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NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL (STA)

Trastuzumab for the treatment of HER2 positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction (mGC)

Roche Submission to the
National Institute for Health and Clinical Excellence
Submitted: 1st March 2010

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Abbreviations

Abbreviation	Full name
5-FU	5-Fluorouracil
AE	Adverse event
aGC	Advanced gastric cancer
AUC	Area under the curve
BNF	British National Formulary
CBR	Clinical benefit rate
CI	Confidence interval
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DoR	Duration of response
ECF	Epirubicin in combination with cisplatin and 5-Fluorouracil
ECOG	PS Eastern Co-operative Oncology Group Performance
ECX	Epirubicin in combination with cisplatin and capecitabine
EMEA	European Medicines Evaluation Agency
EOX	Epirubicin in combination with oxaliplatin and capecitabine
EQ-5D	Euro QoL questionnaire
ERG	Evidence review group
EU	European union
FAS	Full analysis set: (follows the intent-to-treat principle) All randomised patients who received study medication at least once
GOJ	Gastro-oesophageal junction
HCF	Trastuzumab in combination with cisplatin and 5-FU
HCX	Trastuzumab in combination with cisplatin and capecitabine
HCX/F	Trastuzumab in combination with cisplatin and either capecitabine or 5-FU
HER2	Human Epidermal growth factor Receptor 2
HR	Hazard ratio
ICER	Incremental cost effectiveness ratio
ITT	Intention to treat
IV	Intravenous
LY	Life year
LYG	Life year gained
mg/kg	Milligram per kilogram
mg/m^2	Milligram per meter squared
mGC	Adenocarcinoma of the stomach or gastro-oesophageal junction
N/A	Not applicable
NCI	National Cancer Institute
NE	Not Evaluable
NR	Not recorded /reported
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PD	Progressive disease (the period between progression on 1^{st} line and death)
PFS	Progression-free survival
PP	Per protocol population: Randomised patients with major protocol violations were excluded from PP.
PR	Partial response

PS	Performance status
QALY	Quality adjusted life year
RCT	Randomised Controlled Trial
RDI	Relative dose intensity
RECIST	Solid evaluation criteria in solid tumours
SAE	Serious adverse event
SmPC	Summary of product characteristics
TA	Technology appraisal
ToGA	Trastuzumab fOr GAstric cancer
TTP	Time to progression

Section A

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the 'Guide to the single technology appraisal process' – www.nice.org.uk). A (draft) Summary of Product Characteristics (SMPC) for pharmaceuticals and a (draft) technical manual for devices should be provided (see appendix 1, section 9.1).

1 Description of technology under assessment

1.1 Give the brand name, approved name and, where appropriate, therapeutic class. For devices please provide details of any different versions of the same device.

Brand name: Herceptin

Approved name: Trastuzumab

Therapeutic class: Monoclonal antibody (recombinant humanised IgG1 monoclonal antibody)

1.2 Does the technology have a UK marketing authorisation/CE marketing for the indications detailed in this submission? If so, please give the date on which authorisation was received. If not, please state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

On 17 December 2009, positive CHMP opinion was adopted for trastuzumab as an extension of the current indication. The extension includes the treatment of patients with HER2 positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction (GOJ) who have not received prior anti-cancer treatment for their metastatic disease in combination with capecitabine or 5-FU and cisplatin.

EMEA approval was obtained: 19 January 2010.

1.3 What are the (anticipated) indication(s) in the UK? For devices, please provide the (anticipated) CE marking, including the indication for use.

As per the wording adopted by the CHMP opinion, the indication for this appraisal is:

"Herceptin 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 anti-cancer treatment for their metastatic disease.

Herceptin should only be used in patients with metastatic gastric cancer whose tumours have HER2 overexpression as defined by IHC2+ and a confirmatory FISH+ result, or IHC 3+, as determined by an accurate and validated assay"

Trastuzumab has five other indications approved by the EMEA:

Metastatic Breast Cancer (MBC)

Trastuzumab is indicated for the treatment of patients with HER2 positive metastatic breast cancer:

- as monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone receptor positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments.

- in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable.

- in combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease.

- in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive metastatic breast cancer, not previously treated with trastuzumab.

Early Breast Cancer (EBC)

Herceptin is indicated for the treatment of patients with HER2-positive early breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable).

1.4 To what extent is the technology currently being used in the NHS for the proposed indication? Include details of use in ongoing clinical trials. If the technology has not been launched, please supply the anticipated date of availability in the UK.

As trastuzumab has only recently been granted a license for gastric cancer there is very limited use for the treatment of patients with HER2 positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction within the NHS and we are not aware of any ongoing UK trials in this setting.

The CHMP adopted a positive opinion on 17th December 2009. EMEA approval was granted on 19 January 2010, which marks the first time trastuzumab has been approved for use in this indication within the UK.

There is already extensive experience of using trastuzumab in the management of HER2-positive breast cancer within the UK.

1.5 Does the technology have regulatory approval outside the UK? If so, please provide details.

The EMEA license for trastuzumab in patients with HER2-positive metastatic adenocarcinoma of the stomach or GOJ is the first license for trastuzumab in this indication throughout the world.

Trastuzumab is approved by regulatory authorities throughout the world including the USA and the whole of Europe (through EMEA) for the treatment of HER2-positive breast cancer (as per indications listed in section 1.3).

1.6 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

The appraisal of this extension for trastuzumab by the SMC is expected to begin in April 2010 with final publication of the outcomes of the appraisal expected in August 2010.

1.7 For pharmaceuticals, what formulation(s) (for example, ampoule, vial, sustained-release tablet, strength(s) and pack size(s) will be available?

Trastuzumab is available as a vial containing 150 mg of trastuzumab as powder for concentrate for solution for infusion in the UK.

1.8 What is the proposed course of treatment? For pharmaceuticals, list the dose, dosing frequency, length of course and anticipated frequency of repeat courses of treatment.

Roche anticipates that, in the UK, patients with HER2 positive metastatic adenocarcinoma of the stomach or GOJ will receive trastuzumab at the same time as their chemotherapy (capecitabine or 5-FU plus cisplatin) as per the treatment regimen in the registration trial (ToGA). In this regimen, trastuzumab was administered as an IV infusion as follows:

- an initial loading dose of 8 mg/kg body weight on day one of the first cycle (3-weekly cycles);
- followed by 6 mg/kg body weight repeated at 3-weekly intervals.

The planned duration of treatment of trastuzumab is until disease progression. Median progression-free survival (PFS) of the subgroup of patients receiving trastuzumab plus chemotherapy in ToGA (the pivotal study supporting the application for marketing authorisation), who will be eligible for trastuzumab under the license extension, was 7.6 months.

1.9 What is the acquisition cost of the technology (excluding VAT)? For devices, provide the list price and average selling price. If the unit cost of the technology is not yet known, please provide details of the anticipated unit cost, including the range of possible unit costs.

The acquisition cost of 1 vial containing 150 mg of trastuzumab as powder for concentrate for solution for infusion is £407.40.

1.10 What is the setting for the use of the technology?

Trastuzumab is administered as an IV infusion in a hospital outpatient clinic at the same time as the IV chemotherapy drugs the patient will be receiving.

1.11 For patients being treated with this technology, are there any other aspects that need to be taken into account? For example, are there additional tests or investigations needed for selection, or particular administration requirements, or is there a need for monitoring of patients over and above usual clinical practice for this condition? What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

Trastuzumab should only be used in patients with metastatic adenocarcinoma of the stomach or GOJ whose tumours have HER2 overexpression or HER2 gene amplification (in IHC equivocal cases) as determined by an accurate and validated assay. Therefore, HER2 testing is mandatory prior to initiation of trastuzumab therapy.

All candidates for treatment with trastuzumab should undergo baseline cardiac assessment including history and physical examination, ECG, echocardiogram, or MUGA scan or magnetic resonance imaging. Cardiac function should be further monitored during treatment (eg, every three months). (Trastuzumab SmPC January 2010)

Current standard treatment of patients diagnosed with inoperable locally advanced or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction is chemotherapy. Roche market research into the usage of chemotherapy for these patients suggests that, in the UK, triple-therapy which includes epirubicin represent the most widely used chemotherapy.

The SmPC for epirubicin states that patients should undergo baseline assessment of cardiac function prior to initiation of treatment with epirubicin. Furthermore, cardiac function must be carefully monitored during treatment (e.g. ECG before and after each treatment cycle) to minimise the risk of heart failure of the type described for other anthracyclines. The SmPC recommends cardiac function should be assessed by ECG, echocardiography and, if necessary, measurement of ejection fraction by radionuclide angiography.

(Epirubicin SmPC 02/01/2008
http://emc.medicines.org.uk/medicine/18609/SMPC/Epirubicin+Hydrochloride+2+mg+ml+Injection+(Hospira+UK+Ltd)/)

Those patients diagnosed as having HER2 positive disease, who would otherwise receive a combination chemotherapy regimen containing epirubicin, would now be offered trastuzumab in combination with doublet chemotherapy (cisplatin plus capecitabine or 5-FU) and as such would not receive an anthracycline as this is not recommended. Therefore, the need for cardiac monitoring of patients receiving trastuzumab is not over and above usual clinical practice for this condition as it must be performed in a similar manner for patients receiving epirubicin as part of their chemotherapy treatment.

Trastuzumab is administered as an IV infusion. The first infusion should be administered over approximately 90 minutes with subsequent doses administered as a 30-minute infusion, assuming the first dose is well tolerated. Although there is a finite infusion time associated with trastuzumab, it can be given along with other IV drugs, namely chemotherapy and so should not significantly increase the duration of patient's visits.

As per the marketing authorization trastuzumab should be given in combination with cisplatin plus capecitabine or 5-FU for 6 cycles with trastuzumab continued until disease progression.

2 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the Evidence Submission will address.

	Final scope issued by NICE	Decision problem addressed in the submission
Population	Patients with HER2 positive advanced gastric cancer	Patients with HER2 positive (IHC2+/FISH+ or IHC3+) metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease
Intervention	Trastuzumab	Trastuzumab in combination with capecitabine or 5-FU plus cisplatin
Comparator(s)	Cytotoxic chemotherapy regimens which may include 5-fluorouracil or capecitabine in combination with one or more of the following: cisplatin, oxaliplatin, doxorubicin, epirubicin, docetaxel	***Primary analysis*** Epirubicin in combination with cisplatin and capecitabine (ECX) Epirubicin in combination with Cisplatin and 5-FU (ECF) – for patient whom are unsuitable for capecitabine **Secondary analysis** Epirubicin in combination with Oxaliplatin and capecitabine (EOX)
Outcomes	The outcome measures to be considered include:	As per scope

	overall survival progression-free survival response rate adverse effects of treatment health-related quality of life.	
Economic Analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As per scope
Subgroups to be considered	None	None
Special considerations, including issues related to equity or equality	None	None

Section B

3 Executive summary

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based and clearly reference the relevant section of the submission. The summary should cover the following items.

- The UK approved name, brand name, marketing status and principal pharmacological action of the proposed drug.
- The formulation(s), strength(s), pack size(s), maximum quantity(ies), anticipated frequency of any repeat courses of treatment and acquisition cost (see section 1.9).price.
- The indication(s) and any restriction(s).
- The recommended course of treatment.
- The main comparator(s).
- Whether the key clinical evidence in the submission comes from head to head randomised trials (RCTs), from an indirect comparison of two sets of randomised trials involving a common comparator (for example, placebo or other active therapy), or from non-randomised studies.
- The main clinical results of the randomised trials and any relevant non RCTs.
- In relation to the economic evaluation, details of:
- the type of economic evaluation and justification for the approach used
- the pivotal assumptions underlying the model/analysis
- the mean costs, outcomes and incremental ratios from the evaluation.

Background

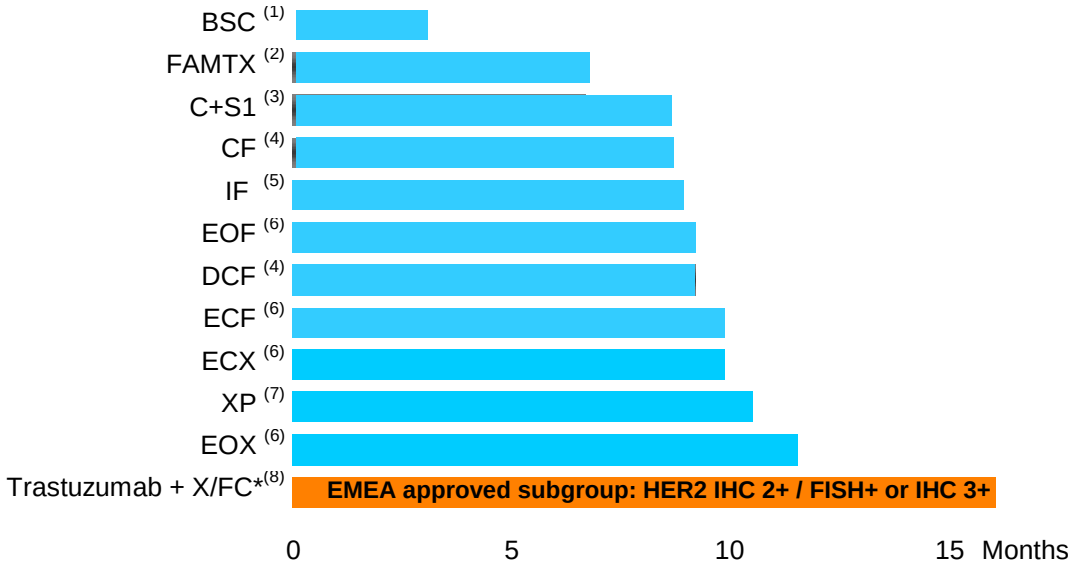
Gastric cancer is the tenth most commonly diagnosed cancer in the UK. Approximately 7,000 new cases are diagnosed each year in England and Wales (CRUK 2009a) and these account for around 4,574 deaths (CRUK 2009b). The mortality rate is high because most patients present with disease too advanced for curative surgical removal of their tumour. For the 80% of patients unsuitable for curative surgery, palliative chemotherapy is an option and it is estimated that, in England and Wales, just over half (around 2,900) of the patients with advanced or metastatic gastric cancer receive such treatment. Palliative chemotherapy modestly improves survival as well as relieving disease-related symptoms.

Treatment practices vary considerable throughout the world, with doublet regimens representing the standard of care in Asia and triplet regimens more common in Europe and the USA. Despite there being no international consensus as to a standard chemotherapy regimen, in the majority of cases, chemotherapy for inoperable locally advanced and metastatic adenocarcinoma of the stomach or GOJ conventionally comprises a

fluoropyrimidine (capecitabine or infusional 5-FU) and cisplatin. In the UK, the anthracycline epirubicin is typically added. As outlined in section 4 (Figure 5) the clear standard of care in the UK is ECX.

The introduction of palliative chemotherapy in the late 1980s and early 1990s, either as single agents, including anthracyclines (Preusser 1988), cisplatin (Leichman 1991), and Mitomycin C (Schnall 1993), or combination chemotherapy (Cullinan 1985; De Lisi 1986; Levi 1986; Cullinan 1994; Barone 1998; Colucci 1995; Loehrer 1994) typically improved survival by 7 months compared to best supportive care - a clinically important improvement in a disease where median survival is otherwise only 4 months (Wagner 2005). Despite the introduction of newer chemotherapy agents and the investigation of novel regimens there have been no further advances in treatment strategies for almost two decades that significantly extend OS. Therefore prognosis remains poor for these patients with median OS being less than one year demonstrating that there is a clear unmet need for new agents.

Figure 1: Median overall survival for best supportive care, current chemotherapy treatment, and chemotherapy plus trastuzumab



*87.1% patients received capecitabine

BSC, best supportive care; FAMTX, methotrexate, 5-FU and doxorubicin;
C+S1, cisplatin plus S1; CF, cisplatin plus 5-FU; IF, irinotecan plus 5-FU;
EOF, epirubicin, oxaliplatin and 5-FU; DCF, docetaxel, cisplatin and 5-FU;
ECF, epirubicin, cisplatin and 5-FU; ECX, epirubicin, cisplatin and Xeloda;
XP, Xeloda plus cisplatin; EOX, epirubicin, oxaliplatin and Xeloda;
X/FC, Xeloda or 5-FU plus cisplatin.

References

1. Murad 1993.
2. Vanhoefer 2000.

3. Ajani 2009; Abstract 8.
4. Van Cutsem 2006.
5. Dank 2008.
6. Cunningham 2008.
7. Kang 2009
8. Van Cutsem 2009.

Trastuzumab

Trastuzumab (Herceptin) is a monoclonal antibody that binds to the HER2 protein that is present in excessive quantities on the surface of the cells making up some gastric and breast cancers. In binding to HER2, trastuzumab exerts a number of effects including inhibition of intracellular signalling and activation of an immune response against the cancer cell.

Trastuzumab has already been shown to be effective in terms of extending survival in both the adjuvant and metastatic treatment of HER2 positive breast cancer and is predicted to change the epidemiology of the disease (Weisgerber-Kriegl 2008). It has received positive reimbursement endorsements from NICE and the SMC for all indications where a review has been completed.

As per the subject of this appraisal the license for trastuzumab has now been extended to include use for the treatment of patients with HER2 positive metastatic adenocarcinoma of the stomach or GOJ who have not previously received chemotherapy for their metastatic disease. See Table 1 for additional trastuzumab key information.

Table 1. Trastuzumab key information

Approved Name	Trastuzumab
Brand Name	Herceptin
Marketing Status	The EMEA granted an extension to the existing license for trastuzumab on 19 January 2010
Indication under appraisal	"Herceptin in combination with capecitabine or 5-fluorouracil and cisplatin (CX/F) is indicated for the treatment of patients with HER2 positive (IHC3+ or IHC2+/FISH+) metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease."
Formulation / Pack size	A vial contains 150 mg of trastuzumab. Reconstituted Herceptin solution contains 21 mg/ml of trastuzumab.
Acquisition Cost	Net price 150mg vial = £407.40
Posology and method of administration	Trastuzumab is administered at an initial loading dose of 8 mg/kg body weight, followed by 6 mg/kg body weight 3 weeks later and then 6 mg/kg repeated at 3-weekly intervals administered as infusions over approximately 90 minutes. If the initial loading dose is well tolerated, the subsequent doses can be administered as a 30-minute infusion

Clinical effectiveness

The clinical trial (ToGA; Van Cutsem 2009a), upon which the license for trastuzumab is based, included patients with inoperable locally advanced and/or metastatic adenocarcinoma of the stomach or GOJ. However, given the small proportion of patients with inoperable locally advanced disease (3.4%) recruited into this study (Van Cutsem 2009a) the license granted by the EMEA was for patients with metastatic adenocarcinoma of the stomach or GOJ only (Trastuzumab SmPC 2010). This is referred to as metastatic gastric cancer (mGC) by the EMEA, in the SmPC for trastuzumab (January 2010) and will also be labelled as such within this submission.

