persuaded that an increase in utility was plausible. However, it accepted the ERG comments that such increases should be capped so that they did not go above those of the general population of a comparable age.

- 4.17 The Committee noted the manufacturer's assumption that sharing vials between patients to minimise wastage would occur in 80% of centres. It considered that this might be an overestimate and that in some centres, particularly smaller centres, sharing vials may not be possible, and therefore there was likely to be large variation in vial sharing. The Committee concluded that there was not enough evidence to estimate the proportion of centres that would vial share in clinical practice, but that 80% could be an overestimate.
- 4.18 The Committee considered the manufacturer's alternative base-case ICER of £62,800 per QALY gained. It noted that this incorporated a hazard ratio for overall survival and progression-free survival of 0.96, but assumed that quality of life increased in progression-free survival. It further noted the results of the manufacturer's probabilistic sensitivity analysis around the alternative base case, in which the mean value of the ICER increased by approximately £5000. It concluded that the manufacturer's alternative base-case ICER was associated with considerable uncertainty and that the ICER would be greater than £62,800 per QALY gained.
- 4.19 The Committee discussed the results of the ERG's exploratory analyses, in which a cap on utility values during progression-free survival was applied (see section 3.40). It considered that this change to the assumptions was appropriate. The Committee agreed that the ICER for the population covered by the marketing authorisation in the manufacturer's base case probably lay between the ERG calculated deterministic ICER of £63,100 per QALY

gained and the ERG calculated probabilistic ICER of £71,500 per QALY gained. The Committee concluded that the ICER for the population covered by the marketing authorisation was in excess of the range normally considered cost effective.

4.20 The Committee considered the manufacturer's estimate of the ICER based on the subgroup of people who tested IHC3 positive in ToGA. It noted that the assumptions in the alternative base case (about cardiac monitoring for epirubicin and trastuzumab, hazard ratios of comparator effectiveness and an increase in utility during progression-free survival) were applied. The Committee expressed the same concerns that the model allowed utility values during progression-free survival to increase more than those of the general population (see section 4.18). It further noted that the estimate of the ICER for the IHC3-positive subgroup was stratified for baseline imbalances in the characteristics of people in the treatment groups, and that the stratified hazard ratio was favourable to trastuzumab (see section 3.39). The Committee noted that the manufacturer's estimate of £43,000 per QALY gained for this population was based on a deterministic estimate (that is, a point estimate of the value of the ICER). The Committee concluded that the manufacturer's ICER for the IHC3-positive subgroup was probably an underestimate.

4.21 The Committee discussed the ERG's exploratory analyses for the IHC3-positive subgroup. It noted that these analyses imposed a cap on utility values during-progression free survival equal to general population utility estimates. Based on previous discussions (see section 4.16), it considered that this was a reasonable parameter change. The Committee noted that using probabilistic analysis increased the ICER by approximately £1500 per QALY gained compared with deterministic analysis. It further noted that

the effect of stratification accounted for £6700 and £7400 per QALY gained for the deterministic and probabilistic analyses respectively. The Committee noted that the ERG's ICERs for the IHC3 subgroup (deterministic and probabilistic, stratified and unstratified) were between £43,200 and £52,000 per QALY gained. The comparator for three of these estimates was epirubicin plus cisplatin and capecitabine; the comparator in the highest estimate (probabilistic unstratified analysis) was epirubicin plus oxaliplatin and capecitabine. The Committee agreed that the most plausible estimate of cost effectiveness of trastuzumab plus cisplatin and capecitabine lay between £45,000 and £50,000 per QALY gained. The Committee concluded that the ICER for the population covered by the marketing authorisation was higher than would normally be considered cost effective.

4.22 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, 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 criteria 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.

4.23 The Committee considered the criteria that needed to be met to consider trastuzumab as a life-extending, end-of-life treatment. First, the Committee considered the life expectancy of people with HER2-positive metastatic gastric cancer. It understood that the ToGA trial reported a median 11.8 months overall survival for people receiving cisplatin plus either capecitabine or 5-fluorouracil. Therefore, the Committee was persuaded that trastuzumab plus cisplatin and either capecitabine or 5-fluorouracil met the criterion for short life expectancy.

