NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Trastuzumab for the treatment of HER2 positive advanced gastric cancer

This briefing presents the key issues arising from the manufacturer's submission, Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that this briefing is a summary of the information available and should be read with the full supporting documents.

The manufacturer was asked to provide the following information:

- A clinical study report for the ToGA trial and further detail relating to the European Medicines Agency (EMA) licensed population, the maximum age of enrolment, and the number of UK centres and patients enrolled. The manufacturer was asked to clarify the population used in the primary analysis.

- A full set of parameter estimates for the survival distributions referred to in the submission and cost-effectiveness results using alternative survival distributions. The manufacturer was asked to justify the use of linear regression for extrapolating the proportion of patients in progression-free survival who were on treatment

- Further details of quality of life data from the ToGA trial including any statistical analyses performed, EuroQol 5 Dimensions (EQ-5D) scores for the total trial population and the EMA licensed population, mean scores and standard errors for each time point. The manufacturer was asked to clarify the number of censored patients and to describe the mixed method fitted to the utility data.

- Further information relating to the comparators in the economic analysis including details of the systematic review process and excluded studies, and numeric and statistical data on the efficacy of comparator regimens. The manufacturer was asked to clarify the reasoning behind the assumption that the treatment effect of adding trastuzumab would be the same for cisplatin plus capecitabine as for cisplatin plus 5-fluorouracil.

- Further clarification relating to the rate of human epidermal growth factor receptor 2 (HER2) positivity in clinical practice, test failures, delays in obtaining test results, the proportion of patients that record a left ventricular ejection fraction (LVEF) of 50% or more in the ToGA trial, dose quantities used in the economic model, and justification for assumptions around cardiac monitoring and costs of monitoring.

Licensed indication

In January 2010 trastuzumab (Herceptin, Roche Products) received a marketing authorisation for use in combination with capecitabine or 5-fluorouracil and cisplatin 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.

The marketing authorisation states that trastuzumab should only be used in patients with metastatic gastric cancer whose tumours have HER2 over-expression as defined by immunohistochemistry 2 positive (IHC2+) and a confirmatory fluorescence in-situ hybridization positive (FISH+) result, or IHC3+, as determined by an accurate and validated assay.

Key issues for consideration

Clinical effectiveness issues

- The main source of clinical evidence for trastuzumab is from the ToGA trial. The population included in the trial had locally advanced or metastatic disease and HER2 positive status defined as either IHC3+ or FISH+.

During the course of the trial, a narrower definition of HER2 positive was adopted, resulting in a subgroup of high HER2 positive patients for which the EMA granted a licence. Does the Committee consider that the ToGA trial demonstrates improvements in clinical outcomes for this subgroup?

- Patients in the ToGA trial were predominantly Asian and had a median age of approximately 60 years. To what extent does the Committee consider that the clinical effectiveness data reported in the ToGA trial can be related to the patient population in England and Wales with HER2+ metastatic gastric cancer?
- Does the Committee consider that the manufacturer's submission appropriately estimates the relative effectiveness of trastuzumab plus cisplatin and capecitabine or 5-fluorouracil relative to treatments used in the NHS for metastatic gastric cancer?
  - The manufacturer identifies triple therapy of epirubicin plus either oxaliplatin or cisplatin and either capecitabine or 5-fluorouracil as the most widely used treatments in the NHS. What is the Committee's view of the most appropriate comparator treatments?
  - The manufacturer concludes that it is not possible to perform an indirect comparison because there are no appropriate trials that compare the overall survival of cisplatin plus capecitabine or 5-fluorouracil (the regimen used in the ToGA trial) with any of the triplet therapies. Is this conclusion appropriate given the currently available evidence base?
  - Unable to perform an indirect comparison, the manufacturer assumes that progression-free and overall survival of epirubicin plus cisplatin and capecitabine can be considered equivalent to that of cisplatin plus capecitabine or 5-fluorouracil observed in the ToGA trial. What is the Committee's view of the evidence to support the assumption of equivalence between epirubicin plus cisplatin and capecitabine and cisplatin plus capecitabine or 5-fluorouracil?

Cost-effectiveness issues

- To assess HER2 status, the ToGA trial used a parallel testing strategy (that is, both IHC and FISH tests were completed at the same time). The manufacturer's model uses a sequential testing strategy (that is, only people testing for IHC2+ have a FISH test). What is the most relevant testing strategy for clinical practice in the NHS? What are the implications of either a parallel or sequential testing strategy on patient outcomes, costs, or generalisability of the data from the ToGA trial?
- The manufacturer has assumed that cardiac monitoring for patients treated with epirubicin was completed once every three weeks, and three monthly for patients treated with trastuzumab. What does the Committee consider to be current clinical practice for cardiac monitoring for epirubicin?
- The ERG conducted exploratory analyses that combined a series of four parameter adjustments which they considered represented an alternative equally plausible scenario. What is the Committee's view of the ERG's combined exploratory analyses and the alternative incremental cost-effectiveness ratios (ICERs) presented?
- The manufacturer provides evidence in the submission that the metastatic gastric cancer population has a life expectancy of less than one year, that the modelled increase in overall survival of adding trastuzumab to current NHS treatment is 4.7 months and that there are 7144 patients who are currently eligible for treatment with trastuzumab in England and Wales. Does the Committee consider that trastuzumab for the treatment of metastatic HER2 positive gastric cancer should be considered within the context of the supplementary advice on end of life?