Trastuzumab in combination with chemotherapy in HER2-positive mGC has demonstrated a step-wise improvement in clinical efficacy without compromising tolerability compared with chemotherapy alone in the BO18255B (ToGA) trial. The study was an international, phase III randomised controlled trial designed to show superior overall survival with the addition of trastuzumab to chemotherapy. Patients with inoperable locally advanced and/or metastatic disease were eligible for entry into the trial. Patients were randomized to treatment with either six cycles of CX/F (cisplatin plus capecitabine or 5-FU) chemotherapy every 3 weeks or the same chemotherapy with trastuzumab (HCX/F) given as an iv infusion every 3 weeks until disease progression. The choice of fluoropyrimidine was investigators choice with the majority of patients (87%) in both arms receiving capecitabine with the remaining 13% receiving 5-FU.

Given the available knowledge regarding HER2 at the time the ToGA trial was set-up, both immunohistochemistry (IHC) and fluorescence in-situ hybridization (FISH) were applied in

parallel to determine HER2 status in the study. Patients' tumour samples were centrally tested by both IHC and FISH with a score of IHC3+ or FISH+ considered HER2-positive and eligible for entry into the ToGA trial. Based on a greater understanding of HER2 and testing procedures gained in the breast cancer setting whilst the ToGA trial was ongoing (Dowsett 2007; Hanna 2007; Walker 2008; Albanell 2009) and the clinical outcomes of the ToGA trial (Van Cutsem 2009a) the gastric cancer HER2 testing algorithm was refined to define HER2 positivity as either IHC2+/FISH+ or IHC3+ (Hoffmann 2008; Chung 2009). This led to an exploratory analysis in the IHC2+/FISH+ and IHC3+ subgroup (high HER2 protein expression) which represents the EMEA approved licensed population for trastuzumab in mGC and hence is the principle population of interest for this Technology Appraisal.

Therefore, the EMEA approved license for trastuzumab in mGC reflects the sub-population within the ToGA trial of patients with high HER2 expressing tumours who gained benefit from the addition of trastuzumab to CX/F chemotherapy, defined as IHC2+/FISH+ or IHC3+. This represented 74% of the ToGA intent to treat population.

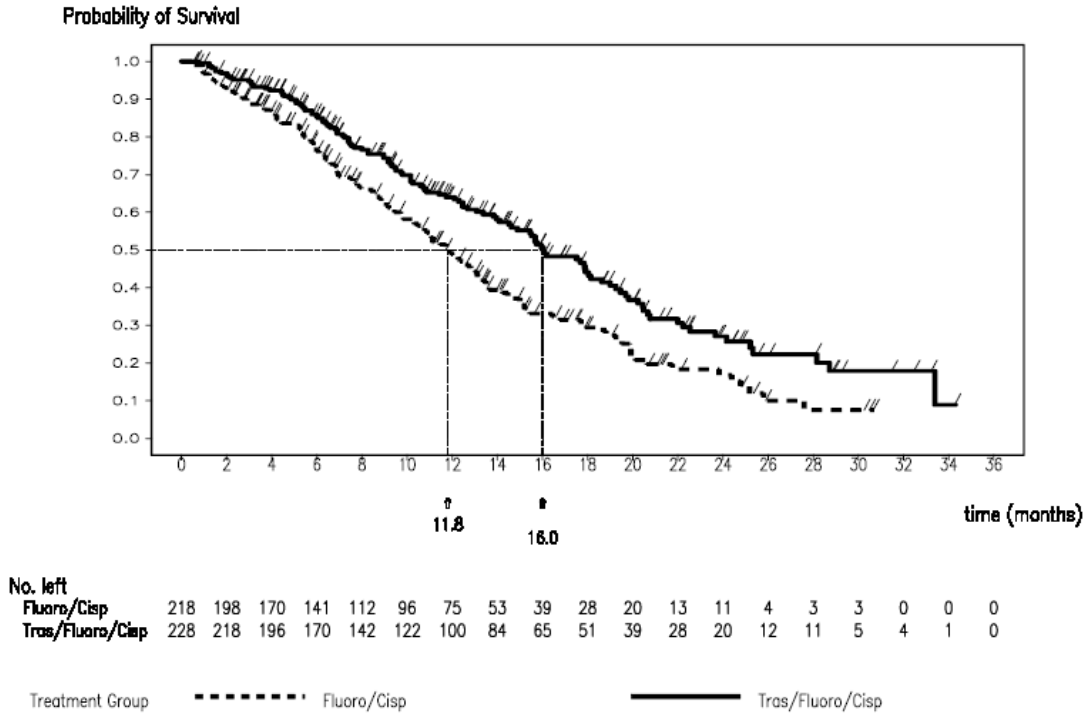
In the EMEA licensed high HER2 expressing subgroup (IHC2+/FISH+ or IHC3+), the addition of trastuzumab to CX/F chemotherapy demonstrated a [redacted] 4.2 month improvement in OS [redacted] compared with CX/F chemotherapy alone which is a clinically meaningful 35% reduction in the risk of death (11.8 vs 16 months for CX/F vs HCX/F, respectively; HR 0.65; 95%CI: 0.51, 0.83; [redacted] [Figure 2]). This represents a significant advance in the treatment of this patient group as median OS is extended beyond one year, to 16 months, for the first time, something that has not been demonstrated with any chemotherapy regimen in a mixed HER2-positive/HER2-negative population (Figure 1). Furthermore, there was a [redacted] 2.1 month delay in progression with the addition of trastuzumab to chemotherapy (5.5 months for CX/F arm vs 7.6 months for HCX/F arm [HR 0.64; 95%CI: 0.51-0.79; [redacted] . In addition, there was a comparable improvement in quality of life (QoL) in both arms of the study as measured by the EORTC-QLQ-C30 and QLQ-ST022 instruments (Satoh 2010). This means that not only were patients in the HCX/F arm progression-free for longer (2.1 months) but also had an improved QoL for a greater period of time than patients who received chemotherapy alone (Trastuzumab SmPC 2010; Satoh 2010).

Given the well established safety profile of trastuzumab in the breast cancer setting, there were no new or unexpected adverse events observed with the addition of trastuzumab to CX/F chemotherapy in patients with mGC.

The EMEA assessment of the license extension was expedited through the 60 day rather than 90 day procedure based on the dramatic improvement in overall survival observed in the high HER2 expressing group; surpassing the 12 month barrier which previously existed with

chemotherapy treatment and extending median OS by 4.2 months to 16 months with the addition of trastuzumab to chemotherapy (11.8 vs 16 months for CX/F vs HCX/F, respectively; HR 0.65; [redacted]

Figure 2: Kaplan-Meier curve of OS (high HER2 expressing group)



Fluoropyrimidine: Investigator preference of Capecitabine or 5-FU
Tras/Fluoro/Cisp: Trastuzumab/Fluoropyrimidine/Cisplatin
Fluoro/Cisp: Fluoropyrimidine/Cisplatin

As mentioned previously in this submission, the ToGA trial recruited patients with inoperable locally advanced and/or metastatic gastric cancer. However, due to the small number of patients with inoperable locally advanced disease recruited (3.4% in FAS population) the license for trastuzumab was restricted to patients with metastatic disease. [redacted]

[redacted]

Economic Analysis

Methods

The evaluation was based on an incremental cost-utility analysis designed to compare the costs and outcomes of each of the interventions of interest against those of the comparator regimens typically used in the UK (ECX, ECF, and EOX).

The economic evaluation conforms to the reference case as described in NICE's Guidance to the Methods of Technology Appraisal. The economic model developed was a three-state area under the curve model, where patients are assumed to be within one of three possible discrete health states at any given time; "progression-free survival", "progressed" or "death". This analysis was based on the mature data set from the ToGA study relating to the licensed population and not the ITT population. The vast majority of patients had progressed at the point of follow-up and therefore relatively little extrapolation was required to estimate mean PFS. At the point of latest follow-up 43.2% and 37.2% of patients were still alive in the trastuzumab-containing arms and chemotherapy alone arms respectively, hence overall survival was extrapolated using parametric methods. First-line treatment duration, dose intensity (HCX/F only), and adverse event incidence (HCX/F only) was also taken directly from the ToGA trial. Dose intensity and adverse event incidence for each of the comparators was taken from the results of a large phase III, non-inferiority study, REAL-2, (Cunningham 2008) that is the only phase III study investigating all of these regimens.

The majority of patients in the ToGA study (87%) received capecitabine as choice of fluoropyrimidine. For this reason a simplifying assumption was made that the survival results of ToGA represent those expected with CX and HCX therapy. For the reasons outlined in section 6.6; it was considered that the efficacy outcomes of CX in ToGA represent those expected from ECX and EOX in the HER2+ve mGC population. Published meta-analysis in advanced Gastric cancer have demonstrated that Capecitabine-based regimens confer an overall survival advantage compared to 5-FU-based regimens (Okines 2009). Therefore the risk of death with 5-FU regimens, HCF and ECF, was assumed to be increased by 15% (HR taken from Okines 2009) over that of HCX and ECX respectively.

Results

Replacing the capecitabine-based regimens (ECX and EOX) with trastuzumab in combination with capecitabine and cisplatin (HCX) resulted in a mean gain in life of 4.7 months. Compared with the 5-FU-based regimen that is typically used in the UK (ECF) trastuzumab in combination with 5-FU and cisplatin (HCF) resulted in an average increase of 4.4 months of life. This difference in absolute survival is not a reflection of trastuzumab having a smaller treatment effect when added to CF but rather is a result of the higher baseline risk of death associated with 5-FU compared with capecitabine based therapy (see Figure 3 below)

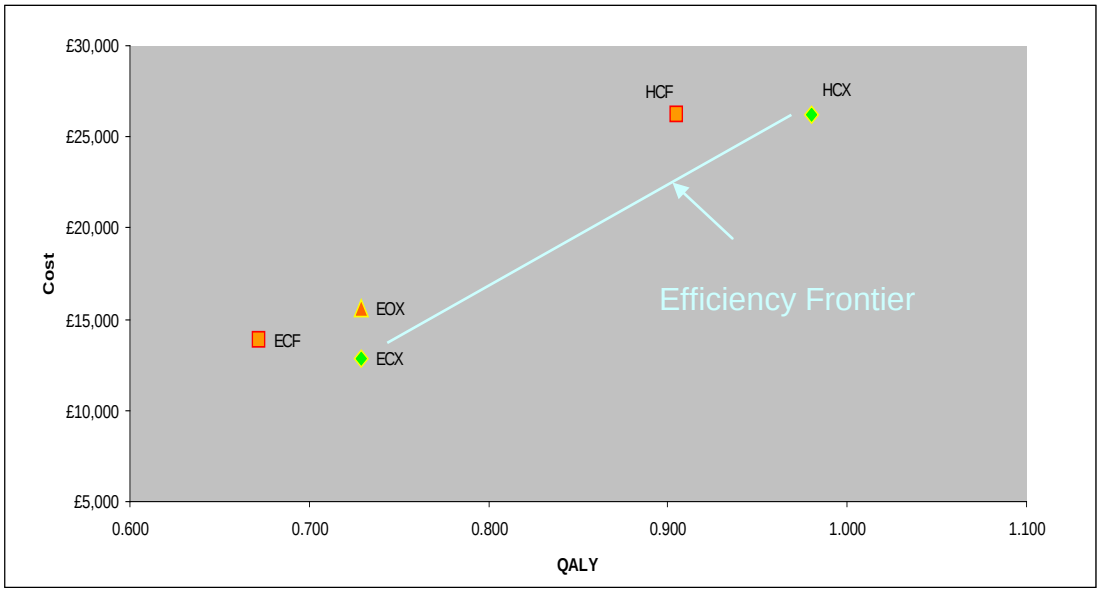
ECX resulted in the lowest total cost (life time cost including post progression and hospice costs etc), of all the regimens with a total cost per patient of £12,820. The total cost per patient for HCX and HCF was £26,156 and £26,113 respectively. The incremental total costs for each comparison of interest is show below.

Table 2: Incremental Cost Per Patient

HCX vs ECX	**£13,336**
HCF vs ECF	**£12,214**
HCX vs EOX	**£10,515**

HCX resulted a greater number of QALYs for approximately the same overall cost as HCF and thus was the dominant trastuzumab containing regimen. ECX was the dominant comparator regimen as it offered equivalent efficacy at a reduced cost relative to the other comparators. Hence ECX and HCX make up the efficiency frontier (see below). The cost and effect of replacing ECX with HCX is also the relevant comparison given that patients in the UK are predominantly treated with ECX.

Figure 3: Economic results plotted on cost effectiveness plane



Comparing the two regimens on the efficiency frontier, ECX and HCX, resulted in an incremental cost per QALY of £53,010.

A small number of patients however may not be suitable for capecitabine making the incremental cost effectiveness of replacing ECF with HCF also of relevance. The ICER when making this comparison was £52,363.

Table 3: Mean ICERs (£/QALY) per patient

HCX vs ECX	**£53,010**
HCF vs ECF	**£52,363**
HCX vs EOX	**£41,795**

Summary

A large well-designed randomised controlled trial (ToGA) demonstrated that for patients with HER2-positive (IHC2+/FISH+ or IHC3+) mGC, the addition of trastuzumab to chemotherapy (capecitabine or 5-FU plus cisplatin) dramatically extends overall survival to [redacted] compared to [redacted] with chemotherapy alone, reducing the risk of death by [redacted].

On average the use of trastuzumab is estimated to extend a patient's life by over 4 months in a population expected to typically live for only a year following diagnosis with metastatic disease. These important benefits are achieved with minimal extra burden of treatment being put upon patients, and no loss of QoL.

In the context of the prognosis for mGC patients, and the step-change improvement in efficacy that treatment with trastuzumab represents, the economic evaluation indicates that

trastuzumab is a cost-effective treatment option, which we believe represents an efficient use of NHS resources.

Criteria for appraisal of end of life (EoL) treatments

The criteria for the supplementary advice on EoL interventions are listed below, along with the key information with respect to Trastuzumab for the treatment of mGC.

Criterion	Applicability
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Yes. mGC patients are currently expected on average to survive less than one year (Wagner 2005, 2006). In ToGA patients within the trastuzumab's licensed population had a median survival of [redacted]
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment, and	Yes. In the licensed population ToGA demonstrated a median increase in survival of [redacted] from the addition of trastuzumab to CX/F. The mean OS advantage calculated via Weibull extrapolation of the data for the comparison of most relevance to the NHS (HCX vs ECX) was **4.7 months**
The treatment is licensed or otherwise indicated, for small patient populations	The eligible population within the mGC indication of the trastuzumab license is estimated to be 492 patients in England and Wales. The combined eligible population across all licensed indications for trastuzumab is estimated to be approximately 7,144 patients including: • mGC, 492 patients (see section 8) • Early and locally advanced breast cancer, 4319 patients (see Appendix 5) • Metastatic Breast Cancer 2587 (see Appendix 5)

The cost per life year gained (ie without applying utility weights and thus assuming full quality of life) is shown in the table below.

Table 4: Cost per LYG

HCX vs ECX	**£34,774**
HCF vs ECF	**£34,772**
HCX vs EOX	**£27,417**

The estimated cost per QALY's of most relevance are approximately £53,000 representing a multiple of 1.76 over £30,000

4 Context

In this background section the manufacturer or sponsor should summarise and contextualise the evidence relating to the decision problem. The information provided will not be formally reviewed by the Evidence Review Group.

4.1 Please provide a brief overview of the disease/condition for which the technology is being used. Provide details of the treatment pathway and current treatment options at each stage.

Epidemiology of gastric cancer

There were 6,706 new cases of gastric cancer reported in England and Wales in 2006 (CRUK 2009a) and 4,574 deaths in 2007 (CRUK 2009b). Compared with historic data these figures demonstrate that in the UK – as in most developed countries - the incidence of gastric cancer and the associated mortality are in steady and dramatic decline, with a 70% reduction in mortality over the last 30 years (CRUK 2009b). However, they also demonstrate that gastric cancer still represents a significant source of morbidity and mortality. This is both because it is still a relatively common cancer and because the prognosis after diagnosis is, generally, poor.

[redacted]

In the UK, it is the seventh most common cancer in men and the fourteenth most common in women. Although one year survival has increased from 14% in the early 1970s to 35% now (in parallel with a decline in post-operative mortality), 5 year survival is still very low, at 15% (CRUK 2009a). The poor long-term outcomes seen in the UK reflect the fact that early diagnosis remains difficult as most patients do not present with clear symptoms in the early stage. Therefore, diagnosis is usually made late, at a point when spread of the tumour either locally or by metastasis precludes complete surgical excision, the only potentially curative treatment. As such, the prognosis for these patients is poor (Parkin 2005) with the average length of survival being approximately 10 months from diagnosis given currently available therapies.

Treatment and outcomes

Surgery forms the primary form of treatment for gastric cancer and UK Cancer Registry data together with a survey of gastric cancer surgery in 23 NHS hospitals suggest that around 37% of patients have some sort of surgery for their cancer (CRUK, 2009b), though only in about 20% is it viewed as curative (Bachman 2002) and for the rest it is carried out with palliative intent. Despite the acknowledged importance of surgery, around two-thirds of UK patients present with inoperable disease. For such patients, palliative chemotherapy is the only treatment option that offers an improvement in survival.

There is no internationally accepted gold-standard for the palliative chemotherapy of gastric cancer with various double- and triple chemotherapy regimens being adopted, many of which have never been tested in head-to-head randomised controlled trials (RCTs). Different regimens have evolved in parallel in different parts of the world – in the Far East, where gastric cancer is a major problem, two drug combinations of cisplatin and a fluoropyrimidine (5-FU or oral equivalent) are standard, whilst in the UK a 3 drug combination incorporating cisplatin, a fluoropyrimidine (capecitabine or 5-FU) and epirubicin has been the most widely used regimen for the last decade. This variation prompted Wagner *et al*. (Wagner 2005, 2006, 2007) to conduct a systematic review and meta-analysis of chemotherapy for advanced gastric cancer (aGC; included trials recruiting patients with locally advanced and metastatic disease). Wagner et al concluded that the case for palliative chemotherapy in aGC is strong and that it provides a convincing benefit with median overall survival of 11 months being reported compared with 4.3 months with Best Supportive Care (BSC) alone (Wagner 2005, 2006, 2007). They estimated that the overall survival hazard ratio (HR) of 0.39 (95% CI, 0.28-0.52) in favour of chemotherapy translates into a mean survival increase of about 7 months – a very substantial benefit given the very poor prognosis in aGC. 5-FU has historically formed the foundation of chemotherapy in aGC and was included in all regimens in the systematic review and the authors concluded that further gain can be achieved by adding in second- and third-agents, most commonly an anthracycline (epirubicin or doxorubicin) and cisplatin, though they note that the benefits of combination chemotherapy over single-agent fluoropyrimidines are modest.