4.24 The Committee then considered whether trastuzumab offers an extension to life of at least an additional 3 months. It noted that the median overall survival gain for the licensed population from the ToGA trial was 4.2 months for trastuzumab plus cisplatin and capecitabine or 5-fluorouracil compared with cisplatin and capecitabine or 5-fluorouracil alone. This produced a modelled mean overall survival gain of 4.8 months for people treated with trastuzumab plus cisplatin and capecitabine compared with people treated with epirubicin plus cisplatin and capecitabine. The Committee further noted that the median overall survival gain for the subgroup of people whose tumours were IHC3-positive in the ToGA trial was 5.6 months for trastuzumab plus cisplatin and capecitabine or 5-fluorouracil compared with cisplatin and capecitabine or 5-fluorouracil alone. This produced a modelled mean overall survival gain of 7.4 months for trastuzumab plus cisplatin and capecitabine compared with epirubicin plus cisplatin and capecitabine. The Committee considered that this was subject to uncertainty because of the absence of appropriate UK practice comparator data. However, on balance the Committee was

persuaded that the addition of trastuzumab to chemotherapy would result in an extension to life of more than 3 months. The Committee therefore considered that trastuzumab plus cisplatin and capecitabine or 5-fluorouracil met the criterion for life extension.

4.25 The Committee considered the size of the patient population. Treatment with trastuzumab would be suitable for approximately 7000 people who have one of the diseases for which trastuzumab is licensed (that is, HER2-positive metastatic gastric cancer, HER2-positive early and locally advanced breast cancer and HER2-positive metastatic breast cancer). The Committee considered that 7000 was at the upper end of the population size for which it understood the supplementary advice to apply. However, the Committee concluded overall that applying the supplementary advice on end-of-life was appropriate.

4.26 The Committee discussed the cost effectiveness of trastuzumab plus cisplatin and capecitabine for the population covered by the marketing authorisation, taking into account the end-of-life criteria. It agreed that the most plausible estimate was between £63,100 per QALY gained (using the deterministic estimate from the ERG's alternative base-case analysis) and £71,500 per QALY gained (using the probabilistic estimate from the ERG's alternative base-case analysis). The Committee therefore considered that, even when taking the end-of-life considerations into account, the magnitude of weight required for the ICER to be in a range normally considered cost effective in the NHS was too high. The estimates exceed what can be considered a reasonable use of NHS resources. Therefore the Committee concluded that trastuzumab plus cisplatin and capecitabine or 5-fluorouracil could not be recommended as an appropriate use of NHS resources for the whole population covered by the marketing authorisation.

4.27 The Committee then discussed the cost effectiveness of trastuzumab plus cisplatin and capecitabine for the subgroup of people whose tumours are IHC3 positive, taking into account the end-of-life criteria. It agreed that the ICER was between £45,000 and £50,000 per QALY gained. The Committee considered that the magnitude of weight required for the ICER to be in a range normally considered cost effective in the NHS was acceptable. The Committee recognised that the ICER range was specifically for trastuzumab plus cisplatin and capecitabine, and not trastuzumab plus cisplatin and 5-fluorouracil. However, accepting the uncertainties around comparator effectiveness estimates for HER2-positive metastatic gastric cancer, the Committee considered it was appropriate to recommend 5-fluorouracil as an alternative to capecitabine for those people who required it. The Committee therefore concluded that trastuzumab plus cisplatin and capecitabine or 5-fluorouracil should be recommended as an option for the treatment of people with HER2-positive, metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior treatment for their metastatic disease and whose tumours express high levels of HER2, as defined by a positive immunohistochemistry score of 3 (IHC3 positive).