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	Patients with HER2 positive (IHC2+/FISH+ or IHC3+) metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anticancer treatment for their metastatic disease
Intervention	Trastuzumab plus cisplatin and capecitabine or 5-fluorouracil (HCX/F)
Comparators	**Primary analysis** Epirubicin plus cisplatin and capecitabine (ECX) Epirubicin plus cisplatin and 5-fluorouracil (ECF) where capecitabine is an unsuitable treatment **Secondary analysis** Epirubicin plus oxaliplatin and capecitabine (EOX)
Outcomes	Outcome measures include overall survival, progression-free survival, response rate, adverse effects of treatment and health-related quality of life
Economic evaluation	The cost effectiveness of treatment with trastuzumab in comparison with current standard therapy is expressed in terms of incremental cost per quality-adjusted life year (QALY). The time horizon is a lifetime horizon of 8 years and costs are considered from the perspective of the NHS and Personal Social Services.

1.2 Evidence Review Group comments

1.2.1 Population

The population specified in the decision problem reflects the scope for this appraisal. The manufacturer's submission focuses on the population specified in the summary of product characteristics (SPC; section 4.1 'Therapeutic indications'). Patients in the regulatory trial (the ToGA trial) had inoperable HER2 positive advanced gastric cancer and had not received prior treatment for their advanced disease. Ninety-seven per cent of patients had metastatic disease.

In the ToGA trial HER2 positive patients were initially defined as those whose tumours were IHC3+ or FISH+. Advances in the understanding of HER2 testing during the ToGA trial resulted in a protocol amendment and the adoption of a narrower definition of HER2 positivity. This group with IHC2+/FISH+ or IHC3+ tumours was the population for which the EMA marketing authorisation was issued. Seventy-four per cent of the total population enrolled in the ToGA trial were within the EMA licensed population.

1.2.2 Intervention

The intervention in the decision problem reflects the scope for this appraisal. The SPC specifies the use of trastuzumab with cisplatin and either capecitabine or 5-fluorouracil. The manufacturer's submission draws on data from the ToGA trial, which compared trastuzumab plus cisplatin and either capecitabine or 5-fluorouracil with cisplatin plus either 5-fluorouracil or capecitabine alone. In both groups approximately 87% of patients received capecitabine.

The marketing authorisation is for a subgroup of the metastatic gastric cancer population, namely those who are HER2 positive. The economic model incorporates both the costs of identifying the HER2 positive subgroup, using the algorithm defined in the marketing authorisation, and also the costs of the intervention.

1.2.3 Comparators

The manufacturer's submission presents data from research involving 112 patient records to indicate that the treatment with the widest use in treating advanced and metastatic gastric cancer in England and Wales is epirubicin plus cisplatin and capecitabine (45% of patient records sampled). The research also suggested that current treatment for gastric cancer includes epirubicin plus cisplatin and 5-fluorouracil (7%), and epirubicin plus oxaliplatin and either capecitabine (6%) or 5-fluorouracil (4%). The manufacturer's submission considers these four regimens to be the most relevant to the

appraisal (page 32 of the manufacturer's submission). Clinical advice received by the ERG supports these comparators as the most widely used in the UK, although it is suggested that epirubicin plus oxaliplatin and capecitabine may be more commonly used than is indicated by the manufacturer's research.

The comparator in the ToGA trial is cisplatin plus either capecitabine or 5-fluorouracil. Although doublet regimens may be used in people unable to take epirubicin, the doses used would be lower than those used in the ToGA trial. The manufacturer's research suggests that 7% of patients in the UK are treated with a chemotherapy regimen of cisplatin plus 5-fluorouracil.

1.2.4 Outcomes

The outcomes are appropriately described in the manufacturer's submission. The primary outcome is overall survival, reflecting the primary outcome in the ToGA trial. Other outcomes were progression-free survival, clinical benefit rate, incidence and severity of adverse events, and quality of life.

1.2.5 Economic evaluation

The time horizon in the economic evaluation is 8 years, which is sufficient to capture all associated costs and benefits in a metastatic gastric cancer population.

1.2.6 Other relevant factors

The manufacturer's submission indicates that trastuzumab meets the criteria for end of life consideration. Patients are currently expected to survive less than one year on average. In the ToGA trial patients receiving treatment with trastuzumab in addition to chemotherapy had a median increase in survival of 4.2 months compared to those who received chemotherapy alone. In the manufacturer's submission the economic analysis compares trastuzumab plus cisplatin and capecitabine with epirubicin plus cisplatin and capecitabine. The mean overall survival advantage, calculated by Weibull extrapolation of the data, is 4.7 months. The population of metastatic gastric cancer patients who may be able to receive trastuzumab in England and Wales is 492. The total

population of patients who may receive treatment with trastuzumab (including the other licensed indications of early, locally advanced and metastatic breast cancer) is approximately 7000 patients.

1.3 Statements from professional/patient groups and nominated experts

Current standard of care for patients with inoperable tumours of the stomach or gastro-oesophageal junction consists of palliative combination chemotherapy utilising platinum (cisplatin or oxaliplatin) and fluoropyrimidine (5-fluorouracil or capecitabine) with or without epirubicin. The specific choice of regimen may be influenced by the presence of co-morbid conditions or concern over specific toxicities. The combination of epirubicin, oxaliplatin and capecitabine is considered the optimal regimen for patients of good performance status. There is no international consensus as to a 'standard regimen'. The incremental survival gain achieved through the addition of epirubicin to the doublet combination of cisplatin and fluoropyrimidine has not been evaluated in large randomised studies.