The additional value of anthracyclines has been particularly debated as head-to-head trials that have compared triplet versus doublet regimens, have not demonstrate any significant survival benefit for the triplet regimen (Yun 2010; Kim 2001; Tobe 1992). Most recently, Yun et al (Yun 2010) conducted a randomised phase II study which compared the anti-tumour activity and safety of doublet (CX) compared with triplet (ECX) chemotherapy as first-line regimens for patients with aGC in an attempt to align Asian and Western treatment practices. The results demonstrated that there were no significant differences in therapeutic efficacy between CX and ECX with respect to the primary endpoint of PFS (6.4 versus 6.5 months;

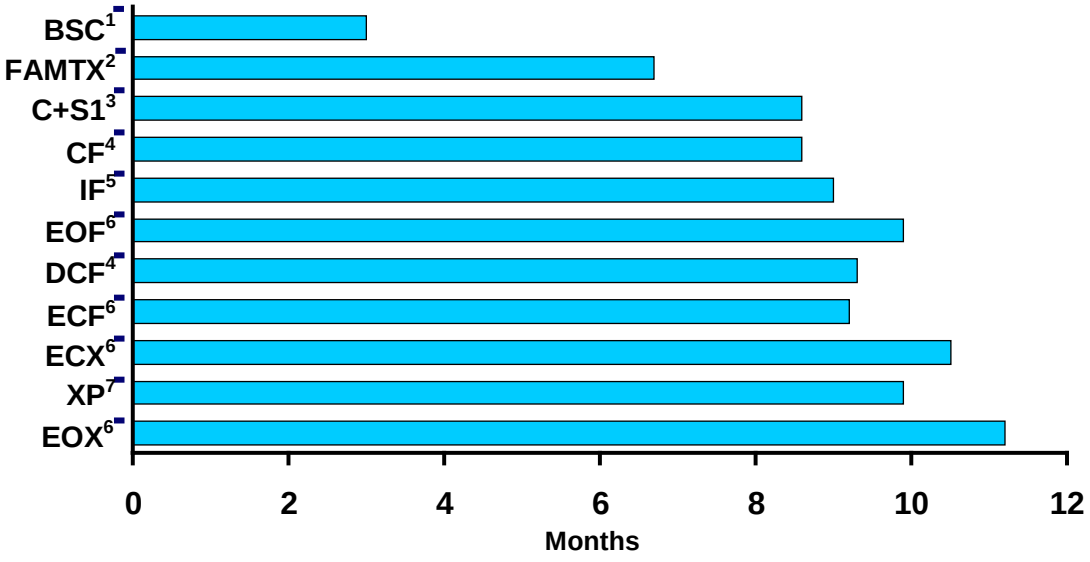
HR: 0.96, 95%CI: 0.58-1.57; p=0.863) and response rate (38% versus 37%, respectively). Notably, this trial wasn't added to the systematic review and meta-analysis by Wagner et al (Wagner 2005, 2006) when it was published as a reprint in 2009, presumably due to the unavailability of the data at that time. Yun et al 2010 concluded that both the CX and ECX regimens are active as first-line chemotherapy for aGC with comparable efficacy and acceptable safety profiles, casting further doubt of the contribution made by anthracyclines in the treatment of aGC. Given the comparable efficacy results, CX is a reasonable standard chemotherapy for untreated aGC patients.

Other recent data have demonstrated improved tolerability and patient convenience with the replacement of 5-FU by capecitabine in both doublet and triplet chemotherapy regimens (Cunningham 2008; Kang 2009).

Despite there being a clear benefit for palliative chemotherapy over BSC, survival of patients diagnosed with advanced or metastatic gastric cancer remains in the region of 7-11 months in the majority of clinical studies, irrespective of the chemotherapy regimen (doublet or triplet, with or without an anthracycline).

Given the lack of evidence to the contrary it is reasonable to assume that doublet and triplet chemotherapy regimens offer comparable efficacy in patients with aGC (Figure 4).

Figure 4: Median OS observed in trials of current therapies in aGC



BSC, best supportive care; FAMTX, methotrexate, 5-FU and doxorubicin; C+S1, cisplatin plus S1; CF, cisplatin plus 5-FU; IF, irinotecan plus 5-FU; EOF, epirubicin, oxaliplatin and 5-FU; DCF, docetaxel, cisplatin and 5-FU; ECF, epirubicin, cisplatin and 5-FU; ECX, epirubicin, cisplatin and Xeloda;

XP, Xeloda plus cisplatin; EOX, epirubicin, oxaliplatin and Xeloda;
X/FC, Xeloda or 5-FU plus cisplatin.

References:
1. Murad 1993.
2. Vanhoefer 2000.
3. Ajani 2009.
4. Van Cutsem 2006.
5. Dank 2008.
6. Cunningham 2008.
7. Kang 2009

Chemotherapy for advanced / metastatic gastric cancer in the UK

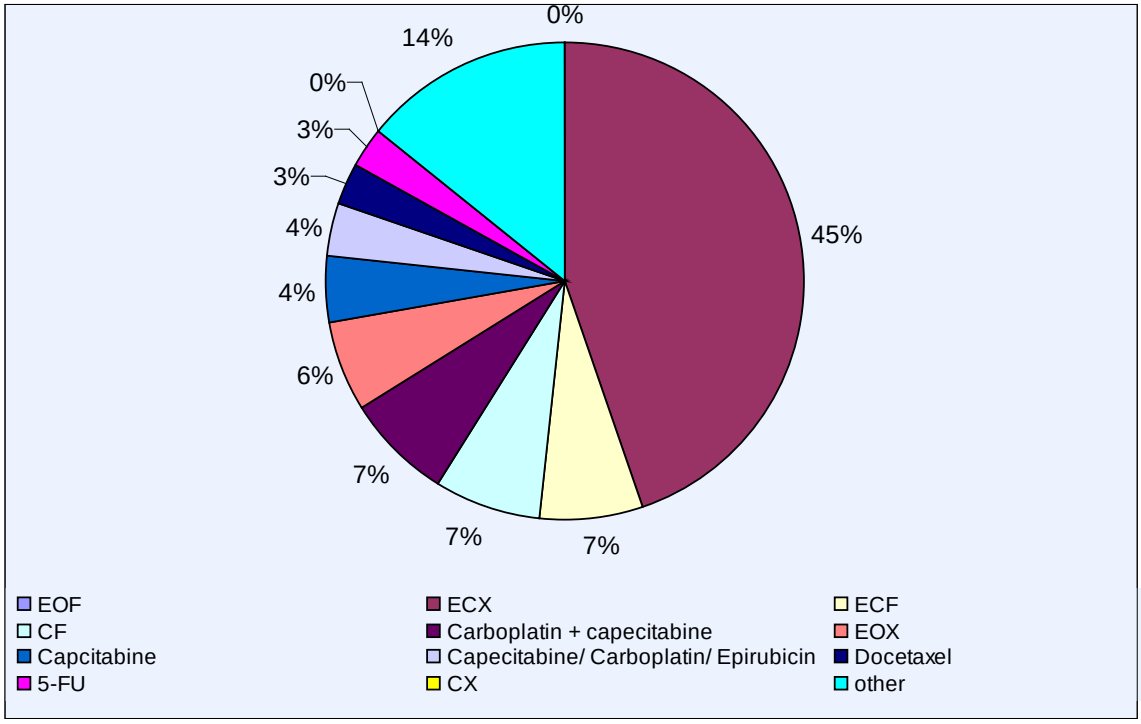
As mentioned previously, there is no internationally accepted standard regimen for the treatment of patients with advanced or metastatic gastric cancer and uncertainty remains regarding the choice of regimen, with parallel evolution of chemotherapy regimens in different geographic areas.

Until recently, ECF was the dominant chemotherapy for advanced and metastatic gastric cancer in the UK. ECF was devised by clinicians working at the Royal Marsden Hospital in London at a time when the role of palliative chemotherapy for advanced and metastatic gastric cancer was still gaining acceptance in the UK and many key UK treatment centres gained experience of it during a large investigator-initiated study comparing ECF versus FAMTX (a regimen of doxorubicin, 5-FU and high-dose methotrexate then used widely in North America. This study, published by Waters et al 1999 (Waters 1999), established ECF as the UK standard of care, a position that it maintained following completion of the REAL study (Ross 2002) in which epirubicin was substituted by mitomycin-c and until the publication of the REAL-2 study (Cunningham 2008). REAL-2 attempted to improve on ECF by making two changes – replacement of continuously infused 5-FU with oral capecitabine in the interests of greater convenience and patient acceptability and the potential for replacement of cisplatin with oxaliplatin. This second change was intended to further improve on the convenience of ECF by using a less toxic platinum derivative that does not require extensive patient hydration with large volumes of IV fluid around the time of administration.

Since, REAL-2 met its co-primary end-point of demonstrating that continuously infused 5-FU could be replaced with oral capecitabine without compromising tolerability or efficacy there has been widespread adoption of ECX in the UK, where, as shown in Figure 5, it now represents the most widely used chemotherapy regimen for advanced and metastatic gastric cancer. This rapid uptake is explained by the advantages to both patients and the NHS of oral over IV fluoropyrimidine therapy. Thus the series of trials which have shaped UK practice are uninformative about the importance of the anthracycline element. Although epirubicin is still a

widely used drug in the treatment of advanced and metastatic gastric cancer in the UK, there is no conclusive evidence of improved efficacy of existing triplet compared with doublet chemotherapy regimens in this setting.

Figure 5: UK market research based on sampled patient records September 2009



Abbreviations and synonyms: C, cisplatin; E, epirubicin; 5FU/ F, 5-FU X/Xeloda, capecitabine. Notes: The number of patient records sampled was 112. (see Appendix xxx for further details)

Recent developments

Apart from the move to oral fluoropyrimidines, the treatment of mGC has remained almost unchanged for a decade despite the clear need for improvement.

This could change as the biology of the disease is better understood and non-specific cytotoxic therapy is augmented by targeted therapies designed to interact with the specific abnormalities of gastric cancer cells. The first of these to be tested successfully in a large randomised phase III trial was trastuzumab, the anti-HER2 antibody already widely used in breast cancer. The recently reported ToGA study (Van Cutsem 2009a) forms the basis of this submission.

HER2 in gastric cancer

HER2 is a transmembrane protein involved in cell growth, differentiation and proliferation in normal cells but overexpression/amplification in breast or gastric tissue can lead to the development of tumours.

Based on the extensive screening programme that took place for the ToGA trial, the overall rate of HER2 positivity for patients with mGC, whose tumours overexpress high levels of HER2 (IHC2+/FISH+ or IHC3+), is 16.6% (Chung 2009).

HER2 is well established as a negative prognostic factor in breast cancer (Chia 2008; Tovey 2008; Joensuu 2003; Slamon 1987) and studies have shown a direct correlation between HER2 expression and poorer survival suggesting HER2 is also negative prognostic factor in gastric cancer (Uchino 1993; Mizutani 1993; Nakajima 1999; Allgayer 2000; Ross 2001; Tanner 2005; Charoin 2004), but there is conflicting evidence in the literature and other studies have failed to show this relationship (Ross 2001). What is clear is that the survival outcomes of patients whose tumours overexpress high levels of HER2 (IHC2+/FISH+ or IHC3+) are likely to be, at best, no better to current standard chemotherapy treatment than patients whose tumours express normal levels of HER2 (Van Cutsem 2009a). Although the prognostic significance of HER2 in mGC remains unclear, HER2 status is of predictive value, in terms of response to trastuzumab, in patients diagnosed with mGC (Van Cutsem 2009a).

4.2 What was the rationale for the development of the new technology?

As discussed in Section 4.1, the mainstay of treatment for patients diagnosed with mGC is chemotherapy. The advances in the treatment of mGC have been marginal over the past 10 years with the exception being the move to oral fluoropyrimidines, meaning prognosis for these patients remains poor, with median overall survival of less than 12 months (Figure 1).

The use of trastuzumab (in combination with chemotherapy) to block the HER2 pathway in breast cancer has significantly improved the prognosis of patients with metastatic disease (Smith 2001; Marty 2005) and is predicted to change the epidemiology of breast cancer (Weisgerber-Kriegl 2008) and it was anticipated that trastuzumab would also extend survival in mGC.

Preclinical investigations have demonstrated increased HER2 overexpression / gene amplification in gastric tumours (Sakai 1986; Yano 2004; Gravalos 2007) and the antitumour activity of trastuzumab in HER2-overexpressing gastric cancer xenograft models (Matsui 2005; Fujimoto-Ouchi 2007; Tanner 2005) thereby providing the rationale for investigating trastuzumab in the clinical setting in patients with mGC.

4.3 What is the principal mechanism of action of the technology?

HER2 (p185, HER2/neu, ErbB-2) is a 185 kDa tyrosine kinase receptor of the epidermal growth factor receptor (EGFR) family involved in the control of cell growth and proliferation. Trastuzumab is a monoclonal antibody that binds to the HER2 protein that is present in

excessive quantities on the surface of the cells making up some gastric and breast cancers with a number of consequences including:

- Activation of antibody-dependent cellular cytotoxicity (ADCC) that results in cell death
- Inhibition of cell proliferation by suppressing HER2-mediated signaling
- Inhibition of HER2-regulated angiogenesis
- Prevention of formation of the truncated HER2 [p95] receptor

Preclinical studies suggest that the mode of action of trastuzumab is the same across different HER2-overexpressing tumour types, including gastric cancer (Im 2002, Kono 2002).

Furthermore, trastuzumab in combination with chemotherapy has shown at least an additive effect in preclinical tumour models (Ouchi 2003; Kim 2008) suggesting that trastuzumab combined with chemotherapy can be active against HER2 amplified gastric cancer cells.

4.4 What is the suggested place for this technology with respect to treatments currently available for managing the disease/condition?

It is anticipated that in patients diagnosed with mGC whose tumours highly overexpress HER2 (IHC2+/FISH+ or IHC3+) trastuzumab will be added to standard doublet chemotherapy with capecitabine or 5-FU plus cisplatin.

4.5 Describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Diagnosis of HER2 positive mGC

Patients diagnosed with mGC will require the HER2 status of their tumour to be assessed in order to determine their eligibility for treatment with trastuzumab. Until now this has not been part of the routine diagnostic procedure. Implementation of validated HER2 testing of gastric tumours by trained personnel is required to ensure high-quality testing. The testing can be performed on tumour samples (biopsy or surgical) already taken as part of routine diagnosis and HER2 status determined using the same techniques and infrastructure that NHS laboratories employ to establish the HER2 status breast cancer tissue. Furthermore, existing quality control applied to breast cancer HER2 testing can be readily adopted and applied to HER2 testing for gastric cancer.

Immunohistochemistry (IHC) is recommended as the first testing modality with fluorescence in-siu hybridisation technique (FISH) being applied in equivocal IHC cases (IHC 2+) (Trastuzumab SmPC 2010).

Optimum chemotherapy regimen

As has been explained above there is little global consensus on the optimum chemotherapy regimen for mGC. Although ECX is widely used in the UK, the clinical data do not support increased efficacy of ECX over CX or ECF over CF (Tobe 1992; Kim 2001; Yun 2010) and there is no universal clinical agreement on the role of epirubicin in this setting (section 4.1).

4.6 Provide details of any relevant guidelines or protocols.

Current UK guidelines and protocols do not take into account the role of HER2 in gastric cancer or the increased survival benefits demonstrated by the addition of trastuzumab to chemotherapy, since their formulation/most recent revision pre-dates the availability of evidence from the ToGA trial, the RCT demonstrating its value.

The following healthcare Technology Appraisals are currently ongoing or due to commence shortly:

- NICE review of capecitabine for advanced gastric cancer.
- SMC review trastuzumab within its licensed indication in 2010.

The last revision of UK guidelines for the treatment and management of advanced / metastatic gastric cancer predates the publication of the ToGA study.

In the USA, the National Comprehensive Cancer Network (NCCN) has added the use of trastuzumab for the treatment of advanced/metastatic gastric cancer and for the treatment of localised advanced or advanced/metastatic oesophageal or gastro-oesophageal junction adenocarcinoma to the NCCN Drugs and Biologics Compendium (NCCN Oesophageal Cancer Clinical Practice Guidelines 2010a; NCCN Gastric Cancer Clinical Practice Guidelines 2010b). Drugs in the Compendium are recognised by the Centres for Medicare and Medicaid Services (CMS), as well as by some large US Health Plans.

The overall survival results of the ToGA trial have been included in the Italian Stomach Cancer Guidelines (AIOM 2009).

5 Equity and equality

The Institute considers equity in terms of how the effects of a health technology may deliver differential benefits across the population. Evidence relevant to equity considerations may also take a variety of forms and come from different sources. These may include general-population-generated utility weightings applied in health economic analyses, societal values elicited through social survey and other methods, research into technology uptake in population groups, evidence on differential treatment effects in population groups, and epidemiological evidence on risks or incidence of the condition in population groups. Evidence submitters are asked to consider whether the chosen decision problem could be impacted by the Institute's responsibility in this respect; including in considering subgroups and access to recommendations that use a clinical or biological criterion.

5.1 Identification of equity and equalities issues

Are there any issues relating to equity or equalities (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

No issues relating to equity or equalities have been identified.

How has the analysis addressed these issues?

Not applicable

6 Clinical evidence

Manufacturers and sponsors are required to submit a systematic review of the clinical evidence that relates directly to the decision problem. Systematic and explicit methods should be used to identify, select and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Where appropriate, statistical methods (meta-analysis) should be used to analyse and summarise the results of the included studies. The systematic review should be presented in accordance with the QUORUM statement checklist (www.consort-statement.org/QUOROM.pdf).
The systematic review is not required to be exhaustive (that is, it is not necessary to include all evidence relating to the use of the technology), but justification needs to be provided for the exclusion of any evidence. Where manufacturers have identified a study but do not have access to the level of detail required, this should be indicated.
The Institute has a strong preference for evidence from 'head-to-head' randomised controlled trials (RCTs) that directly compare the technology and the appropriate comparator(s). Wherever such evidence is available, and includes relevant outcome evidence, this is preferred over evidence obtained from other study designs. When head-to-head RCTs exist, evidence from mixed treatment comparison analyses may be presented if it is considered to add information that is not available from the head-to-head comparison. If data from head-to-head RCTs are not available, indirect treatment comparison methods should be used Formal assessments of heterogeneity should be included.