Summary of the Appraisal Committee’s key conclusions

TAXXX (STA)	Appraisal title: Trastuzumab for the treatment of HER2-positive metastatic gastric cancer	FAD section
Key conclusion		
Trastuzumab, in combination with cisplatin and capecitabine or 5-fluorouracil, is recommended as an option for the treatment of people with HER2-positive, metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who: <ul style="list-style-type: none"> • have not received prior treatment for their metastatic disease and • have tumours expressing high levels of HER2 as defined by a 		1.1

<p>positive immunohistochemistry score of 3 (IHC3 positive).</p> <p>The Committee agreed that the ICER for this group was between £45,000 and £50,000 per QALY gained. It considered that it was appropriate to apply the end-of-life criteria. On this basis, the Committee was persuaded that the magnitude of weight required for the ICER to be in a range normally considered cost effective in the NHS was acceptable.</p>		<p>4.25 and 4.27</p>
<p>Current practice</p>		
<p>Clinical need of patients including the availability of alternative treatments</p>	<p>Current NHS treatment for metastatic gastric cancer is a triple regimen of an anthracycline, a platinum agent and a fluoropyrimidine.</p>	<p>4.2</p>
	<p>Chemotherapy is associated with overall survival of 11.8 months (based on the chemotherapy alone group in the ToGA trial) and reduces disease symptoms.</p>	<p>4.23</p>
	<p>Treatment with anthracyclines such as epirubicin has side effects.</p>	<p>4.11</p>
<p>The technology</p>		
<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>The Committee noted comments from consultation that no treatment options for metastatic gastric cancer currently target HER2 overexpression, and that trastuzumab offers a new option for this patient group.</p>	<p>4.2</p>
<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>The Committee did not discuss the position of the treatment in the pathway of care because the marketing authorisation for trastuzumab specifies metastatic disease that has not been previously treated.</p>	<p>N/A</p>
<p>Adverse effects</p>	<p>The Committee noted that the adverse effects of trastuzumab are known through its use in breast cancer treatment. It noted that trastuzumab is associated with cardiotoxicity, but that there was a similar incidence of cardiac events between the trastuzumab and comparator groups and</p>	<p>4.11</p>

	that this was low.	
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	<p>The Committee did not raise any issues about the quality of the evidence.</p> <p>See 'Relevance to general clinical practice in the NHS' below.</p>	N/A
Relevance to general clinical practice in the NHS	<p>The Committee was persuaded that the population in the ToGA trial could be considered applicable to the UK population.</p> <p>UK clinical practice is normally a triplet regimen that includes an anthracycline, a platinum agent and a fluoropyrimidine. The regimen given in the ToGA trial was a double regimen of a platinum agent and a fluoropyrimidine therapy. Double regimens are not often used in UK clinical practice. The Committee concluded that the comparator in the ToGA trial did not represent current practice in the UK.</p>	<p>4.3</p> <p>4.2</p>
Uncertainties generated by the evidence	<p>The Committee heard from clinical specialists that adding epirubicin to cisplatin and a fluoropyrimidine provides sufficient additional benefit to be standard practice. However, this has not been subject to rigorous evaluation.</p> <p>The Committee recognised that none of the studies for the comparators were completed in a HER2-positive population. The Committee acknowledged the lack of ideal evidence for this comparison. However, it considered, based on the evidence and the views of the clinical specialists, that epirubicin provided some additional benefit when added to a cisplatin and fluoropyrimidine combination.</p>	4.5
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee considered that it is biologically plausible that people with very high levels of HER2 (IHC3 positive) may benefit from trastuzumab more than the whole population covered by the marketing authorisation.	4.9