While trastuzumab can be delivered within oncology units or centres with no specific need for additional professional input, there will be an impact on histopathology services (HER2 immunohistochemistry [IHC] and fluorescence in-situ hybridization [FISH] testing) and cardiac monitoring. Cardiac assessment (either MUGA or ECHO) will be required at baseline and every 3 months while on treatment.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

The manufacturer's submission identified one randomised controlled trial that compared trastuzumab plus cisplatin and capecitabine or 5-fluorouracil with cisplatin plus capecitabine or 5-fluorouracil alone. This study (ToGA) was an

open-label randomised controlled trial in patients (n = 594) with inoperable locally advanced, recurrent or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction, whose tumours were HER2 positive. Patients were eligible for enrolment to the trial if they had not received prior treatment for their advanced or metastatic disease.

The trial enrolled patients who tested HER2+ defined as either a positive IHC 3+ test or FISH test. IHC and FISH tests were completed at the same time. The approved licensed population was for a subgroup of the people in the trial (n = 446) defined as those whose tumours over-expressed HER2, determined through an IHC2+ score and a confirmatory FISH+ result, or ICH 3+ (that is, high levels of HER2 protein). For further details, see page 60 of the manufacturer's submission. Due to the small number of people with locally advanced disease recruited into the trial (3.4% of the full population), the licence was restricted to people with metastatic disease only.

The control group in the ToGA trial received oral capecitabine (1000 mg/m^2) twice daily for 14 days, or an intravenous infusion of 5-fluorouracil (800 mg/m^2) on days one to five of each three weekly cycle, in addition to intravenous cisplatin (80 mg/m^2) on day one of each cycle. The treatment group received the chemotherapy regimen with the addition of trastuzumab (8 mg/kg loading dose on day one, followed by 6 mg/kg intravenous infusion every three weeks) until disease progression. The choice of fluoropyrimidine was at the investigator's discretion. Eighty-seven per cent of patients received capecitabine in each arm.

The majority (approximately 75%) of patients were male. Over half were recruited from Asian countries. Only 23 patients at 6 centres were from the UK out of 594 patients randomised at 122 centres.

The Data Monitoring Committee made the decision to stop the trial early in accordance with a planned interim analysis of the primary outcome. At the

time of the clinical cut-off, the median duration of survival follow-up was 17.1 months in the comparator group and 18.6 months in the trastuzumab group.

Results of ToGA

The ToGA trial demonstrated improved overall survival in both the full analysis set (that is, the total trial population) and the high HER2 positive subgroup (that is the EMA licensed subgroup). In the EMA subgroup (74% of the full analysis set) the hazard ratio (HR) was 0.65 (95% confidence interval [CI] 0.51 to 0.83), which corresponded to a median survival of 16 months for the trastuzumab group compared with 11.8 months for the comparator group. For the EMA subgroup, excluding the 3.4% of patients with locally advanced disease, the results were (**confidential information removed**).

Progression-free survival was also improved for patients treated with trastuzumab in the EMA subgroup (hazard ratio 0.64; 95% CI 0.51 to 0.79) corresponding to a 2.1 month difference in time to progression/death. In the full analysis set there was a statistically significantly higher response rate in the trastuzumab group for both partial response (41.8% versus 32.1%, p = 0.01) and for overall response rate (47.3% versus 34.5%, odds ratio 1.70, 95% CI 1.22 to 2.38, p = 0.002). The rate of complete response was also higher in the trastuzumab group (5.4% versus 2.4%), but this was not statistically significant (p = 0.06).

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 Symptom) and QLQ-ST022 (containing 22 items associated with dysphagia, pain, reflux, eating restrictions, anxiety, dry mouth, body image and hair loss). The analysis was based on patients who completed the quality of life questionnaire in the full analysis set. Both treatment groups in the trial showed improvements in quality of life after completion of chemotherapy; however, a greater number of patients were progression free in the trastuzumab treatment group than in the

comparator group. No statistical analysis of differences in quality of life between the treatment groups is presented.

Slightly more patients in the trastuzumab treatment group experienced adverse events than patients in the comparator group (99% compared with 98%). A similar proportion of grade 3 and 4 adverse events occurred in both treatment groups (68% in both groups). The most frequent were disorders of the blood and lymphatic system, gastrointestinal disorders, and metabolism and nutritional disorders (page 87 of the manufacturer's submission). More patients in the trastuzumab group experienced asymptomatic reductions in left ventricular ejection fraction (LVEF); however, this did not translate into a statistically significant difference in any category of symptomatic cardiac events (table 10, page 90 of the manufacturer's submission).

Table 1: Summary of outcome data reported in the manufacturer's submission for the EMA subgroup of the ToGA trial (see page 8 of the ERG report and pages 61–73 of the manufacturer's submission).

Outcome	HCX/F	CX/F	Statistical results
OS (median)	16.0 months	11.8 months	HR 0.65 (95% CI 0.51 to 0.83)
PFS (median)	7.6 months	5.5 months	HR 0.64; (95% CI 0.51 to 0.79)
Response rate (%)*	47.3	34.5	OR 1.70 (95% CI 1.22 to 2.38)
QoL	Graphical presentation of EORTC data only.		
Adverse events*	Statistically significantly more grade 1 and 2 adverse events (multiple categories) in HCX/F group. Statistically significantly more asymptomatic LVEF reductions in HCX/F group did not translate into increased symptomatic cardiac events. No statistically significant differences in Grade 3 or 4 events.		