In the absence of valid RCT evidence, evidence from other study designs will be considered, with reference to the inherent limitation inferred by the study design. The Institute also recognises that RCT data are often limited to selected populations, short time spans and selected comparator treatments. Therefore good-quality observational studies may be submitted to supplement RCT data. Any potential bias arising from the design of the studies used in the assessment should be explored and documented.

6.1 Identification of studies

Describe the strategies used to retrieve relevant clinical data both from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in appendix 2, section 9.2.

Search strategy

Literature searching was carried out by an experienced information scientist working in the Medical Information Department of Roche Products Ltd as a trastuzumab product specialist. The following electronic databases were interrogated: Embase, Medline, Medline in Process, Embase Alert, Biosis (1993 to date and BIOL most recent update). A broad strategy was used to identify citations referring to human clinical trials, gastric cancer (and variants thereof) and trastuzumab (and variants thereof). Individual studies and meta-analyses were sought. The full search strategy is included in Appendix 2, Section 9.2

The Cochrane Library was interrogated via Wiley Interscience online at http://www.mrw.interscience.wiley.com/cochrane/cochrane_search_fs.html. A broad search strategy was used with a search carried out for any record containing the words “gastric” or “gastroesophageal”, and “trastuzumab” or “Herceptin” in the title or abstract body.

In addition abstracts from esteemed congresses were searched. Unless otherwise specified a broad search strategy was used with a search carried out for any abstract containing the words “gastric” or “gastroesophageal”, and “trastuzumab” or “Herceptin” in the title or abstract body. The following congresses were searched:

- the American Society of Clinical Oncology (ASCO) Annual Meeting for the years 2004-2009 were interrogated through the Journal of Clinical Oncology.
- the ASCO Gastrointestinal Cancers Symposium for the years 2007-2010 were interrogated via the ASCO website

(http://www.asco.org/ASCOv2/Meetings/Abstracts). A search was carried out for any abstract containing the word “trastuzumab” or “Herceptin” in the title.

- the European Society for Medical Oncology (ESMO) World Congress on Gastrointestinal Cancer for the years 2006-2009 were interrogated through the Annals of Oncology. A search was carried out for any abstract containing the word “trastuzumab” or “Herceptin” in the title or abstract body

- the ESMO Congresses for the years 2006 and 2008 were interrogated through the Annals of Oncology website

- Posters from the European CanCer Organisation (ECCO) 14 Congress 2007 were searched via http://www.posters2view.com/ecco14/welcome.php

- Abstracts from the joint ECCO 15 – 34th ESMO Multidisciplinary Congress 2009 were interrogated via the meetings website (http://ex2.excerptamedica.com/CIW-09ecco/)

The Roche internal “Publication Planning” database for Herceptin (trastuzumab) was also interrogated for citations relating to gastric cancer (though this did not identify any publications not already found using the external sources just described).

Clinical sections of the application to the EMEA for the extension of the Herceptin (trastuzumab) Marketing Authorisation to include aGC were reviewed for additional studies of relevance.

The outputs of literature searches were scrutinised by a single reviewer (Medical Manager at Roche Products Ltd, with 3 years experience of working with trastuzumab) to determine whether citations should be accepted or rejected and whether additional information was needed to do this (i.e. abstract or full text publication if not provided by the search). Where studies were selected for inclusion in this submission data extraction was done by the same individual responsible for scrutinising literature search outputs.

6.2 Study selection

6.2.1 Complete list of RCTs

Provide a list of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the assessors.

Where data from a single study have been drawn from more than one source (for example, a poster and a published report) and/or where trials are linked (for example, an open-label extension to an RCT), this should be made clear.

The ToGA trial

- Satoh T et al. Quality of life results from a phase III trial of trastuzumab plus chemotherapy in first-line HER2-positive advanced gastric and GE junction cancer. 2010 Gastrointestinal Cancers Symposium; 2010 January 22-24th; Orlando, Florida. Abstract 7 and Poster.

- Van Cutsem E et al. Trastuzumab added to standard chemotherapy (CT) as first-line treatment in human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer (GC): efficacy and safety results from the Phase III ToGA trial. ECCO 15 - 34th ESMO Multidisciplinary Congress; 2009 September 20-24th; Berlin, Germany. Abstract 7BA and Oral Presentation (Van Cutsem 2009b).

- Chung H et al. Human epidermal growth factor receptor 2 (HER2) in gastric cancer (GC): results of the ToGA trial screening programme and recommendations for HER2 testing. ECCO 15 - 34th ESMO Multidisciplinary Congress; 2009 September 20-24th; Berlin, Germany. Abstract PD-6511 and Poster.

- Bang Y et al. Trastuzumab with chemotherapy in untreated HER2-positive advanced or metastatic gastric cancer: Efficacy results from the ToGA trial. Annals of Oncology 2009; 20 (June Suppl): 7s, Abstract O-0015 and Oral Presentation (Bang 2009a).

- Bang Y et al. Pathological features of advanced gastric cancer (GC): Relationship to human epidermal growth factor receptor 2 (HER2) positivity in the global screening programme of the ToGA trial. J Clin Oncol 2009; 27 (May 20 Suppl.): 15s, Abstract 4556 and Poster (Bang 2009b).

- Van Cutsem E et al. Efficacy results from the ToGA trial: A phase III study of trastuzumab added to standard chemotherapy (CT) in first-line human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer (GC). J Clin Oncol 2009; 27 (May 20 Suppl.): 15s, Abstract LBA4509 and Oral Presentation (Van Cutsem 2009a).

6.2.2 Inclusion and exclusion criteria

State the inclusion and exclusion criteria that were used to identify the studies detailed in the list of relevant RCTs. If additional inclusion criteria were applied to select studies that have been included in the systematic review, these need to be listed separately.

Trials listed in Section 6.2.1 were excluded from the review if:-

Inclusion criteria

Records which evaluated the following were included:

1. Trastuzumab had to be the major focus of the study, in order to eliminate references which merely mentioned trastuzumab as part of a discussion of treatments for advanced/metastatic adenocarcinoma of stomach or gastro-oesophageal junction

2. Advanced/metastatic adenocarcinoma of the stomach or gastro-oesophageal junction had to be a major focus of the study, in order to eliminate papers addressing the use of trastuzumab in other types of cancers

3. Studies in which patients received trastuzumab therapy in combination with capecitabine or 5 fluorouracil and cisplatin, to be consistent with the trastuzumab licence.

4. Studies in which patients received study therapy for the first-line treatment of their disease, to be consistent with the trastuzumab licence.

5. Comparative efficacy and safety endpoints associated with the treatment of advanced/metastatic adenocarcinoma of the stomach or gastro-oesophageal junction were the focus for the data, i.e., PFS, OS, ORR, QoL, safety

Exclusion criteria

Records which evaluated the following were excluded:

1. Studies in which trastuzumab was administered in combination with chemotherapeutic agents other than capecitabine or 5 fluorouracil and cisplatin (as per licence) and/or in non-relevant populations, i.e. non first-line setting in advanced/metastatic disease

2. Animal studies or *in vitro* research – only human data are required

6.2.3 List of relevant RCTs

List all RCTs that compare the technology directly with the appropriate comparator(s) with reference to the specification of the decision problem. If there are none, state this.

Where studies have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. A flow diagram of the numbers of studies included and excluded at each stage should be provided at the end of section 5.2, as per the QUORUM statement flow diagram (www.consort-statement.org/QUOROM.pdf). The total number of studies in the QUORUM statement should equal the total number of studies listed in section 6.2.1.

Where data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or where trials are linked (for example, an open-label extension to an RCT), this should be made clear.

Applying the rules outlined in Section 6.2.2 had the following impact on the “Complete list of studies” identified in Section 6.2.1:

ToGA clinical trial – no impact so included in systematic review. Please see Section 6.2.1 for a complete list of ToGA clinical trial data sources

6.2.4 List of relevant non-randomised controlled trials

Provide details of any non-randomised controlled trials that are considered relevant to the decision problem. Provide justification for their inclusion.

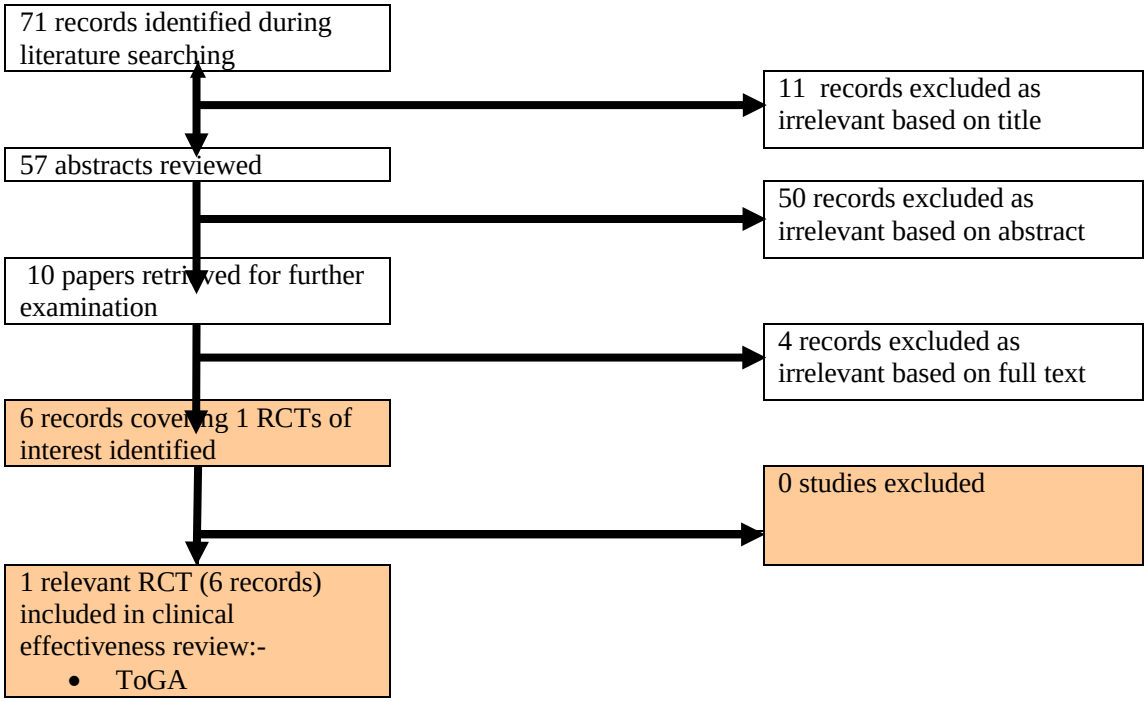
None identified

6.2.5 Ongoing studies

Provide details of relevant ongoing studies from which additional evidence is likely to be available in the next 12 months.

None known

Figure 6: QUORUM flow diagram of study selection process used in Roche's submission*



*Includes all records identified during literature searching except Roche internal documents (regulatory documents, trial protocols, DRAMs and CSRs) whose existence was already known and which were requested directly from the appropriate Roche personnel

6.3 Summary of methodology of relevant RCTs

As a minimum, the summary should include information on the following aspects of the RCT, but the list is not exhaustive. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (http://www.consort-statement.org/). The methodology should not be submitted in confidence without prior agreement with NICE. Where there is more than one RCT, the information should be tabulated.

6.3.1 Methods

Describe the RCT design (for example, duration, degree and method of blinding, and randomisation) and interventions.

CONSORT ITEM	TOGA
Scientific Background.	Approximately, 80% of patients diagnosed with gastric cancer have advanced or metastatic disease which is unresectable due to either locally advanced growth or metastatic spread (CRUK 2009c). For these patients, or patients recurring after surgery, the main therapeutic option is chemotherapy (De Vivo R 2000; Allum 2002).The efficacy of chemotherapy with palliative intent compared to best supportive care is widely accepted (Wagner 2005, 2006). However, despite clinical studies investigating different combination chemotherapy regimens, median overall survival remains less than 12 months; therefore there is a high unmet need to identify new treatments for patients diagnosed with metastatic gastric cancer. The human epidermal growth factor receptor, HER2, is a transmembrane glycoprotein with intrinsic tyrosine kinase activity. As discussed in section 4.2, HER2 is overexpressed in a proportion of gastric cancers (Sakai 1986; Yano 2004; Gravalos 2007) and preclinical data have demonstrated trastuzumab is active in this setting (Matsui 2005; Fujimoto-Ouchi 2007; Tanner 2005). Along with the strong precedent already set by trastuzumab in metastatic breast cancer (mBC), where a survival benefit was seen in phase III trials of trastuzumab in combination with chemotherapy in the first-line treatment of mBC, this provided the rationale for a randomised phase III trial of chemotherapy vs chemotherapy plus trastuzumab in HER2 positive mGC. Therefore, the ToGA trial was designed to investigate the efficacy and safety of adding trastuzumab to a reference chemotherapy regimen of CX versus the same chemotherapy alone in patients with HER2 positive mGC as first-line therapy.

Objectives	The overall purpose of this study was to compare the efficacy and safety of trastuzumab in combination with chemotherapy (HCX/F) versus chemotherapy alone (CX/F) as first-line therapy in patients with inoperable locally advanced or recurrent and/or metastatic HER2 positive adenocarcinoma of the stomach or gastro-oesophageal junction. **Primary objective** To show a significant difference in overall survival (OS) with HCX/F versus CX/F in the treatment of HER2 positive advanced or metastatic GC. **Secondary objectives** • Progression free survival (PFS), overall response rate (CR+PR), clinical benefit rate (CR+PR+SD), and duration of response in the two treatment arms. • Safety profile in the two treatment arms. • Quality of life in the two treatment arms. • Pain intensity, analgesic consumption, and weight gain/loss in the two treatment arms. • Pharmacokinetics of trastuzumab in gastric cancer and to compare with historic data in patients with metastatic and adjuvant breast cancer.
Interventions	Patients were randomly allocated on a 1:1 basis to one of the following chemotherapy regimens CX/CF (control arm) Each 3-weekly cycle, with chemotherapy given for 6 cycles: Capecitabine 1000 mg/m^2 oral twice daily for 14 days every 3 weeks *Or* 5-FU 800 mg/m^2/day i.v. infusion on days 1-5 *And* Cisplatin 80 mg/m^2 i.v. on day 1 **HCX/F (experimental arm)** Each 3-weekly cycle, with chemotherapy given for 6 cycles, and trastuzumab continued until disease progression: Trastuzumab 8 mg/kg i.v. loading dose on day 1, followed by 6 mg/kg i.v.infusion every 3 weeks Capecitabine 1000 mg/m^2 oral twice daily for 14 days every 3 weeks *Or* 5-FU 800 mg/m^2/day i.v. infusion on days 1-5 *And* Cisplatin 80 mg/m^2 i.v. on day 1 The fluoropyrimidine was chosen at the Investigator's discretion and could be determined on an individual patient basis (rather than decided upfront for each centre). 87% patients in each arm receive capecitabine.

Randomisation-generation	Roche, as sponsor produced the randomisation list, which was stratified by ECOG performance status, chemotherapy regimen, extent of disease, cancer site, and measurability of the disease.
Randomisation – concealment	This was an open-label study, neither investigators nor patients were blind to treatment allocation.
Randomisation-implementation	Clinphone (Nottingham, England) administered the randomisation through a telephone calling system using secure access codes. The investigator site was informed over the telephone at the time of individual patient enrollment what the treatment allocation was, and to which treatment arm the patient had been randomised.
Blinding	This was an open label study.

6.3.2 Participants

Provide details of the inclusion and exclusion criteria, and describe the patient characteristics at baseline. Highlight any differences between study groups.

Consort item	TOGA
Eligibility criteria	**Patient population** Patients with inoperable locally advanced or recurrent and/or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction, whose tumours are HER2 positive, and who have received no prior treatment for their advanced/metastatic disease. **Inclusion criteria** To be eligible for inclusion in the study, each patient had to fulfil all the following criteria: Disease specific inclusion criteria 1. Histologically confirmed adenocarcinoma of the stomach or gastro-oesophageal junction with inoperable locally advanced or recurrent and/or metastatic disease, not amenable to curative therapy. 2. Measurable disease, according to the Response Evaluation Criteria in Solid Tumors (RECIST), assessed using imaging techniques (CT or MRI), or non-measurable evaluable disease. 3. HER2 positive tumour (primary tumour or metastasis) as assessed by the central laboratory (IHC3+ or FISH+). 4. ECOG Performance status 0, 1 or 2 5. Life expectancy of at least 3 months. General inclusion criteria 6. Male or female. 7. Age ≥ 18 years. 8. Signed informed consent.