<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>The Committee noted that trastuzumab plus cisplatin and capecitabine or 5-fluorouracil compared with cisplatin plus capecitabine or 5-fluorouracil gave a median gain in overall survival of 4.2 months for the full population and 5.6 months for the IHC3 subgroup. The evidence came from the ToGA trial.</p>	<p>4.4 and 4.9</p>
<p>Evidence for cost effectiveness</p>		
<p>Availability and nature of evidence</p>	<p>Because the comparator in the ToGA trial was not the same as that used in clinical practice, the Committee considered whether the comparator in clinical practice offered similar benefit to that seen in the trial. It heard from clinical specialists that adding epirubicin to cisplatin and a fluoropyrimidine (as per clinical practice) provides sufficient additional benefit to be standard practice, but it has not been subject to rigorous evaluation.</p> <p>The Committee concluded that it was appropriate to consider the ICERs that had used a hazard ratio of 0.96.</p>	<p>4.5 and 4.13</p>
<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The Committee concluded that it was appropriate to consider the ICERs that had used a hazard ratio of 0.96. However, it considered that there was considerable uncertainty in this estimate.</p> <p>Some uncertainty remained about the frequency of cardiac monitoring for epirubicin. However, the Committee noted that the ICER was not very sensitive to this parameter. It therefore agreed to consider the ICERs that assumed equal frequency of cardiac monitoring for trastuzumab and epirubicin.</p> <p>The Committee concluded that there was not enough evidence to estimate the proportion of centres that would vial share in clinical practice.</p>	<p>4.13</p> <p>4.14</p> <p>4.17</p>
<p>Incorporation of health-related quality of life benefits and utility</p>	<p>The Committee was persuaded that because of the disease symptoms associated with gastric cancer it was</p>	<p>4.10 4.16</p>

values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	plausible that quality of life could increase during progression-free survival. The Committee was persuaded that an increase in utility was plausible. However, it accepted the ERG comments that such increases should be capped so that they did not go above those of the general population of a comparable age.	
Are there specific groups of people for whom the technology is particularly cost effective?	The Committee concluded that the most plausible estimates of cost effectiveness for the IHC3 positive subgroup were between £45,000 and £50,000 per QALY gained, and those for the full population covered by the marketing authorisation were between £63,100 and £71,500 per QALY gained.	4.21 and 4.19
What are the key drivers of cost effectiveness?	The Committee noted that, although the effect of changing the hazard ratio to 0.96 had been relatively minor, the effect of changing the hazard ratio to 0.77 increased the ICER by up to £50,000 per QALY gained.	4.13
Most likely cost-effectiveness estimate (given as an ICER)	The Committee agreed that the ICER for the population covered by the marketing authorisation was between £63,100 and £71,500 per QALY gained (using the ERG exploratory analyses). The Committee agreed that the ICER for the IHC3 subgroup was between £45,000 and £50,000 per QALY gained (using the ERG exploratory analyses).	4.26 4.27
Additional factors taken into account		
Patient access schemes (PPRS)	The manufacturer did not submit a patient access scheme.	N/A
End-of-life considerations	The Committee was persuaded that the criterion for short life expectancy was met.	4.23
	On balance the Committee was persuaded that the addition of trastuzumab to chemotherapy would provide an extension	4.24

	<p>to life of more than 3 months.</p> <p>An estimated 7000 patients have one of the diseases for which trastuzumab is licensed (that is, HER2-positive metastatic gastric cancer, HER2-positive early and locally advanced breast cancer and HER2-positive metastatic breast cancer) and may be offered treatment with trastuzumab. The Committee considered that 7000 was at the upper end of the population size for which it understood the supplementary advice to apply. However, the Committee concluded overall that applying the supplementary advice on end-of-life was appropriate.</p> <p>Using the estimates of the most plausible ICER, the Committee concluded that, for the total population covered by the marketing authorisation, the magnitude of weight that would need to be applied to the ICER was too high. However, the Committee concluded that, for the IHC3-positive subgroup, the magnitude of weight that would need to be applied to the ICER was in a range normally considered to be cost effective and was acceptable.</p>	<p>4.25</p> <p>4.26</p> <p>4.27</p>
<p>Equalities considerations, social value judgements</p>	<p>The Committee heard that the incidence of gastric cancer is increased in certain social classes but did not consider that the recommendations would lead to differential access to the technology according to social class.</p>	<p>N/A</p>

5 Implementation

- 5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually 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. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.