*Data for the full analysis set; HCX/F, Trastuzumab plus cisplatin and capecitabine or 5-FU; CX/F, Cisplatin and 5-FU or capecitabine; OS, overall survival; HR, hazard ratio; PFS, progression-free survival; QoL, quality of life; EORTC, European Organisation for Research and Treatment of Cancer; LVEF, left ventricular ejection fraction

Comparator data presented in the manufacturer's submission

The manufacturer's submission identifies that the most commonly used treatment regimens in England and Wales, and therefore the relevant comparators, are triplet chemotherapy regimens including epirubicin, plus either oxaliplatin or cisplatin and either capecitabine or 5-fluorouracil. The

manufacturer's literature searches indicated that there are no trials directly comparing trastuzumab with these treatment regimens. Four studies are indentified in which at least one of the treatment arms evaluated is epirubicin plus cisplatin and capecitabine (Yun and REAL-2) or 5-fluorouracil (Kim, REAL-2, Tobe), or epirubicin plus oxaliplatin and capecitabine (REAL-2) or 5-fluorouracil (REAL-2) (table 3, page 27 of the ERG report). The manufacturer analysed the available data for these trials and concluded that it is not possible to conduct a network meta-analysis. This is because none of the identified trials allows a comparison of overall survival between cisplatin plus capecitabine and the triplet therapies.

The manufacturer's submission provides a narrative summary of the studies and concludes that there is no established advantage in adding epirubicin to a chemotherapy regimen. The manufacturer cites evidence from two studies that report no statistically significant overall survival benefit. Kim (2001) and Tobe (1992) report hazard ratios for epirubicin plus cisplatin and 5-fluorouracil compared with cisplatin plus 5-fluorouracil of 0.83 (95% CI 0.42 to 1.61), and 0.57 (95% CI 0.27 to 1.2) respectively. Similarly, the manufacturer concludes that there is no evidence of a statistically significant difference in efficacy between epirubicin plus cisplatin and capecitabine and cisplatin plus capecitabine on the basis of the progression-free survival estimate from a third study by Yun (2010) (hazard ratio 0.96, 95% CI 0.58 to 1.57).

Because trastuzumab plus cisplatin and capecitabine may potentially replace epirubicin plus oxaliplatin and capecitabine, the manufacturer provides evidence from the REAL-2 trial (Cunningham 2008) showing that there is no significant difference between oxaliplatin and cisplatin (hazard ratio 0.92; 95% CI 0.8 to1.1). From this evidence the manufacturer concludes that there is no difference in treatment effect between epirubicin plus either cisplatin or oxaliplatin and capecitabine for either progression-free or overall survival.

Finally, a meta-analysis comparing capecitabine regimens with 5-fluorouracil regimens (Okines 2009) reports that the hazard ratio of overall survival with 5-

fluorouracil to be less favourable than for capecitabine (hazard ratio 1.15). From this the manufacturer concludes that the overall survival for trastuzumab plus cisplatin and 5-fluorouracil is less favourable than when the same regimen is combined with capecitabine.

In summary, on the basis of the evidence available, the manufacturer assumes that progression-free survival can be considered equivalent for the triplet regimens that are most widely used in the UK and, in turn, that these can be considered equivalent to the comparator group of the ToGA trial. For overall survival the manufacturer assumes that epirubicin plus either cisplatin or oxaliplatin and capecitabine are equivalent to the comparator group of the ToGA trial, but that epirubicin plus cisplatin and 5-fluorouracil has a hazard ratio of 1.15 (that is, increased mortality) compared to the comparator group in the ToGA trial.

2.2 Evidence Review Group comments

The manufacturer's submission identifies the only relevant clinical trial evaluating trastuzumab in the treatment of metastatic gastric cancer. The ToGA trial is a well-conducted phase III randomised controlled trial (RCT) with appropriate validity assessment. The trial was open label and outcome assessors were not blinded, but this was appropriate for the therapies assessed and the primary outcome of overall survival. The ToGA trial appears to demonstrate improved overall survival when trastuzumab is added to cisplatin plus either capecitabine or 5-fluorouracil.

The ERG notes that the ToGA trial was stopped early based on a Data Monitoring Committee recommendation. The ERG considers that it is unclear what impact this might have had on the estimate of effectiveness. The ERG also notes that the finding of significance comes from a subgroup analysis. However the ERG does not consider the use of this subgroup to be a serious concern, because the subgroup is defined as a result of HER2 status and

therefore has credibility as a distinct population. It is also the case that HER2 positive patients represented 74% of the total trial population.

The ERG comments that the comparator used in ToGA is not the standard UK treatment, and, where employed in frailer patients, is used at lower doses. The most relevant comparators in the context of UK clinical practice are the triplet regimens of epirubicin, plus cisplatin or oxaliplatin and either capecitabine or 5-fluorouracil. The ERG accepts the manufacturer's view that it is not possible to construct a meaningful network analysis that links the intervention and the comparators. However, the manufacturer's submission uses an absence of individual trial evidence for a statistically significant difference to infer that there is no such difference. The ERG considers these assumptions are not supported by the evidence presented in the manufacturer's submission. The assumption of no difference between these regimens also requires a second assumption that evidence from known HER2 positive patients in the ToGA trial is comparable with evidence from trials where patients had unknown HER2 status.