	Exclusion Criteria Any of the following excluded a patient from the study: Cancer-related exclusion criteria 1. Previous chemotherapy for advanced/metastatic disease (prior adjuvant/neoadjuvant therapy was allowed if at least 6 months had elapsed between completion of adjuvant/neoadjuvant therapy and enrolment into the study; adjuvant/neoadjuvant therapy with platin was not allowed). 2. Lack of physical integrity of the upper gastrointestinal tract or malabsorption syndrome (e.g. patients with partial or total gastrectomy could enter the study, but not those with a jejunostomy probe). 3. Patients with active (significant or uncontrolled) gastrointestinal bleeding. 4. Residual relevant toxicity resulting from previous therapy (with the exception of alopecia), e.g. neurological toxicity ≥ grade 2 NCI-CTCAE. 5. Other malignancy within the last 5 years, except for carcinoma *in situ* of the cervix, or basal cell carcinoma. Haematological, biochemical and organ function 6. Neutrophil count < 1.5 × 10^9/L, or platelet count < 100 × 10^9/L. 7. Serum bilirubin > 1.5 × upper limit of normal (ULN); or, AST or ALT > 2.5 × ULN (or > 5 × ULN in patients with liver metastases); or, alkaline phosphatase > 2.5 × ULN (or > 5 × ULN in patients with liver metastases, or > 10 × ULN in patients with bone but no liver metastases); or, albumin < 25 g/L. 8. Creatinine clearance < 60 mL/min. Other study drug-related exclusion criteria

	9. History of documented congestive heart failure; angina pectoris requiring medication; evidence of transmural myocardial infarction on ECG; poorly controlled hypertension (systolic BP > 180 mmHg or diastolic BP > 100 mmHg); clinically significant valvular heart disease; or high risk uncontrollable arrhythmias. 10. Baseline LVEF < 50% (measured by echocardiography or MUGA). 11. Patients with dyspnoea at rest due to complications of advanced malignancy or other disease, or who require supportive oxygen therapy. 12. Patients receiving chronic or high dose corticosteroid therapy. (Inhaled steroids and short courses of oral steroids for anti-emesis or as an appetite stimulant are allowed). 13. Clinically significant hearing abnormality. 14. Known dihydropyrimidine dehydrogenase (DPD) deficiency. General exclusion criteria 15. History or clinical evidence of brain metastases. 16. Serious uncontrolled systemic intercurrent illness, e.g. infections or poorly controlled diabetes. 17. Positive serum pregnancy test in women of childbearing potential. 18. Subjects with reproductive potential not willing to use an effective method of contraception. 19. Patients who had received any investigational drug treatment within 4 weeks of start of study treatment. 20. Radiotherapy within 4 weeks of start of study treatment (2 week interval allowed if palliative radiotherapy given to bone metastastic site peripherally and patient recovered from any acute toxicity). 21. Major surgery within 4 weeks of start of study treatment, without complete recovery. 22. Patients with known active infection with HIV, HBV, or HCV. Patients with known HIV, HBV or HCV positivity are not allowed to participate in the PK assessments (pertinent to all patients randomised to trastuzumab arm of study). **Patient characteristics at baseline** The above inclusion and exclusion criteria plus the randomisation process used produced two well-balanced patient treatment groups (see Table 5 below)

Table 5: Summary of patient demographics enrolled in the ToGA study

Characteristic	CX/F n=290	CX/F plus trastuzumab n=294
Sex, % Male / Female	75 / 25	77 / 23
Age, median (range) years	59.0 (21-82)	61.0 (23-83)
Weight, median (range) kg	60.3 (28-105)	61.5 (35-110)

Region, n (%)		
Asia	166 (56)	158 (53)
C/S America	26 (9)	27 (9)
Europe	95 (32)	99 (33)
Other	9 (3)	14 (5)
Type of GC (central assessment)		
Intestinal	74.2[a]	76.8 [b]
Diffuse	8.7[a]	8.9[b]
Mixed	17.1[a]	14.3[b]
Prior gastrectomy	21.4	24.1

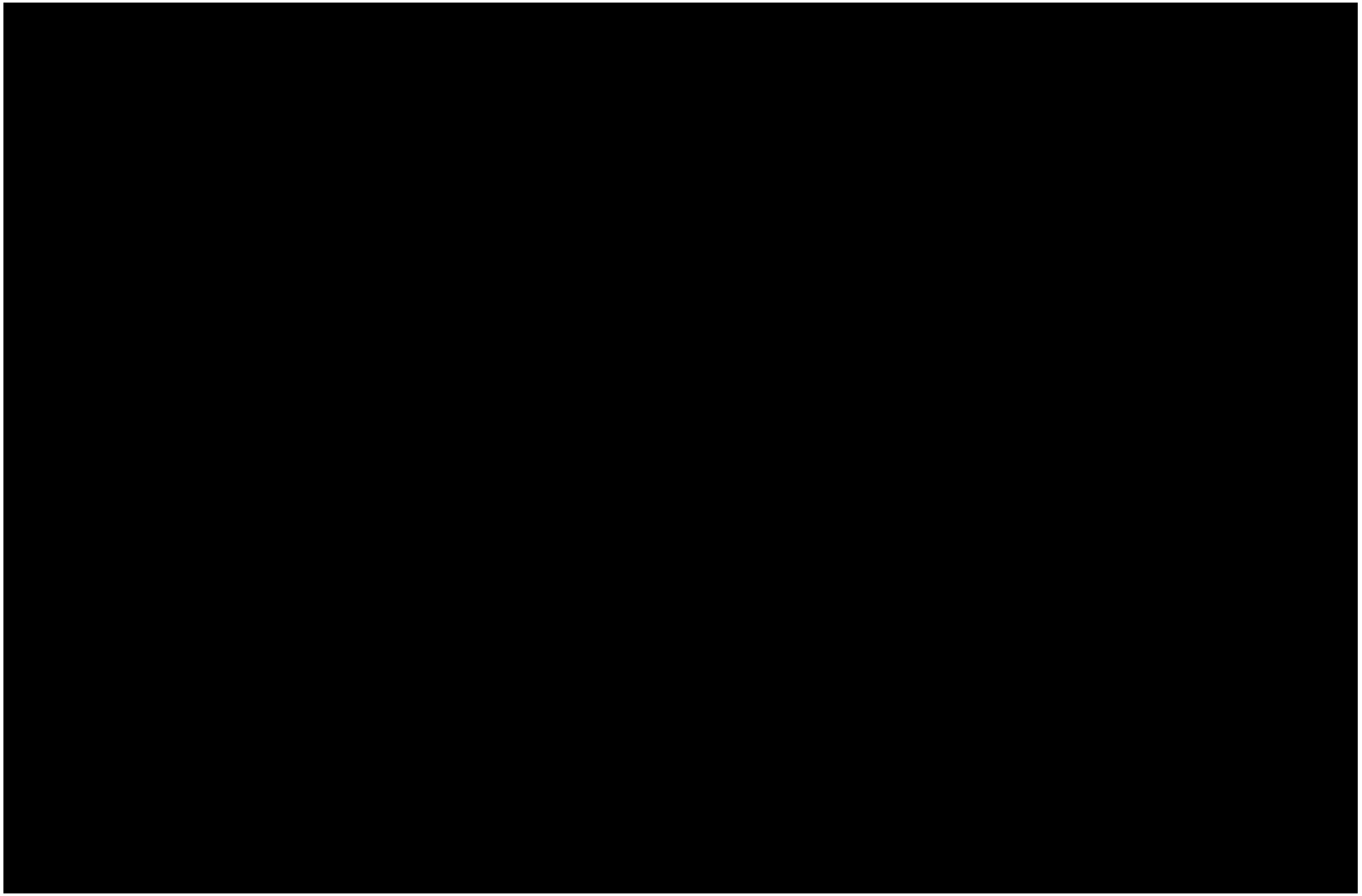
X/F, capecitabine/5-FU; C, cisplatin a[a]n=287; [b]n=293

6.3.3 Patient numbers

Provide details of the numbers of patients who were eligible to enter the RCT, randomised, and allocated to each treatment. Provide details of and the rationale for patients who crossed over treatment groups and/or were lost to follow up/ withdrew from the RCT. This information should be presented as a CONSORT flow chart.

CONSORT ITEM	TOGA
Sample Size	The sample size for the study was derived from the statistical hypothesis under test. The sample size calculation was based on the assumptions of 1 year survival of 30.5% with the CX/F regimen and 43.5% with the HCX/F regimen which corresponds to a median overall survival time of 7 months for the patients receiving CX/F and 10 months for the patients receiving HCX/F. It was estimated that recruitment of 187 patients per arm would allow a significant difference in OS to be demonstrated based 248 events (α-level of 0.05 and a power of 80%). The original protocol stated that an interim efficacy analysis would assess this assumption and the number of patients would be revised if required, to reach 248 events in a reasonable timeframe. Depending on the interim efficacy data, the maximum total number of patients would be up to 470. The sample size was increased following the recommendation of the IDMC. Based on the lower than expected event rate and the reported longer median survival for patients treated with capecitabine and cisplatin in another study (Kang 2009), the IDMC was of the opinion that with a sample size of 374 patients, the study was underpowered. In order to detect an intended difference of 3 months between the two arms and taking into account that the overall survival in the control arm could be as long as 10 months, the sample size calculation was based on the following assumptions: • A 1-year survival of 43.5% with the CX/F regimen and 52.7% with HCX/F regimen. This corresponded to a median OS of 10 months for the patients receiving CX/F and 13 months for the patients receiving HCX/F. • There was an exponential distribution of survival. The planned sample size for this study was 292 patients per treatment arm (α-level of 0.05 and a power of 80%) to show a significant difference with respect to the primary endpoint of overall survival.
Participant flow	See Figure 7 below
Recruitment	A total of 594 patients were randomized in the study at 122 centers in 24 countries between September 2005 and December 2008

Figure 7: Patient disposition in the TOGA study



6.3.4 Outcomes

Provide details of the outcomes investigated and the measures used to investigate those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the specification of the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of quality of life and social outcomes, and any arrangements to measure concordance. Data provided should be from prespecified outcomes rather than post-hoc analyses. Where appropriate, also provide details of the principal outcome measure(s), including details of length of follow-up, timing of assessments, scoring methods, evidence of reliability/validity, and current status of the measure (such as approval by professional bodies or licensing authority).

CONSORT ITEM	TOGA
Outcomes	**Primary study end-point** Significant difference in overall survival (OS; time from the date of randomisation to the date of the death) in patients receiving trastuzumab combined with fluoropyrimidine (5-FU or capecitabine) plus cisplatin compared with those receiving fluoropyrimidine (5-FU or capecitabine) plus cisplatin. **Secondary** • Progression-free survival (PFS; time between the day of randomisation and the first documentation of progressive disease or date of death, whichever occurs first) in patients receiving trastuzumab combined with fluoropyrimidine (5-FU or capecitabine) plus cisplatin compared with those receiving fluoropyrimidine (5-FU or capecitabine) plus cisplatin. • Overall response rate (CR+PR) • Clinical benefit rate (CR+PR+SD) • Duration of response • Safety profile • Quality of life using EORTC QLQ-C30 and gastric module ST022 • Assessment of pain intensity using visual analogue scale (VAS), analgesic consumption, assessment of weight gain/loss. • Utility assessment questionnaire (EQ-5D). • Pharmacokinetics of trastuzumab in gastric cancer and to compare with historic data in patients with metastatic and adjuvant breast cancer. • Pre-planned subgroup analysis investigating the interaction between treatment and HER2 status At the time of the clinical cut-off (January 7, 2009), the median duration of survival follow-up (calculated using a reverse Kaplan-Meier method) was 17.1 (range 0-31) months in the CX/F arm and 18.6 (range 1-34) months in the HCX/F arm. According to the IDMC charter, relevant tables and listings were supplied by a Roche statistician who was independent from the sponsor study team.

6.3.5 Statistical analysis and definition of study groups

State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for

example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were preplanned or post-hoc.

CONSORT ITEM	ToGA
Statistical methods	**Hypothesis to be tested** **Primary endpoint (Overall survival)** The null hypothesis to be tested was that the survival distribution of the overall survival time was the same in the two treatment groups (trastuzumab/fluoropyrimidine/cisplatin [HCX/] compared with fluoropyrimidine /cisplatin [CX/F]). The alternative hypothesis is that the survival distribution of the overall survival time is different in the two groups. If the hazard ratio of HCX/F versus CX/F with respect to OS is assumed to be constant (λ), then the null and alternative hypotheses to be tested are: H0: λ = 1 vs. H1: λ ≠ 1 This null hypothesis was be tested using a 2-tailed log-rank test; p-values and the estimated hazard ratio with the corresponding two-sided 95% confidence interval was to be reported. For the OS, the overall significance level was 5%. Based on the assumption that median overall survival is 7 months for patients in the fluoropyrimidine/cisplatin treatment arm and 10 months in the trastuzumab plus fluoropyrimidine /cisplatin arm (survival difference of 3 months), 248 deaths were needed to yield 80% power (p<=0.05). The total sample size was set at 374 patients (allowing for a 10% patient drop-out rate). The IDMC performed an interim safety review, on May 31, 2007. After a review of the number of events during this time, the IDMC reported overall median survival in excess of 12 months for the entire population in the trial which was considered longer than expected.

	Based on the lower than expected event rate and the reported longer median survival for patients treated with capecitabine and cisplatin in another study (Kang 2009), the IDMC was of the opinion that with a sample size of 374 patients, the study was underpowered and recommended an increase in the sample size to allow the detection of a difference in median overall survival between both treatment arms. In order to detect an intended difference of 3 months between the two arms and taking into account that the overall survival in the control arm could be as long as 10 months, the hazard ratio increased from 0.7 to 0.77. The amended protocol assumptions were median OS in the comparator arm of 10 months and 13 months in the experimental arm, the total sample size was increased to 584 patients and total number of events to 460 to allow the completion of the trial within a reasonable time frame. A planned interim efficacy and safety analysis was implemented after 50% events (230 events defined as death). The dataset provided to the IDMC for the interim analysis was based on 241 events. The IDMC considered the data insufficiently mature strongly recommended an additional interim analysis with the same outputs, after either: • 75% of events (345 events) OR • 18 weeks from the first treatment of the last patients randomised if this date occurred before 75% of events Following the recommendation of the IDMC, the protocol and statistical analysis plan were amended. The second interim efficacy and safety analysis was performed after 75% of events (348 events). Therefore, as the stopping boundaries were based on 345 events, they were adjusted accordingly to reflect the number of events (ie, 348 events). The boundary was adjusted to 0.0188 for this analysis and to 0.0437 for the final analysis.
Statistical methods	The statistical analysis was performed on the primary parameter OS (using the FAS population) and a log-rank test was used to compare the treatment groups. If the test was significant, the IDMC were to provide a recommendation for the study to be stopped and fully evaluated, data disclosed and the study amended if appropriate. If the test was not significant, the results of the interim analysis were not to be displayed and the study was to continue as planned. **Secondary parameters (time-to-event)** The primary focus is on the descriptive analysis in 6.3.4 above. However, if large treatment differences were seen then the hypothesis (H0: no treatment difference in hazard rate versus H1: there is a treatment difference in hazard rate) was to be tested on time to event endpoints by a two-sided log-rank test at the 5% significance level. This was to be only of an exploratory nature.

Statistical methods cont…	**Statistical methodology applied** The primary analysis carried out on the Per Protocol population (see definition below) used Cox regression stratified by geographic region and adjusted for prespecified prognostic factors. A secondary analysis was an unadjusted Cox regression stratified by geographic region. Equality of treatment effect, measured by HR CX/CF across subgroups of prespecified prognostic factors was tested using Cox regression. Survival functions were plotted using the Kaplan-Meier method. Overall response rates (ORRs) for CX and CF were compared with the Cochran Mantel Haenszel test stratified by geographic region. **Analysis populations** **Full analysis set (FAS, follows the intent-to-treat principle**) All randomised patients who received study medication at least once **Per protocol population (PP)** Randomised patients with major protocol violations were excluded from PP. The following randomised patients were considered non-evaluable for efficacy:: 1. Prior chemotherapy for advanced/metastatic disease as listed in the inclusion/exclusion criteria for the protocol. 2. No study medication received. 3. Incorrect medication received given randomisation. 4. Patients who failed to meet the tumour assessment criteria specified in the inclusion/exclusion criteria for the protocol. 5. Absence of documentation of over-expression/amplification of HER2 as specified in the protocol. 6. Baseline LVEF < 50%. 7. ECOG performance status > 2. The main analysis was defined as the analysis of the primary variable using the FAS. Supporting analyses of the primary efficacy variables were to be performed for the PP set. Other variables were to be analyzed for the FAS set. **Safety**. All randomised patients receiving study medication at least once. **Censoring** For both the primary and secondary endpoints, censored observations are taken into account in the analyses if no death is observed by the date of analysis and therefore no end date exists. The censoring date would be the last date of “last tumour measurement”, “last date in drug log”, or “last follow-up”.

6.3.6 Critical appraisal of relevant RCTs

The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study meeting the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. If there is more than one RCT, tabulate the responses, highlighting any ‘commercial in confidence’ data. The critical appraisal will be validated by the Evidence Review Group. The following are suggested criteria for critical appraisal, but the list is not exhaustive.

- How was allocation concealed?
- What randomisation technique was used?
- Was a justification of the sample size provided?
- Was follow-up adequate?

- Were the individuals undertaking the outcomes assessment aware of allocation?
- Was the design parallel-group or crossover? Indicate for each crossover trial whether a carry-over effect is likely.
- Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?
- How do the included in the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.
- For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?
- Were the study groups comparable?
- Were the statistical analyses used appropriate?
- Was an intention-to-treat analysis undertaken?
- Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?

	ToGA
How was allocation concealed?	This was an open-label study
What randomisation technique was used?	Robust – using a central IVRS system
Was justification of sample size given?	Yes. Sample size was based on a statistical assessment of likely and meaningful outcomes including reasonable assumptions on outcomes in the control arm.
Was follow-up adequate?	Yes. At the time of the clinical cut-off (January 7, 2009), the median duration of survival follow-up was 17.1 months in the CX/F arm and 18.6 months in the HCX/F arm. This is more than the median OS in the patient group in question. As an overwhelming difference was observed between the two arms as a result of this analysis (75% events / 345 deaths occurred), the IDMC made the decision to stop the trial and report the results.

Were the individuals undertaking assessment aware of allocation?	Yes – see comment above on blinding. However, the primary end-point in this study – OS - is not amenable to observer bias. The interim efficacy analysis was performed by an independent Roche statistician not involved in the study and reviewed by the IDMC.
Was the design parallel group or cross-over?	Parallel-group. Minimal cross-over/carry-over are likely. Second-line treatment is uncommon in this condition. Only 1% patients in each arm received second-line treatment with anti-HER2 therapy.
Was the study conducted in the UK?	Yes – it was a multinational study conducted at approximately 120 centres, in a number of countries, including the UK.
How do the patients in the study reflect those seen in clinical practice?	The most obvious difference is in their ethnicity – because of the countries where the study was conducted, just over 50% of patients were from Asian countries, whereas Caucasians clearly make up the majority of UK patients. Although there were more males than females in the study, this is reflected in UK clinical practice as more males than females are diagnosed with stomach cancer (CRUK 2009a) and approximately 80% of the patients recruited into each arm of the REAL-2 study were male (Cunningham 2008). Previous trials investigating novel chemotherapy agents / regimens in patients with advanced / metastatic gastric cancer did not select for HER2 status – prior to the development of trastuzumab as a HER2-directed therapy in this disease as there was no clinical significance and as such not part of routine diagnostic assessment. Therefore, it is not known how patients with HER2 positive tumours perform in response to the various chemotherapy regimens under investigation versus their HER2 negative counterparts.
Do dosage regimens used reflect those in the product SMPC?	Yes. The regulatory approval for trastuzumab in gastric cancer was based on this trial and the dosage recommendations in the trastuzumab SmPC (January 2010) reflect the trial treatment

Were the study groups comparable?	Yes, Patient characteristics were well balanced between the two arms in both the FAS population(Table 5) [redacted]
Were the statistical analyses appropriate?	Yes. They were carried out according to a prospective statistical plan prepared with statistician input. The protocol defined a subgroup analysis of interaction between treatment with trastuzumab and HER2 status in terms of the level of HER2 protein overexpression (IHC 0, 1+, 2+, 3+). This analysis was appropriate as HER2 expression is the target for trastuzumab therapy. The results of the pre-planned HER2 subgroup analysis triggered the additional exploratory analyses in an attempt to investigate the patient subgroup who had the greatest benefit from treatment in terms of OS and PFS. The results of the exploratory analyses are presented in section 6.4 below and represent the population on which the EU license was granted by the EMEA.
Was an ITT approach taken to efficacy analysis?	Yes as defined in the protocol for the primary endpoint of OS.
Were there other confounding factors?	No

6.4 Results of the relevant comparative RCTs

Provide the results for all relevant outcome measure(s) pertinent to the decision problem. If there is more than one RCT, tabulate the responses, highlighting any 'commercial in confidence' data. The information may be presented graphically to supplement text and tabulated data. Data from intention-to-treat analyses should be presented wherever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given.