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/guidance/TAXXX). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local 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 Related NICE guidance

Published

- Capecitabine for the treatment of advanced gastric cancer. NICE technology appraisal guidance 191 (2010). Available from www.nice.org.uk/guidance/TA191

7 Review of guidance

- 7.1 The guidance on this technology will be considered for review in August 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.

Andrew Stevens
Chair, Appraisal Committee
September 2010

Appendix A: Appraisal Committee members 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 Kathryn Abel

Reader and Consultant Psychiatrist, Director of the Centre for Women's Mental Health, University of Manchester

Dr David Black

Director of Public Health, Derbyshire County Primary Care Trust

Dr Daniele Bryden

Consultant in Intensive Care Medicine/Anaesthesia, Sheffield Teaching Hospitals NHS Trust

Professor Mike Campbell

Statistician, Institute of Primary Care and General Practice, University of Sheffield

David Chandler

Lay Member

Dr Mary Cooke

Lecturer School of Nursing, Midwifery and Social Work, University of Manchester

Dr Chris Cooper

General Practitioner, St John's Way Medical Centre, London

Professor Peter Crome

Consultant Physician, Bucknall Hospital

Dr Christine Davey

Senior Researcher, North Yorkshire Alliance R and D Unit

Richard Devereaux-Phillips

Public Affairs and Reimbursement Manager UK and Ireland, Medtronic

Dr Rachel A Elliott

Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Wasim Hanif MD FRCP

Consultant Physician and Honorary Senior Lecturer, University Hospital Birmingham

Dr Alan Haycox

Reader in Health Economics, University of Liverpool Management School

Professor Catherine Jackson

Professor of Primary Care Medicine, University of St Andrews

Dr Peter Jackson

Clinical Pharmacologist, University of Sheffield

Henry Marsh

Consultant Neurosurgeon, St George's Hospital

Professor Gary McVeigh

Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital

Dr Eugene Milne

Deputy Medical Director, North East Strategic Health Authority

Dr Neil Myers

General Practitioner

Dr Richard Nakielny

Consultant Radiologist, Sheffield Teaching Hospitals Foundation Trust

Dr Katherine Payne

Health Economics Research Fellow, University of Manchester

Dr Danielle Preedy

Lay Member

Dr Martin J Price

Head of Outcomes Research, Janssen-Cilag

Dr Peter Selby

Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Dr Surinder Sethi

Consultant in Public Health Medicine, North West Specialised Services Commissioning Team

Professor Andrew Stevens

Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

John Stevens

Director, Centre for Bayesian Statistics in Health Economics, University of Sheffield

Dr Matt Stevenson

Technical Director, School of Health and Related Research, University of Sheffield

Professor Paul Trueman

Health Economics Research Group, Brunel University

Dr Judith Wardle

Lay Member

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.

Joanne Holden

Technical Lead

Zoe Garrett

Technical Adviser

Lori Farrar

Project Manager

Appendix B: Sources of evidence considered by the Committee

- A The Evidence Review Group (ERG) report for this appraisal was prepared by Centre for Reviews and Dissemination, University of York:
- CRD and CHE Technology Assessment Group. Trastuzumab for the treatment of HER2 positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction, May 2010
- B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.
- I Manufacturer/sponsor:
- Roche Products (trastuzumab)
- II Professional/specialist and patient/carer groups:
- Cancer Research UK
 - Royal College of Nursing
 - Royal College of Pathologists
 - Royal College of Physicians
 - United Kingdom Oncology Nursing Society
- III Other consultees:
- Department of Health
 - Welsh Assembly Government

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

- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- NHS Quality Improvement Scotland
- National Institute for Health Research Health Technology Assessment Programme
- NHS Centre for Reviews and Dissemination and Centre for Health Economics – York

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

- Dr David Watkins, Clinical Research Fellow, nominated by NCRI/RCP/RCR/ACP/JCCO – clinical specialist
- Professor Marco Novelli, Consultant Pathologist, nominated by Royal College of Pathologists – clinical specialist

D Representatives from the following manufacturer/sponsor attended Committee Meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Roche Products