The ERG notes that the Kim, Tobe and Yun trials identified by the manufacturer are all small phase II trials and may have been underpowered to detect a statistically significant benefit of treatment, further undermining the manufacturer's assumption of no difference in efficacy between cisplatin plus capecitabine or 5-fluorouracil and epirubicin plus cisplatin and capecitabine or 5-fluorouracil. The ERG considers that the decision by the manufacturer not to use a published meta-analysis (Wagner, 2010) potentially omits important data. The manufacturer's stated reasons for excluding the study are that the largest trial assessed a comparison between epirubicin plus cisplatin and 5-fluorouracil and mitomycin plus cisplatin and 5-fluorouracil, the other two trials were small and one was published in abstract form only. However, these other two trials are the same trials that the manufacturer's submission uses to suggest no evidence of benefit of epirubicin plus cisplatin and 5-fluorouracil over cisplatin plus 5-fluorouracil (that is, Kim and Tobe). The ERG considers

that the pooled estimate from the meta-analysis, which found a benefit for triplet regimens including epirubicin, cannot be dismissed from the assessment of relative efficacy of regimens with and without epirubicin.

The ERG considers that there is uncertainty around the manufacturer's assertion that improved quality of life is longer in the trastuzumab group than in the comparator group of the ToGA trial, corresponding to the increased duration of progression-free survival. This is because no statistical test results were reported for quality of life. At the ERG's request the manufacturer confirmed that no statistical results are available for this outcome.

In summary the ToGA trial appears to provide evidence of superior overall survival in the trastuzumab group compared to the comparator group in the EMA population. However the manufacturer's submission uses a lack of individual trial evidence of a statistically significant benefit of adding epirubicin to cisplatin plus capecitabine or 5-fluorouracil to infer that treatment outcomes from the comparator group in the ToGA trial are equivalent to those from triplet regimens including epirubicin. The manufacturer's attempts to demonstrate this equivalence are not adequately justified. Furthermore, the manufacturer's submission can only partially address the decision problem because there is no evidence as to the efficacy of current standard treatment with epirubicin containing triplet regimens in the known HER2 population.

2.3 Statements from professional/patient groups and nominated experts

The ToGA study recruited patients from five continents including a significant proportion from Asia. Consequently the data are not directly comparable to the UK patient population. The use of second-line chemotherapy in the ToGA study was significantly higher than would be anticipated in UK practice with 41% of patients receiving second-line treatment. Second-line chemotherapy is not a standard of care in the NHS setting and data from the REAL 2 study indicate that only 14% of patients receive second-line treatment.

The ToGA study stipulated the delivery of cisplatin plus capecitabine or 5-fluorouracil for a total of 6 cycles. In the UK, providing there is ongoing benefit, chemotherapy may be continued for up to 8 cycles (6 months).

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

The manufacturer uses a Markov economic model to assess the cost effectiveness of trastuzumab when added to chemotherapy in the treatment of patients with HER2 positive metastatic gastric cancer. The model has three distinct health states: progression free, disease progression and death. The model has a cycle length of one month and an 8-year time horizon (considered to be a lifetime horizon). Both costs and benefits are discounted at a rate of 3.5%. One-way sensitivity analysis is undertaken for treatment effectiveness (including survival curve extrapolation models), utility values, unit costs and various resource use assumptions. Probabilistic sensitivity analysis is also undertaken to explore parameter uncertainty in the model (page 149 of the manufacturer' submission).

The treatment strategies assessed in the manufacturer's model are:

- trastuzumab plus cisplatin and capecitabine (HCX)
- trastuzumab plus cisplatin and 5-fluorouracil (HCF)
- epirubicin plus cisplatin and capecitabine (ECX)
- epirubicin plus cisplatin and 5-fluorouracil (ECF)
- epirubicin plus oxaliplatin and capecitabine (EOX).

Clinical effectiveness estimates

The clinical estimates (transition probabilities) are derived from the progression-free and overall survival estimates from the ToGA trial (EMA population) for the trastuzumab regimens. Progression-free survival is extrapolated, using a Weibull function, from month 13 due to the level of uncertainty around the estimate from low patient numbers after month 12.

Overall survival was modelled using a Weibull function with extrapolation beyond the trial. The proportion of patients who progress to the progressive disease state in the model in each cycle is calculated as the difference between those in overall survival and those in progression-free survival.

The progression-free and overall survival estimates for trastuzumab plus cisplatin and capecitabine are assumed to equal trastuzumab plus cisplatin and capecitabine or 5-fluorouracil from the ToGA trial given that 87% of patients in the trial took capecitabine. The progression-free survival estimate for trastuzumab plus cisplatin and 5-fluorouracil is also assumed to be equal to trastuzumab plus cisplatin and capecitabine or 5-fluorouracil in the ToGA trial because no significant interaction between base chemotherapy and treatment was observed ($p = 0.6328$). However, due to the finding of a survival advantage of capecitabine over 5-fluorouracil in the meta-analysis by Okines, the hazard ratio of overall survival for trastuzumab plus cisplatin and 5-fluorouracil compared with trastuzumab plus cisplatin and capecitabine is assumed to be 1.15.

Further assumptions are made regarding the effectiveness estimates of the comparator regimes (described in the comparator data section of the pre-meeting briefing). It is assumed that epirubicin plus cisplatin and either capecitabine or 5-fluorouracil have the same progression-free survival as that reported for the comparator group in the ToGA trial and that epirubicin plus cisplatin and capecitabine has the same overall survival as the comparator group in the ToGA trial. In accordance with the assumption of greater efficacy of capecitabine over 5-fluorouracil, the hazard ratio of overall survival of epirubicin plus cisplatin and 5-fluorouracil compared with epirubicin plus cisplatin and capecitabine is 1.15. Finally, the manufacturer's submission assumes that the progression-free survival and overall survival estimates of epirubicin plus oxaliplatin and capecitabine are equal to those of epirubicin plus cisplatin and capecitabine. (These assumptions are summarised in figure 3 and table 8 of the ERG report on page 53.)