For each outcome for each included RCT the following information should be provided.

- The unit of measurement.

- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
- A 95% confidence interval.
- The number of patients included in the analysis.
- The median follow-up time of analysis
- State whether intention-to-treat was used for the analysis and how data were imputed if necessary.
- Discuss and justify definitions of any clinically important differences.
- Where interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.
- If the RCT measures a number of outcomes, discuss whether and how an adjustment was made for multiple comparisons in the analysis.
- Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.

6.4.1 Patient population for trastuzumab in mGC

6.4.1.1 EMEA approved license population (IHC2+/FISH+ or IHC3+)

The EMEA approved license population is defined as patients with metastatic adenocarcinoma of the stomach or GOJ (mGC) whose tumours have HER2 overexpression as defined by an IHC2+ score and a confirmatory FISH+ result, or IHC 3+ (Trastuzumab SmPC 2010) and represents the subgroup of patients relevant to this Technology Appraisal. This represents the primary population of interest for the purpose of evaluating the clinical effectiveness of trastuzumab.

6.4.1.2 ToGA trial population (FAS IHC3+ or FISH+)

When the ToGA trial was initiated, less was known about HER2 and as a result patients tumour samples were centrally tested by both IHC and FISH with a score of IHC3+ or FISH+ considered HER2-positive and eligible for entry into the ToGA trial.

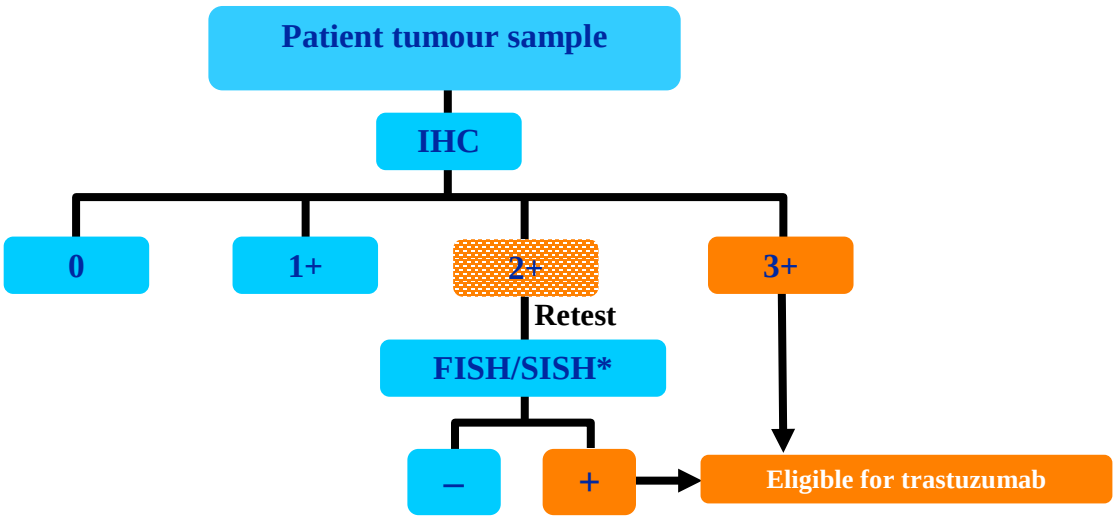
6.4.1.3 Rationale for change in definition of HER2 positivity

The definition of HER2 positivity as defined in the inclusion criteria of the ToGA trial (IHC3+ or FISH+) was in accordance with knowledge of HER2 at the time the ToGA trial was initiated and the ASCO-CAP guidelines pulished in 2007 (Wolff 2007). However, based on a greater understanding of HER2 and testing procedures gained more recently in the breast cancer setting (Dowsett 2007; Hanna 2007; Walker 2008; Albanell 2009), whilst the ToGA trial was ongoing, and the clinical outcomes of the trial (Hoffmann 2008; Van Cutsem 2009a) the gastric cancer HER2 testing algorithm was refined to define HER2 positivity as either IHC2+/FISH+ or IHC3+ (Van Cutsem 2009; Chung 2009 (Figure 8 below). This led to the

exploratory analysis in the IHC2+/FISH+ and IHC3+ subgroup which represents the license population for trastuzumb in mGC. Therefore, the specific subgroup of patients who gain the greatest benefit from trastuzumab is clearly defined by the EMEA license and easily identifiable through existing HER2 testing techniques and as such avoids unnecessary treatment of patients who are unlikely to respond.

The efficacy results of the EMEA approved license population which are of relevance to this Technology Appraisal are reported below. The results on the Full Analysis Set (FAS) are included for completeness in Appendix C1.

Figure 8: HER2 testing algorithm for mGC



Results of the ToGA trial

6.4.2 Patient disposition

The FAS population comprised all patients who were randomised in the study and received study medication at least once. Of 594 patients recruited to the study, 296 patients were randomiszed to the CX/F arm and 298 patients to the HCX/F arm. A total of 10 patients (6 patients in CX/F, 4 patients in HCX/F) were excluded from the analysis because they did not receive any study medication. Thus, the primary efficacy population (FAS) consisted of 584 patients (290 patients in CX/F, 294 patients in HCX/F). Patient disposition is summarized in Figure 5 for all randomised patients.

There were a total of 446 patients in the EMEA licensed high HER2 expressing subgroup (IHC2+/FISH+ or IHC3+), 218 patients in the CX/F arm and 228 patients in the HCX/F arm. Two patients in the CX/F arm and five patients in the HCX/F arm had no IHC score recorded and were therefore not included in either of these subgroups.

6.4.3 Duration of follow-up

At the time of the clinical cut-off (January 7, 2009), the median duration of survival follow-up (calculated using a reverse Kaplan-Meier method) was 17.1 (range 0-31) months in the CX/F arm and 18.6 (range 1-34) months in the HCX/F arm.

6.4.4 Censoring

For both the primary and secondary endpoints, censored observations were taken into account in the analyses if no death was observed by the date of analysis and therefore no end date existed. The censoring date was the last date of “last tumour measurement”, “last date in drug log”, or “last follow-up”.

6.4.5 Primary endpoint: Superiority of OS (FAS population: IHC3+ or FISH+)

The analyses reported are based on the pre-planned second interim analysis after 75% events (345 deaths) had occurred. The second interim analysis was performed with the possibility to consider stopping the trial if an overwhelming difference was seen between the two treatment arms. The IDMC concluded the trial had crossed the statistical boundary and the study was positive and therefore the second interim analysis was considered as the definitive analysis for this study.

The efficacy data for the FAS population (IHC3+ or FISH+) is included here to illustrate that the ToGA trial met its primary endpoint of demonstrating a significant improvement in OS in patients receiving HCX/F compared with CX/F chemotherapy alone using Kaplan-Meier estimates and Cox regression analyses.

In the FAS population, the hazard ratio for HCX/F versus CX/F was 0.74 (95% CI 0.60-0.91). This indicates a 26% reduction in the risk of death for patients treated with HCX/F compared with CX/F based on the non-stratified analysis (two-sided Log-Rank test) of OS. The results demonstrated that the addition of trastuzumab to CX/F provided a clinically relevant and statistically significant improvement (P=0.0046) in the primary endpoint of OS (median 11.1 months vs 13.8 months) compared to CX/F alone (see Figure 9 below). Given the current understanding of the patients who benefit from trastuzumab in this setting (as described above) the results for the EMEA approved license population are presented below as they reflect the subgroup of patients who gain the greatest benefit from the addition trastuzumab to chemotherapy (IHC2+/FISH+ and IHC3+). [redacted]

For further information on the efficacy data reported for the FAS population please refer to Appendix C1.

6.4.6 Rationale for EMEA licensed population: IHC2+/FISH+ or IHC3+

It was anticipated that by applying the refined gastric cancer HER2 testing algorithm to the ToGA trial population (FAS; IHC3+ or FISH+) it would be possible to identify the specific subgroup of patients who gain the greatest benefit from trastuzumab and thereby avoiding unnecessary treatment of patients who are unlikely to respond.

Two new subgroups were defined based on IHC scoring, ie. the level of HER2 protein expression on the cell surface as this is the target for trastuzumab (if not otherwise indicated all patients were FISH positive):

- Group 1 ("low HER2 expressing group"): IHC 0/FISH+ and IHC 1+/FISH+ (no or very low levels of HER2 protein could be detected by IHC). This group consisted of 70 patients in CX/F, 61 patients in HCX/F

- Group 2 ("high HER2 expressing group"): IHC 2+/FISH+ and IHC 3+ including IHC 3+/FISH negative or IHC 3+/FISH no result (medium to high levels of HER2 protein expressed on the tumour cell surface). This group consisted of 218 patients in CX/F, 228 patients in HCX/F (EMEA license population)

[redacted]

[redacted]x

Table 6: Summary of patients demographic characteristics (high HER2 expressing group)

[redacted]

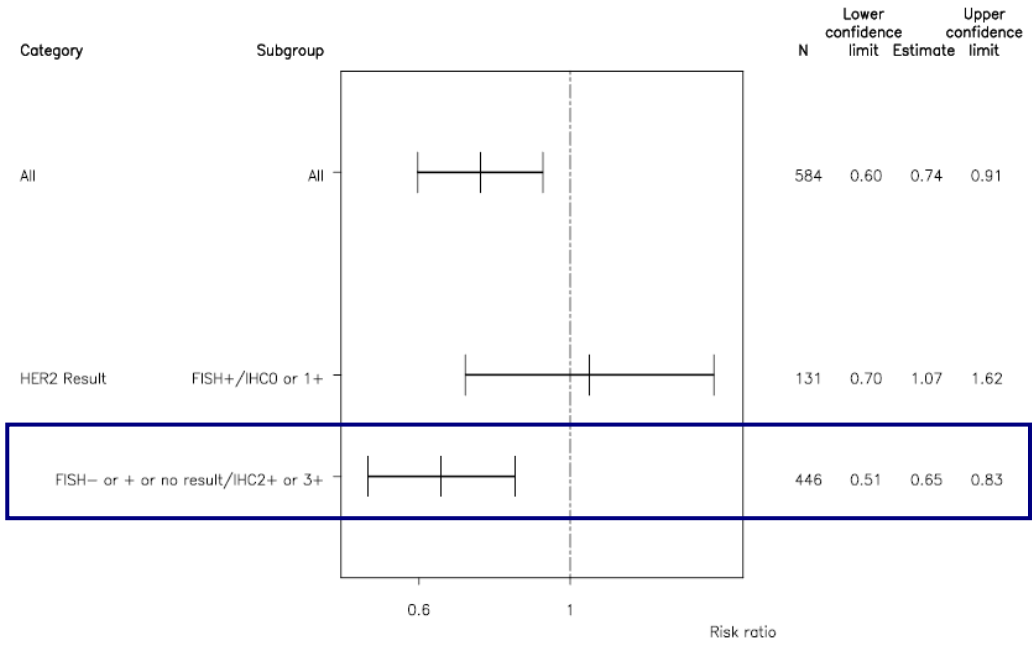
[redacted]

6.4.7: Results for EMEA license population (IHC2+/FISH+ or IHC3+)

6.4.7.1: OS (IHC2+/FISH+ or IHC3+)

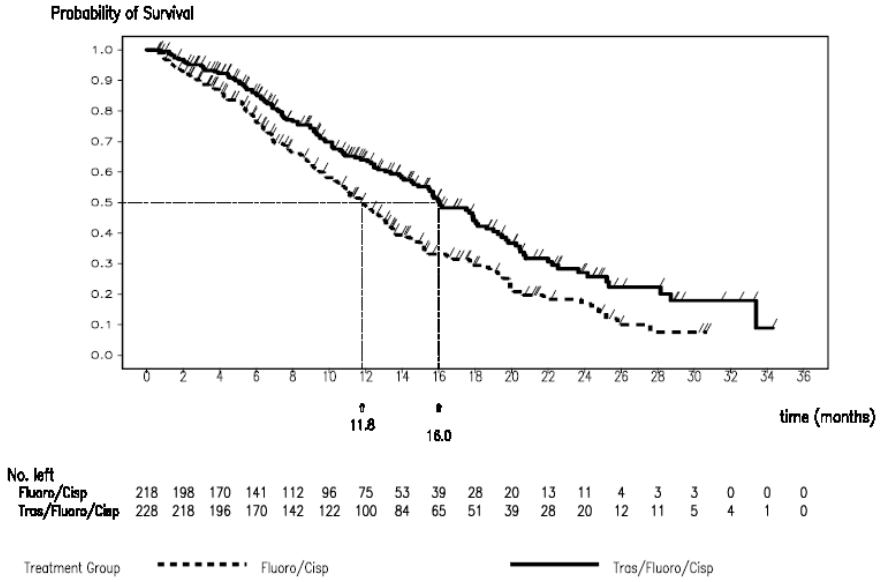
A [redacted] difference was seen between the high and low HER2 expressing subgroups with regard to OS (limited treatment effect observed in the low HER2 expressing subgroup (Figure 9). [redacted]

Figure 9: Forest plot of hazard ratios for overall survival by HER2 status: FAS (IHC3+ and FISH+) vs low HER2 expressors (FISH+/IHC 0 or IHC 1+) versus EMEA license high HER2 expressors (IHC 3+ or IHC 2+/FISH+)



The median survival time for the high HER2 expressing subgroup (Group 2 above, EMEA license population) was 11.8 months for patients in the chemotherapy alone arm versus 16 months in the trastuzumab plus chemotherapy arm, representing a significant 4.2 month increase in median OS with the addition of trastuzumab to chemotherapy (HR of 0.65; 95% CI 0.51-0.83; [redacted] (Figure 10). [redacted]

Figure 10: Kaplan-meier curve of OS (high HER2 expressing group)



Fluoropyrimidine: Investigator preference of Capecitabine or 5-FU
Tras/Fluoro/Cisp: Trastuzumab/Fluoropyrimidine/Cisplatin
Fluoro/Cisp: Fluoropyrimidine/Cisplatin

[redacted]

[redacted]

6.4.7.2: PFS (IHC2+/FISH+ or IHC3+)

[redacted]

In the high HER2 expressing subgroup, there was a [redacted] 2.1 month improvement in median PFS; the median PFS increased from 5.5 months in the CX/F arm to 7.6 months in the HCX/F arm (HR 0.64; 95% CI [0.51-0.79];[redacted]

[redacted]

Figure 11: [redacted]

[redacted]

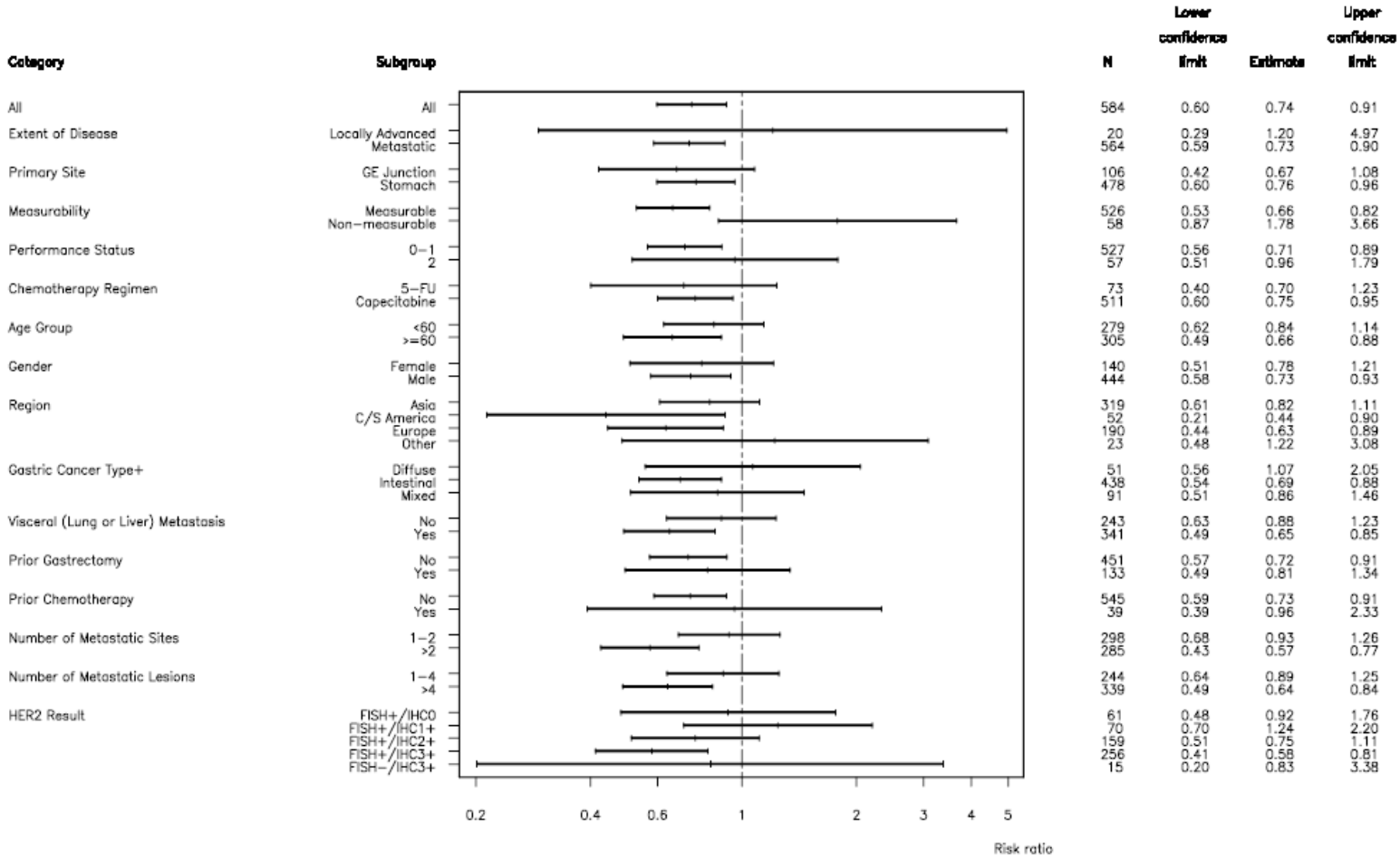
Other secondary efficacy endpoints (TTP, ORR, CBR, and DoR) in this study are reported for the FAS population only. All demonstrated clinical significance for the addition of trastuzumab to CX/F chemotherapy with similar hazard ratios and and can be found in Appendix C1. There is no reason to assume similar benefits in these secondary endpoints would not be observed in the EMEA approved population given the OS and PFS results.