Utility

Estimates of utility for the progression-free health state in the manufacturer's model are from the ToGA trial. EQ-5D data were collected at baseline and then every 3 weeks until disease progression, after which point no utility data were obtained. The baseline utility is estimated to be 0.7292, which increases by 0.000142 daily during progression-free survival. For the post-progression state in the model, a utility value of 0.577 is used from the recent NICE technology appraisal of sunitinib, a second-line treatment for gastrointestinal stromal tumours (NICE technology appraisal guidance 179). (Details are on page 128 of the manufacturer's submission).

Resource use

Costs are from an NHS perspective and include HER2 testing, drug acquisition, drug administration, treatment of adverse events, monitoring and care costs associated with time spent in progression-free survival, and supportive care costs in progressive disease.

The costs for IHC and FISH tests assume that the tests are given sequentially, so that only those patients who test IHC2+ require a FISH test. Treatment duration for each drug in the trastuzumab regimen is calculated from the ToGA trial. For the comparator regimens in the model, treatment duration is based on the comparator regimen in the ToGA trial. The treatment duration of epirubicin is assumed to be equal to that of cisplatin.

Unit costs for cardiac monitoring for patients receiving either trastuzumab or epirubicin are based on the ERG report from the NICE guidance on trastuzumab for early breast cancer (NICE technology appraisal guidance 107), published in 2006. Cardiac monitoring is assumed to take place once every cycle with epirubicin and once every three months with trastuzumab (see page 139 of the manufacturer's submission). Assumptions and costs associated with infusions, pharmacy preparation, pump costs for the delivery of 5-fluorouracil and district nurse visits are given on page 136 of the manufacturer's submission.

The costs of treatment-related adverse events observed in the ToGA trial are incorporated for the trastuzumab regimens. Adverse event data from REAL2 provide the comparable information for the epirubicin regimens. Unit costs for treating adverse events are given on page140 of the manufacturer's submission. Adverse events are not discounted in the analysis.

Results

During clarification, the manufacturer provided a revised analysis. The revised estimates are reported in the premeeting briefing.

The combination of trastuzumab plus cisplatin and capecitabine provides a mean gain of 4.7 months of life compared with epirubicin plus either cisplatin or oxaliplatin and capecitabine. The combination of trastuzumab plus cisplatin and 5-fluorouracil provides a mean gain of 4.3 months of life compared with epirubicin plus cisplatin and 5-fluorouracil. The manufacturer's submission compares the cost effectiveness of all five regimens simultaneously and demonstrates that three of these are ruled out by either dominance (epirubicin plus oxaliplatin and capecitabine and epirubicin plus cisplatin and 5-fluorouracil) or extended dominance (trastuzumab plus cisplatin and 5-fluorouracil). With regard to the two remaining regimens, epirubicin plus cisplatin and capecitabine appeared both less costly and less effective than trastuzumab plus cisplatin and capecitabine. The incremental cost-effectiveness ratio (ICER) was £51,927 per QALY gained. The probability that trastuzumab plus cisplatin and capecitabine was cost effective at £30,000 was 0%. Additionally, the manufacturer's submission presents the results of pair-wise analyses. The results of these are given in table 2.

Table 2 Base-case cost-effectiveness results.

Intervention	Total costs (£)	QALYs gained	Incremental cost per QALY gained (£)
HCX vs ECX	13,064	0.252	51,927
HCF vs ECF	11, 858	0.233	50,838
HCX vs EOX	10,242	0.252	40,711

QALY, quality-adjusted life year; HCX, trastuzumab plus cisplatin and capecitabine; ECX, epirubicin plus cisplatin and capecitabine; HCF trastuzumab plus cisplatin and 5-fluorouracil; ECF, epirubicin plus cisplatin and 5-fluorouracil; EOX, epirubicin plus oxaliplatin and capecitabine.

Sensitivity analyses

The manufacturer presents the results of one-way sensitivity analysis for various parameters. The results are presented on pages 156, 160 and 163 of the manufacturer's submission. In deterministic analyses the lowest ICER for the comparison of trastuzumab plus cisplatin and capecitabine with epirubicin plus cisplatin and capecitabine is £48,337 per QALY gained (using a Weibull or Log Logistic function to estimate the distribution for overall survival). Probabilistic sensitivity analysis is undertaken to explore the impact of parameter uncertainty around utilities, costs, adverse events, survival curve distributions and progression-free survival monthly Kaplan-Meier estimates. The results of the probabilistic sensitivity analysis illustrate that the ICER of trastuzumab plus cisplatin and capecitabine compared with epirubicin plus cisplatin and capecitabine ranges from £37,180 to £95,238 per QALY gained.

3.2 Evidence Review Group comments

The economic model is appropriate for the decision problem. The manufacturer's approach to estimating lifetime cost effectiveness is appropriate and meets the requirements of the NICE reference case. As a result of the manufacturer's response to clarification, the ERG provides a revised base-case estimate in which a number of errors are corrected (table 3). In addition, the ERG raises concerns relating to some of the key assumptions made in the model, and provides exploratory analysis to assess the impact of these uncertainties on the ICER (table 4).

Clinical effectiveness estimates

The ERG explores the assumptions regarding overall and progression-free survival in the model. In particular the ERG highlights that 5-fluorouracil regimens are considered to have lower survival than capecitabine regimens. The ERG considers that it would be equally plausible that, if capecitabine confers an overall survival advantage over 5-fluorouracil, it might also confer an advantage for progression-free survival. However the ERG notes that adopting the same effectiveness for progression-free survival as for overall survival would not change the cost-effectiveness conclusions because epirubicin plus cisplatin and 5-fluorouracil would still be more expensive and therefore dominated by epirubicin plus cisplatin and capecitabine.

The ERG questions the manufacturer's assumption that the effectiveness of epirubicin plus cisplatin and capecitabine is equal to that of cisplatin plus capecitabine. The evidence is from a small trial with an overall sample size of 89, and it is unlikely to be powered to detect a significant effect of treatment (Yun 2010). The ERG considers that a more conservative approach might be to use the hazard ratio estimate of 0.96 (95% CI 0.58 to 1.57) from the Yun study for both progression-free and overall survival to reflect a marginal improvement in efficacy of epirubicin plus cisplatin and capecitabine compared to cisplatin plus capecitabine. The impact of this on the ICER is explored in additional analysis (exploratory analysis 5, table 4). Similarly, the manufacturer's assumption that progression-free and overall survival estimates for epirubicin plus oxaliplatin and capecitabine are equal to epirubicin plus cisplatin and capecitabine can be considered in a sensitivity analysis using a hazard ratio estimate from the REAL-2 study (exploratory analysis 6, table 4).

Utility

The ERG questions some of the assumptions made by the manufacturer regarding the utility values in the model, and, in particular, the assumption that utilities increase in the progression-free survival health state. The ERG

considers that a more realistic assumption would be that quality of life neither increases nor decreases over time while in the progression-free survival state, corresponding to a baseline utility score until disease progression. The ERG suggests that this may still represent an optimistic estimate of utility in progression-free survival if the impact of adverse events on utility and a general decline in utility over time is not taken into account. The ERG therefore explores the effect of declining utility over time for both the progression-free survival and progressed disease health states in the model (exploratory analysis 8, table 4) The ERG also considers it is likely that differences in the mode of administration and the duration of treatments may result in differential utilities for progression-free survival between the treatment strategies (exploratory analysis 9, table 4).

Resource use

Drug acquisition costs were adequately calculated and unit costs were appropriately sourced in the manufacturer's submission. The ERG notes that the manufacturer's assumptions around the proportion of patients on trastuzumab treatment beyond 19 months, the relative dose intensities and the proportion of centres that share vials have a limited impact on the results. Regarding drug administration, the manufacturer's application of an average number of cycles per month to each treatment strategy favours trastuzumab. The ERG considers that it would be more consistent to calculate different cycles per month for each drug combination.

The ERG comments that the manufacturer's submission does not consider the impact of population heterogeneity in the economic analysis. The proportion of patients who have a high HER2 positive status may be different in England and Wales from the proportion found to be eligible in the ToGA trial. The ERG notes that, while 17.8% of metastatic gastric cancer patients were eligible for treatment with trastuzumab in the ToGA trial, in the UK subgroup of patients the HER2 positivity rate was higher at 26% (n = 132).

The ERG further notes that in the ToGA trial IHC and FISH tests were completed at the same time. If tests are not carried out at the same time, there may be some delay to those patients who require a confirmatory test before commencing treatment. The impact of this delay has not been evaluated in the manufacturer's submission. The results of the ToGA trial may not be generalisable to the population in the NHS if HER2 testing is likely to be carried out sequentially. In addition, the costs of repeat tests are not included in the manufacturer's analysis despite 458 FISH failures and 176 IHC failures from 3812 samples in the ToGA trial. The ERG conducted exploratory analysis to assess the impact of HER2 testing assumptions (exploratory analyses 3, 10 and 11, table 4).

Clinical specialists advising the ERG considered that, although cardiac monitoring is in the marketing authorisation for epirubicin, it is not routine practice in the UK. Therefore, the assumption of testing once every 3 weeks may be too high an estimate. It may be more realistic to assume the same level cardiac testing between epirubicin and trastuzumab. The impact of this is explored in the sensitivity analysis (exploratory analysis 12, table 4).

While adverse events are not discounted, the ERG considers that these are unlikely to have a significant impact on the ICER. More importantly, it is possible that the cost of adverse events for trastuzumab is underestimated given the censoring of trastuzumab treatment duration in the ToGA trial. The ERG explores this uncertainty by using the same adverse event costs for trastuzumab plus cisplatin and capecitabine as for epirubicin plus cisplatin and capecitabine (exploratory analysis 13, table 4).

ERG exploratory analysis

Following ERG corrections to a series of relatively minor calculation errors and logical inconsistencies in the manufacturer's Excel model (details on page 88 of the ERG report), the ICER for the dominant strategy (trastuzumab plus cisplatin and capecitabine) over the most relevant comparator (epirubicin plus

cisplatin and capecitabine) in the incremental analysis decreases from £51,927 per QALY gained to £49,005 per QALY gained (see table 3).

Table 3 ERG exploratory analysis – revised estimates for manufacturer's base case.

Intervention	Total costs (£)	QALYs gained	Incremental cost per QALY gained (£)
HCX vs ECX	12,332	0.251	49,005
HCF vs ECF	11,180	0.233	47,907
HCX vs EOX	10,303	0.251	40,942

QALY, quality-adjusted life year; HCX, trastuzumab plus cisplatin and capecitabine; ECX, epirubicin plus cisplatin and capecitabine; HCF trastuzumab plus cisplatin and 5-fluorouracil; ECF, epirubicin plus cisplatin and 5-fluorouracil; EOX, epirubicin plus oxaliplatin and capecitabine.