6.4.7 Preplanned subgroup efficacy analyses

The preplanned subgroup analyses illustrated below are only reported for the FAS (IHC3+ or FISH+) population but there is no reason to assume the results would not be similar for the high HER2 expressors given they comprised over 76% of the FAS population.

Overall, the risk of death was reduced in the HCX/F arm compared to the CX/F arm in almost all of the subgroups analyzed (Figure 12).

Figure 12: Forest plot of hazard ratios for overall survival by subgroup (FAS)



+ assessed by central laboratory; GE=Gastroesophageal; Fluoropyrimidine: Investigator preference of capecitabine or 5-FU; GE=Gastroesophageal ; + assessed by central laboratory

6.4.8 Quality of life in the ToGA study

Quality of Life (QoL) was assessed in the two treatment arms as a secondary objective of the ToGA study using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 (Global Health Status, Functioning and Symptom) and QLQ-ST022 (assesses treatment induced changes over time). The QLQ-ST022 module contains 22 items regarding dysphagia, pain, reflux, eating restrictions, anxiety, dry mouth, body image, and hair loss. Results are reported below for the FAS (IHC3+ or FISH+) population but there is no reason to believe the outcomes would differ for the EMEA approved subgroup which comprised approximately 76% of the FAS.

QoL was assessed on day 1 prior to the first dose of study drug and then every three weeks (on day 1 of each cycle prior to dosing) until disease progression. The analysis was based on patients who completed the questionnaire in the FAS population, and patient compliance was high in both arms throughout the study (around 90% in both arms) (Satoh 2010).

The results of both the EORTC QLQ-C30 and QLQ-ST022 instruments demonstrate that over time patients QoL improved in both study arms and this was sustained after completion of chemotherapy (Satoh 2010). This was not only in terms of the Global Health Status (Figure 13) of the patients but also in their appraisal of their current level of functioning (physical, role, emotional, cognitive, and social (Figure 14) and the symptoms they were experiencing (Figure 15). Pain scores and analgesic use were similar in both arms (Satoh 2010).

Figure 13: Global health status score, QOL over time (mean +/- SEM)

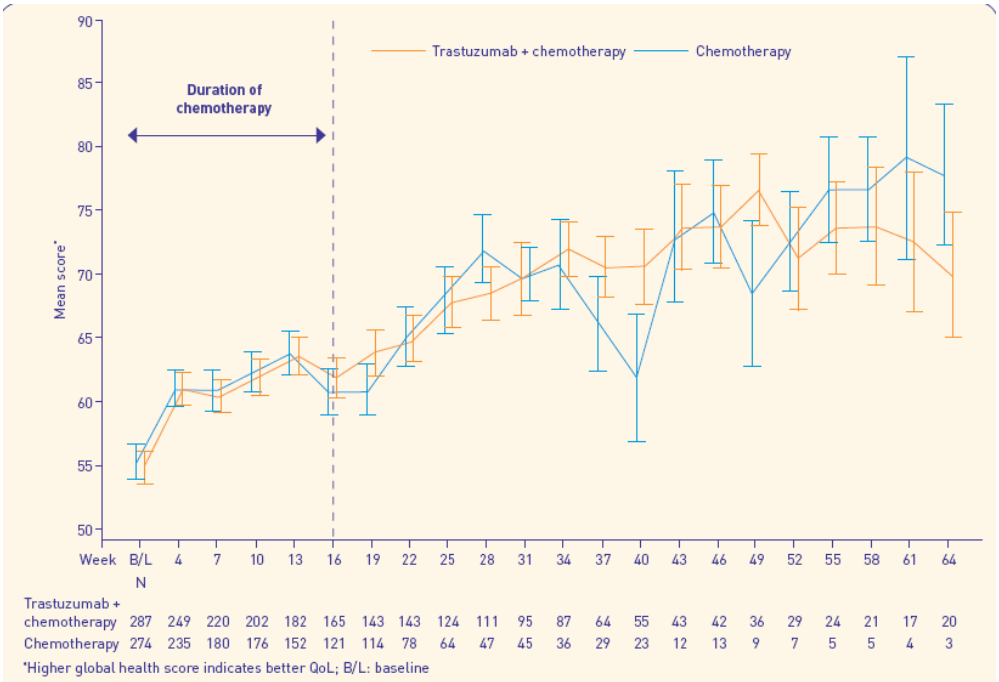


Figure 14: Physical functioning score over time (mean +/- SEM)

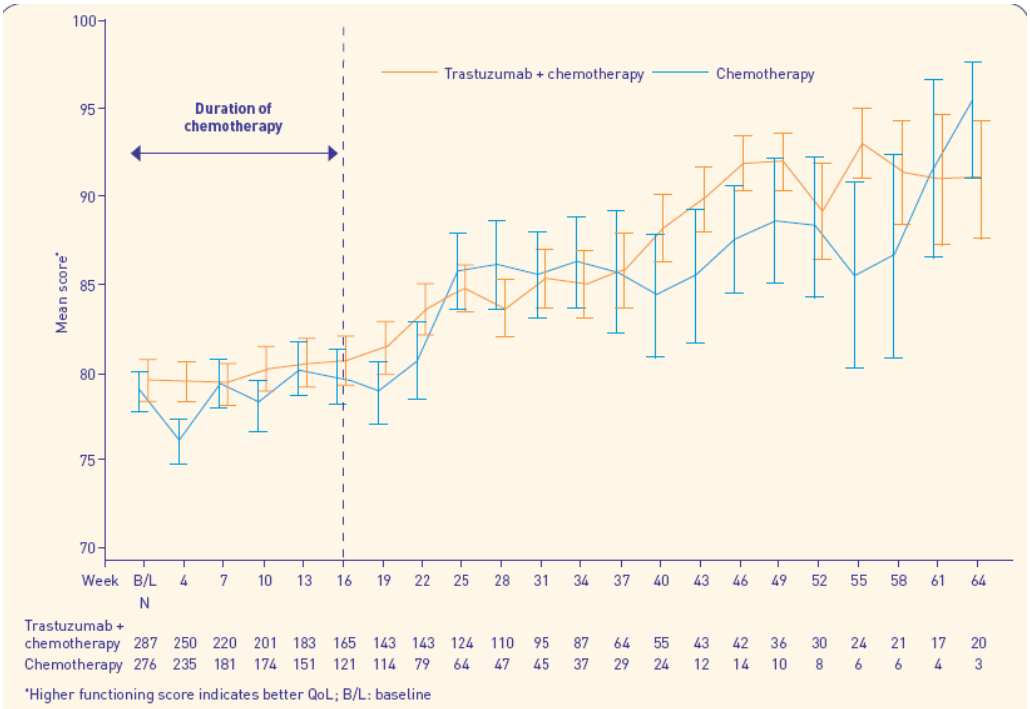
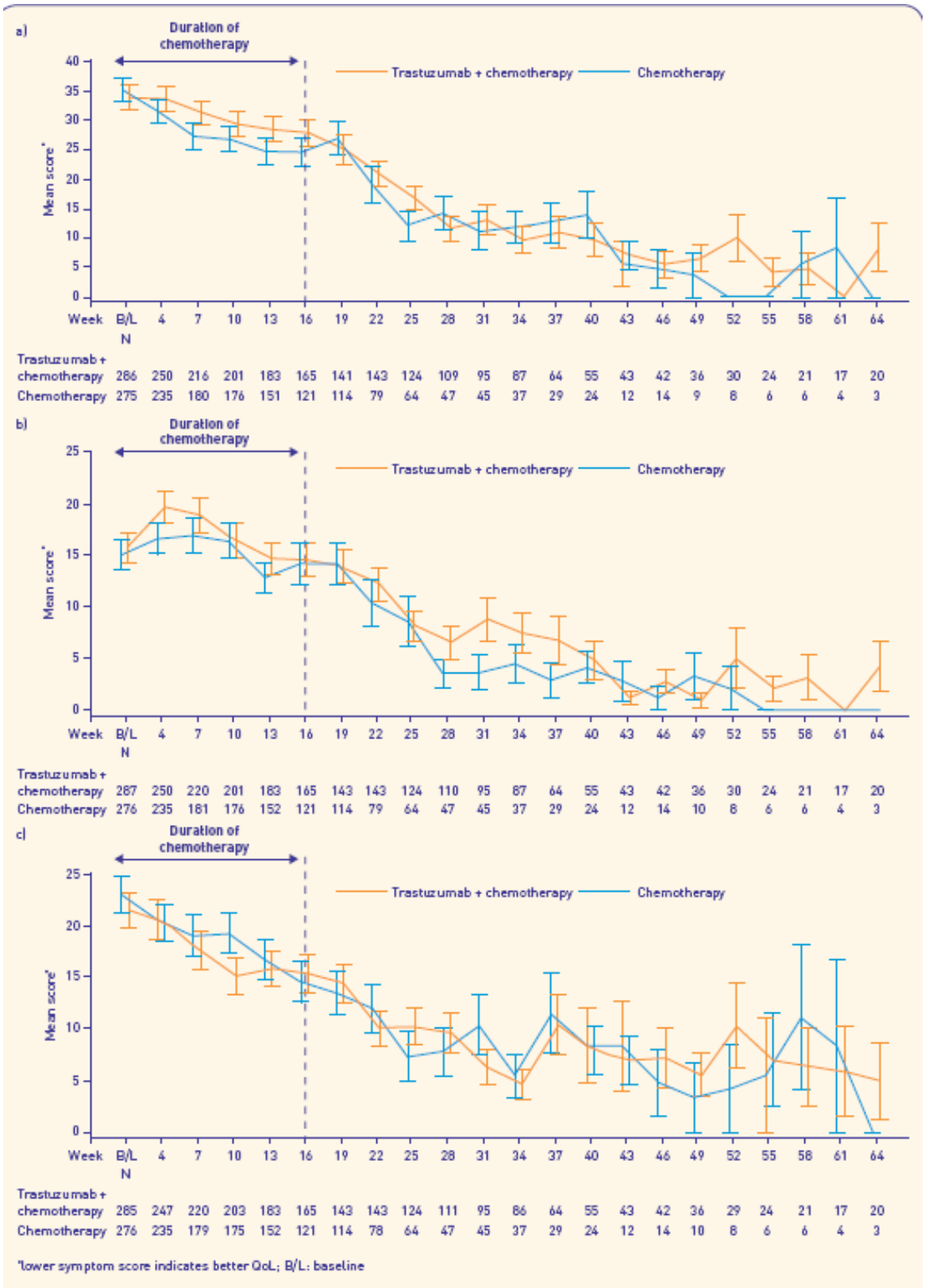


Figure 15: Symptom scores over time (a) appetite loss, (b) nausea/vomiting and (c) constipation (mean +/- SEM)



The fact that QoL improves in both arms and continues to improve beyond the administration of chemotherapy may be explained by the symptomatic response to treatment such as patients regaining the ability to eat.

This is supported by the outcome of the disease-specific score results (EORTC QLQ-ST022) which suggest improvements in disease and treatment-related symptoms - dysphagia, reflux symptoms and eating restrictions in both arms (Satoh 2010).

The improvements in global QoL outcomes demonstrate the value of systemic treatment with patients experiencing benefits in terms of relief from cancer-related symptoms during chemotherapy treatment which increase after treatment is complete and are maintained.

Furthermore, the results of the QoL questionnaires demonstrate that the addition of trastuzumab to chemotherapy and continuation of trastuzumab to disease progression does not have detrimental effect on patients QoL. Importantly, QoL data were only collected up to the point of PFS in both arms of the ToGA study (Satoh 2010). Based on the fact that QoL improved to a similar extent in both arms of the trial, it is reasonable to suppose that most of the QoL benefit of treatment is associated with response/stabilization of disease. This means that for the period of time treatment keeps the patient progression free, their QoL will mirror that of any other treatment that keeps them progression free – hence no difference for the two study arms in terms of average scores. However, as more patients were progression free at each time point for the trastuzumab plus chemotherapy group compared with the chemotherapy alone group, patients receiving trastuzumab should continue to experience QoL gains for a greater period of time.

NB. In addition, EQ-5D data were collected as part of the ToGA trial, please refer to the economic section for further details.

6.5 Meta-analysis

Where more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. If a meta-analysis is not considered appropriate, the rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal. If any of the relevant RCTs listed in response to section 0 are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored. The following steps should be used as a minimum.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis where appropriate.
- Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

The ToGA trial represents the only randomised clinical trial of trastuzumab in patients with HER2 positive mGC.

6.6 Indirect/mixed treatment comparisons

Data from head-to-head RCTs should be presented in the reference-case analysis, if available. If data from head-to-head RCTs are not available, indirect treatment comparison methods should be used.
An 'indirect comparison' refers to the synthesis of data from trials in which the technologies of interest have not been compared in head-to-head trials, but have been compared indirectly using data from a network of trials that compare the technologies with other interventions.
When head-to-head RCTs exist, evidence from mixed treatment comparison analyses may be presented if it is considered to add information that is not available from the head-to-head comparison. A 'mixed treatment comparison' refers to an analysis that includes trials that compare the interventions of interest head-to-head and trials that compare them indirectly. This mixed treatment comparison must be fully described and presented as additional to the reference-case analysis (a 'mixed treatment comparison' includes trials that compare the interventions head-to-head and indirectly).
When multiple technologies are being appraised that have not been compared within a single RCT, data from a series of pairwise head-to-head RCTs should be presented. Consideration should also be given to presenting a combined analysis using a mixed treatment comparison framework if it is considered to add information that is not available from the head-to-head comparison.
The principles of good practice for standard meta-analyses should also be followed in mixed and indirect treatment comparisons.

- When evidence is combined using indirect or mixed treatment comparison frameworks, trial randomisation must be preserved. Where this is not possible the data should be treated as observational.
- Provide a clear description of the methods of synthesis
- Provide a rationale for the identification and selection of the RCTs, including the rationale for the selection of treatment comparisons that have been included.
- Perform a statistical assessment of heterogeneity. The degree of, and the reasons for, heterogeneity should be explored as fully as possible
- The methods and results of the individual trials should be documented. If there is doubt about the relevance of a particular trial, sensitivity analysis should also be presented in which these trials are excluded.
- The heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies should be reported.
- Evidence from a mixed treatment comparison may be presented in a variety of ways such as in tables or diagrams.

Introduction and Background

There is no global consensus on the optimal chemotherapy regimen to treat mGC. The current usage of epirubicin based chemotherapy, which now represents the standard of care in the UK, was devised by clinicians working at the Royal Marsden Hospital in London at a time when the role of palliative chemotherapy for advanced and metastatic gastric cancer was still gaining acceptance in the UK. A study published by Waters et al 1999 (Waters 1999) comparing ECF versus FAMTX (a quadruplet regimen of doxorubicin, 5-FU and high-dose methotrexate, then used widely in North America) established ECF as the UK standard of care. Since then the REAL-2 study (Cunningham 2008) demonstrated that continuously infused 5-FU could be exchanged for oral capecitabine, and now the use of the resulting regimen ECX is widespread in the UK. In other parts of the world, most notably Asia, treatment of the disease has evolved along a different path with the double regimens of CX and CF becoming standard of care. It is worth noting that the triplet therapies are not the product of the addition of epirubicin to the doublet regimens used in ToGA but instead they use a lower dose of cisplatin and a different dosing schedule for 5-FU and capecitabine.

A systematic review and meta-analysis did report a modest benefit in OS for the addition of epirubicin to 5-FU/cisplatin containing regimens (Wagner 2005, 2006). However, this finding is questionable due to differences in the included studies. Of the 3 studies combined in the meta-analysis, by far the largest (Ross 2002) did not assess a doublet regimen and compared two triple regimens, the data from the second study was only reported in limited abstract format (Kim 2001), whilst the third study (Tobe 1992) only included a total of 43 evaluable patients, had no statistical power to detect a difference between the two treatments, it also recruited patients with more severe disease than in the two other studies. In addition the conclusions and robustness of this paper has been previously critised in a article by Adjani et al (Ajanif 2006) who considered the results “uninterpretable”.

Since the reference regimens used in the ToGA study are not the same as the comparators of most relevance to the UK NHS some form of indirect comparison of comparative survival is required. To this end, Roche performed a systematic literature review to attempt to identify randomised clinical trial evidence that would allow a comparison of efficacy, in terms of survival, between triplet and doublet regimens in the treatment of patients with aGC. The study was also of interest to other Roche affiliates (ie in other countries) and thus the range of interventions included in the search was broader than that required for the scope of this appraisal.

Methodology

The objective was to identify studies that report on the efficacy of double or triple regimens in the treatment of aGC. A structured approach was taken by conducting an update of an existing Cochrane Collaboration review (Wagner 2005).

Systematic Literature Review

A systematic literature search was performed to identify trials containing at least one treatment regimen of interest. This search was an extension of a previous Cochrane review and meta-analysis on chemotherapies for aGC that identified studies published until 2005 (Wagner 2005). The systematic search was extended to include Medline, EMBASE, SciSearch, CancerLit, and the Cochrane Library using a combination of free-text and MESH terms. Search terms were based on the previous review by Wagner and full-text studies published in English language journals from January 2005 until October 2009 were identified (see section 10.8 in Appendix 3). Review of the title and abstract was conducted and full-text articles obtained for those that met the inclusion criteria, below. A standardised data extraction form was applied to extract details of study design, patient selection criteria, study population characteristics, interventions, outcome measures and reported results from each included article. Study quality of included articles was assessed using the JADAD score (Jadad 1996), which is a numerical score between 0 (weakest) - 5 (strongest) as a measure of study design and/or reporting quality.