The ERG presents additional analyses which explore the impact of various assumptions on the ICER. The results of the ERG's exploratory analyses are shown in table 4. The ERG combines four individual parameter adjustments, to present and alternative base case analysis that they considered to be as equally plausible as the manufacturer's analysis:

- hazard ratio of 0.87 for epirubicin plus oxaliplatin and capecitabine compared with epirubicin plus cisplatin and capecitabine
- hazard ratio of 0.96 for epirubicin plus cisplatin and capecitabine compared with cisplatin plus capecitabine,
- a utility decrement in progression-free survival and progressed disease states over time
- equal cardiac monitoring for epirubicin and trastuzumab

In this cumulative analysis the oxaliplatin regimen is no longer dominated. The ICER of trastuzumab plus cisplatin and capecitabine compared with epirubicin plus oxaliplatin and capecitabine increases to £66,982 per QALY gained. If parallel testing is used, this estimate increases to £71,637 per QALY gained.

Table 4 Results of ERG Exploratory Analysis

Exploratory analysis	Comparison	ICER
Manufacturer base case (revised)	HCX vs ECX	£51,927
Manufacturer base case following ERG corrections	HCX vs ECX	£49,005
Assumptions about natural history (section 6.3.1 page 90 ERG report)		
1. Alternative combinations of distributions for progression free survival and overall survival	HCX vs ECX	£39,830 to £54,287
Assumptions about model population (section 6.3.1 page 92 ERG report)		
2. Using data for the total trial population instead of EMA high HER2+ subgroup	HCX vs ECX	£62,576
3. Varying the HER2 positive rate between 5% and 30%	HCX vs ECX	£48,395 (rate 30%) £52,866 (rate 5%)
Assumptions about comparators and efficacy (section 6.3.2 page 93 ERG report)		
4. Assuming same efficacy as in manufacturer's submission but costs only of CX: i. Using REAL-2 dose of cisplatin ii. Using ToGA dose of cisplatin	HCX vs CX	 i. £53,775 ii. £53,567
5. Using HR of 0.96 (instead of 1) reducing efficacy of CX in comparison with ECX (Yun): i. Used for PFS only ii. Used for both PFS and OS	HCX vs ECX	 i. £49,754 ii. £52,709
6. Using HR of 0.87 (instead of 1) reducing efficacy of ECX in comparison with EOX (REAL-2): i. Used for PFS only ii. Used for OS only iii. Used for both PFS and OS	HCX vs EOX	i. No difference ii. EOX no longer dominated. £50,745 iii. EOX no longer dominated. £54,114
Assumptions about utilities (section 6.3.3 page 97 ERG report)		
7. Lowering the utility estimates for the PFS ad PD states by 20%	HCX vs ECX	£60,724
8. Utilities in both the PFS and PD states decrease by 0.003502 per year	HCX vs ECX	£51,309
9. Patients receiving treatment in PFS and PD states have 5% utility decrement	HCX vs ECX	£50,123
Assumptions about resource utilisation (section 6.3.4 page 98 ERG report)		
10. Repeat tests for 6% of IHC tests and 9.4% of FISH tests	HCX vs. ECX	£49,128
11. IHC and FISH tests undertaken in parallel (equal number of both tests)	HCX vs ECX	£51,618
12. Cardiac monitoring for epirubicin equal to trastuzumab	HCX vs ECX	£50,816
13. Adverse event costs same for HCX as ECX	HCX vs ECX	£52,384
Cumulative impact (section 6.4 page 100 ERG report)		
14. Alternative base-case 1 – using **sequential** testing. Combines analyses 5, 6, 8 and 12.	HCX vs EOX	EOX no longer dominated. **£66,982**
15. Alternative base-case 1 – using **parallel** testing. Combines analyses 5, 6, 8 and 12.	HCX vs EOX	EOX no longer dominated. **£71,637**

ICER, incremental cost-effectiveness ratio; ERG, Evidence Review Group; PFS, progression-free survival; OS, overall survival; HCX, trastuzumab plus cisplatin and capecitabine; ECX, epirubicin plus cisplatin and capecitabine; MS, manufacturer's submission; CX, cisplatin; HR, hazard ratio; EOX, epirubicin plus oxaliplatin and capecitabine; PD, IHC, immunohistochemistry; FISH, fluorescence in-situ hybridization HCF trastuzumab plus cisplatin and 5-fluorouracil; ECF, epirubicin plus cisplatin and 5-fluorouracil

3.3 Further considerations following premeeting briefing teleconference

No equalities issues were raised in the submissions.

Exploratory analysis	Comparison	ICER
Manufacturer base case (revised)	HCX vs ECX	£51,927
Manufacturer base case following ERG corrections	HCX vs ECX	£49,005
Further assumptions about comparators and efficacy (ERG report addendum)		
Using HR of 0.77 (instead of 1) reducing efficacy of CX in comparison with ECX/EOX (Wagner meta-analysis): i. Used for OS only ii. Used for both PFS and OS	HCX vs ECX	 i. £84,373 ii. £99,797

4 Authors

Joanne Holden (Technical Lead), Zoe Garrett (Technical Adviser) with input from the Lead Team (Peter Selby, John Stevens, Judith Wardle).

Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A The Evidence Review Group (ERG) report for this appraisal was prepared by York CRD and CHE Technology Assessment Group:

- 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 Submissions or statements were received from the following organisations:

I Manufacturer/sponsor:

- Roche Products

II Professional/specialist, patient/carer and other groups:

- Royal College of Pathologists
- Royal College of Physicians