Study inclusion criteria

Study design - Randomised controlled trials

Patients - Adults (≥18 yrs) with aGC and/or gastro-esophageal junction cancer

Interventions - Epirubicin + Cisplatin + 5FU (ECF)

- Epirubicin + Cisplatin + capecitabine (ECX)
- Epirubicin + Oxaliplatin + 5FU (EOF)
- Epirubicin + Oxaliplatin + capecitabine (EOX)
- Docetaxel + Cisplatin + 5FU (DCF)
- 5FU + Leucovorin + Oxaliplatin (FLO, “FOLFOX”)
- 5FU + Leucovorin + Irinotecan (ILF, “FOLFIRI”)
- S1 + Cisplatin (S-1/C)
- Capecitabine + Cisplatin (XP)
- 5FU + Cisplatin (FP)

Comparisons - Any comparison between regimens allowed by the evidence network

- Trials evaluating at least one of the treatment arms of interest

Outcomes - Overall survival (OS) and Progression free survival (PFS)

Results of Systematic Literature Review

The search strategy identified 357 potentially relevant studies of which 301 were excluded because they did not meet the inclusion criteria (Figure 16). Of the 56 abstracts identified for full-text review, 40 were excluded for various reasons, resulting in 16 publications that were considered potentially eligible for inclusion. A further 9 citations were excluded because they only reported one treatment of interest or were not helpful in closing the network of studies and were therefore not contributing to the research question of interest. This resulted in 7 studies that were selected for further trial assessment. Out of these 7 studies only 3 were of relevance to the UK decision problem given the interventions of interest:

- REAL-2 (Cunningham 2008)
- Tobe 1992
- Kim 2001

Following completion of the systematic literature search, a single phase II clinical trial was published as an e-publication (as of Feb 1st, 2010) comparing epirubicin, cisplatin and capecitabine (ECX) with cisplatin and capecitabine (CX, Yun et al 2010). As the Yun study provides the only head-to-head evidence for ECX vs CX in aGC patients, it was included in the trial assessment and data tables so as to include all available data (section 10.8, Appendix 3).

Assessment of heterogeneity across trials

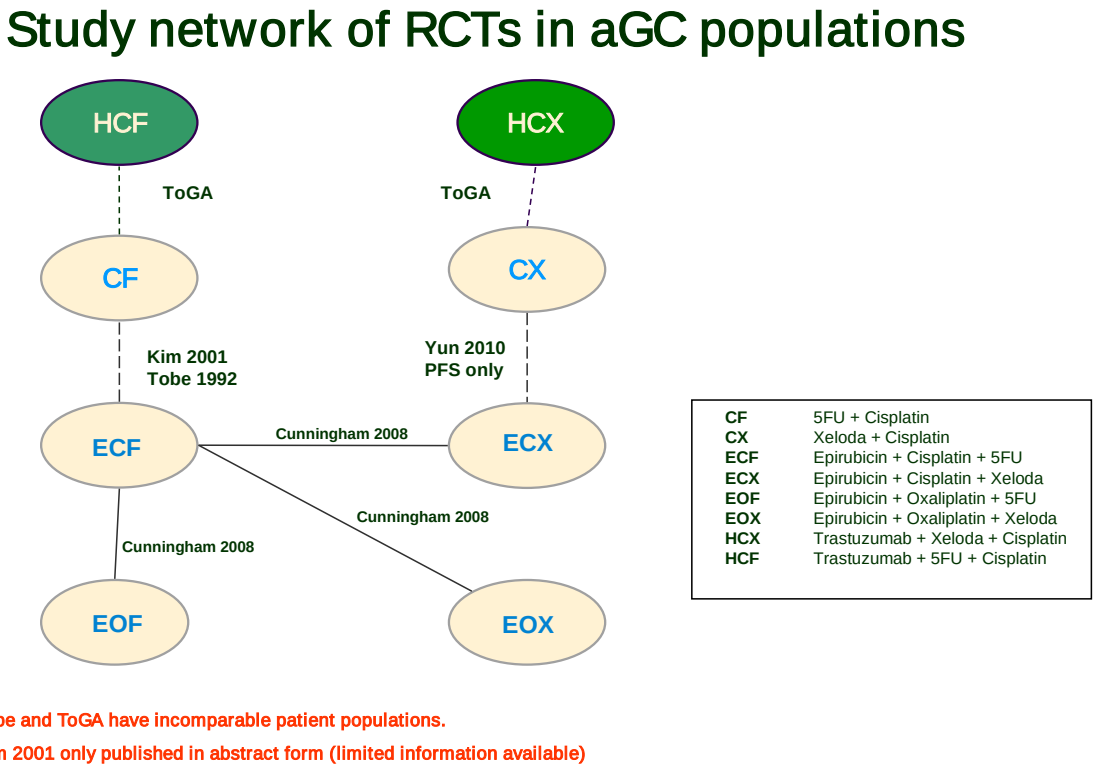
None of the identified trials were conducted in a population exclusively HER2-positive patients and hence are not comparable with the patient population recruited in ToGA.

Tobe 1992 (epirubicin-based triple regimen), recruited patients with more severe disease than those in other trials and, given the age of the publication, the standard of care available to these patients is likely to have been different to that available to patients recruited into more recent studies. For this reason it was not considered appropriate for to be included in an a network meta-analysis with the other studies.

Kim (2001) was only published as an abstract. Abstracts are typically excluded from meta-analysis or indirect comparisons as very little data is provided about the patient population characteristics included, limiting the ability to evaluate comparability across studies.

Yun et al (2010) and Real-2 (Cunningham 2008) recruited patients with slightly different characteristics, however, it was felt potentially these 2 studies could be included in a network however the primary end point in Yun was PFS and OS was not reported

An overview of the patient characteristics and reported outcomes from all 4 trials is provided in section 10.8 in Appendix 3 along with an assessment of the study quality, as measured by the JADAD score.



Tobe and ToGA have incomparable patient populations.

Kim 2001 only published in abstract form (limited information available)

Assessment of feasibility of using a network meta-analsysis to compare the triplet regimens used in the UK (ECX, ECF, and EOX) with the doublet regimens used in ToGA for the treatment of aGC

It was considered, for the following reasons, that the results of any network meta-analysis between the doublet regimens utilized within the ToGA study and the triplet regimens typically used in the UK would not be feasible or produce reliable and meaningful results for the following reasons:

1. 87% of patients in ToGA received capecitabine based therapy. None of the identified trials would complete the network allowing the comparison of overall survival between CX and any of the triplet therapies.

2. None of the studies identified that could potentially allow comparison of CF with the triplet regimens were considered suitable for inclusion in the network due lack of comparability between the studies.

Due to the limited number of trials identified and concerns about the interpretation of any quantitative analysis comparing treatments across trials, it was decided that the results should be compared via qualitative reporting and assessment of the trial characteristics.

Feasibility of using a network meta-analysis to compare the triplet regimens used in the UK (ECX, ECF, and EOX) with the trastuzumab based therapy

In addition to the limitations indicated above in comparing doublet and triplet therapies using a network meta-analysis inclusion of the ToGA study into any network would be highly questionable given the following reasons:

1. The ToGA trial is the first trial to be conducted and show a survival advantage in a subpopulation of exclusively HER2-positive inoperable locally advanced and metastatic gastric cancer patients. To date trials investigating chemotherapy regimens have been conducted in patients with unknown HER status (ie. mixed HER2-positive and HER2-negative group) and the clinical benefit in each subpopulation is not known/reported.

2. Data evaluating the prognostic or predictive effect of HER2-status on outcomes achieved with non-trastuzumab containing chemotherapy regimens is currently lacking. It is likely that HER2-positivity would act as a confounding variable on any indirect effect estimates and thus potentially bias any comparative estimate across trials.

Summary and Interpretation of evidence

The different evolutionary paths of the triplet therapies and the doublet regimens has resulted in a paucity of data comparing the two. Across the small amount of clinical trial evidence that is available there is large variability in patient populations and data reporting. Hence the systematic review has identified only a limited number of studies reporting efficacy of triple or double regimens in aGC. Having assessed the individual trials comparing double and triple regimens in the treatment of aGC, the limitations of the studies in terms of the size and comparability of patient populations, and quality of published data meant that the analyses were limited to reporting a qualitative assessment of the trial characteristics, which was then discussed with clinical experts (Appendix E2).

In the individual studies, superior efficacy of the triplet regimens over the doublet regimens used in the ToGA trial has not been demonstrated neither has oxaliplatin been shown to be superior to cisplatin. Although conducted in small numbers of patients, no statistically significant overall survival benefit of ECF versus CF was reported by either Tobe et al (Tobe 1992) (OS HR: 0.57, 95%CI:0.27-1.20, 1992) or Kim et al (Kim 2001) (OS: 0.83, 95%CI: 0.42-1.61). Recently, a trial comparing ECX versus CX has also reported no significant benefit in terms of the primary end point of PFS (OS not reported) for the triplet when compared to a doublet regimen (Yun 2010, PFS HR: 0.96, 95%CI: 0.58-1.57). Given the lack of evidence to the contrary it is reasonable to assume that epirubicin in combination with cisplatin and either capecitabine or 5-FU offers comparable efficacy to cisplatin in combination with capecitabine or 5-FU alone in the HER2 positive patient population.

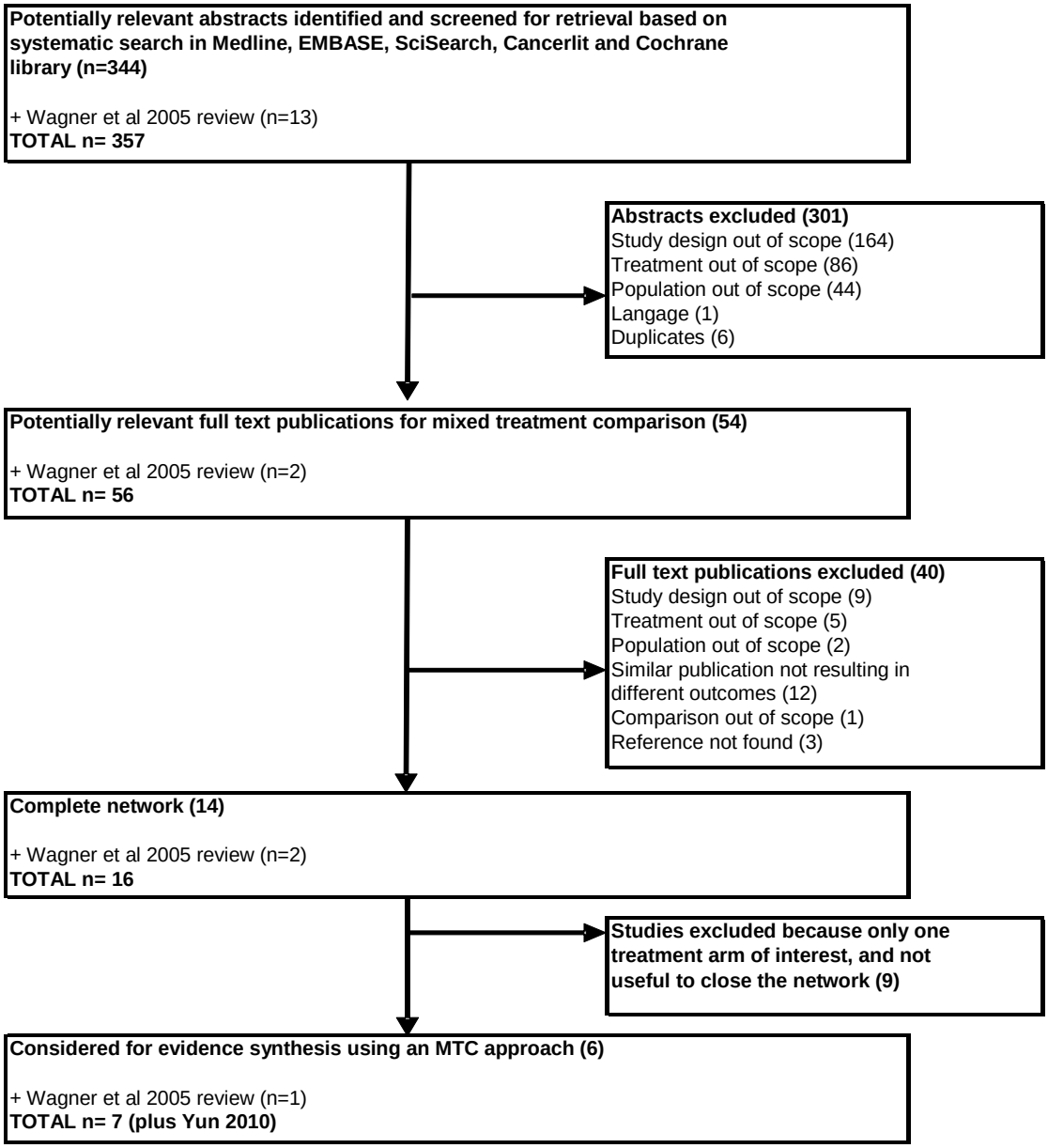
This assumption was validated following discussions with 8 oncologists experienced in the treatment of gastric cancer. (Roche NICE Advisory Board, London, Feb 2010 see Appendix E2). The oncologists also highlighted how the CX regimen within the ToGA study was at a much higher dose than the typical UK dose of CX when combined with Epirubicin. Therefore the specific assumption applied in the context of the economic evaluation is that the ECX regimen as used in UK clinical practice is assumed equivalent to the efficacy observed in the ToGA CX regimen.

Since HCX may potentially replace a minority of EOX use it is of potential relevance to the decision problem to consider the comparative efficacy of EOX compared to the cisplatin based triplet therapies more commonly used. One study (Cunningham 2008) was identified investigating the EOX regimen. In this two-by-two designed study, patients were randomized to receive either ECF, ECX, EOF or EOX. The primary end point was non-inferiority in overall survival for the therapies containing capecitabine as compared with 5-FU and for those containing oxaliplatin as compared with cisplatin. The results showed that oxaliplatin was as effective as cisplatin (0.92 CI, 0.80 to 1.10). It is reasonable, therefore, to assume a class effect, in terms of efficacy, between cisplatin and oxaliplatin.

Meta-analysis (Okines, 2009) showed OS was superior in the aGC patients treated with capecitabine combinations compared to 5-FU regimens therefore it is plausible that ECX, EOX may be superior to ECF and HCX superior to HCF in the population of interest. This hypothesis is supported by a trend toward OS advantage of CX over CF observed in ToGA (Table 40 of CSR: Multivariate Cox Regression for Overall Survival; HR 0.80 CI: 0.54-1.16). This overall survival advantage of capecitabine over 5-FU has been incorporated into the economic analysis.

Our interpretation of the evidence was validated with clinical experts (appendix E2) who indicated that our conclusions seemed reasonable given the evidence. Some of the clinical experts commented that potentially any loss in survival resulting from the removal of epirubicin could be made up for by the higher cisplatin dose (33% higher) used in the double regimens. The assumption of capecitabine offering a survival benefit over 5-FU based upon the published meta-analysis, received a mixed response form the oncologists, where it was considered that any such benefit was likely to be very modest.

Figure 16: Flow-chart of identified studies



6.7 Safety

This section should provide information on the safety of the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, they may demonstrate that the technology shows a relative lack of adverse effects commonly associated with the comparator, or the occurrence of adverse effects not significantly associated with other treatments.

If any of the main trials are designed primarily to assess a safety outcome (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse effect), these should be reported here in the same detail as described in the previous sections relating to the efficacy trials.

Give a brief overview of the safety of the technology in relation to the decision problem. Give incidence rates of adverse effects if appropriate.

6.7.1 Trials of evidence to this review

The largest body of safety data relating to the indication in this appraisal comes from the ToGA phase III clinical trial discussed in the description of comparative efficacy.

6.7.2 Exposure to trial medication

More patients in the HCX/F arm received 6 cycles of chemotherapy compared to the CX/F arm (59.5% vs 49.3% for capecitabine/5-FU and 48.3% vs 56.5% for cisplatin). The median number of cycles of trastuzumab was 8 cycles (range 1-49), the median duration of treatment received was 4.9 months (range 0.03-33.18). Patients in the trastuzumab-containing arm, on average, remained on treatment for longer than patients in the chemotherapy alone arm because of delayed progression and also they lived longer so there was more time to experience an adverse event (Table 7).

The dose intensity for the FAS population (planned versus received dose) was 100% for trastuzumab, 90% for cisplatin, 86% for capecitabine and 97% for 5-FU and the exposure was balanced between the arms. However, patients in the trastuzumab arm tended to remain on chemotherapy for longer because they had longer progression-free intervals and so less disease progression on chemotherapy.

Table 7: Exposure to trial medication

Treatment	F+C n=290		F+C + trastuzumab n=294	
	Median	**Range**	**Median**	**Range**
Trastuzumab				
Cycles			8	1-49
Treatment duration, months			4.9	0.03-33.21
Dose intensity, %			100.1	84.8-156.7
Cisplatin				
Cycles	5	1-16	6	1-14
Treatment duration, months	3.4	0.03-15.19	3.5	0.03-12.89
Dose intensity, %	91.1	23.5-103.7	89.4	52.0-108.6
Capecitabine				
Cycles	5	1-20	6	1-20
Treatment duration, months	3.9	0.03-15.65	3.9	0.10-16.83
Dose intensity, %	86.7	3.6-110.0	85.9	14.3-107.5
5-FU				
Cycles	4	1-11	6	1-6
Treatment duration, months	2.9	0.13-7.56	3.6	0.16-5.10
Dose intensity, %	95.7	33.4-102.0	98.3	61.1-101.5

6.7.3 Safety analyses from the ToGA study

Comparison of the safety profiles of the two treatment groups constituted a secondary objective of the study. The intensity of AEs was graded according to NCI-CTC.

The safety analysis population included a total of 584 patients who received at least one dose of at least one component of the study medication (FAS). Within the safety population, 294 patients were randomised to receive HCX/F, and 290 were allocated to receive CX/F.

An overview of the safety data reported in this study (up to the clinical cut-off January 7, 2009) is shown in the table below (Table 8).

Table 8: Overview of safety experience

	Number of Patients (%)	
	FP N = 290	**FP+H N = 294**
Any AEs	284 (98%)	292 (99%)
Grade ≥ 3 AEs	198 (68%)	201 (68%)
Serious AEs	81 (28%)	95 (32%)
AEs leading to discontinuation of at least one treatment	48 (17%)	48 (16%)
AEs leading to dose modifications/interruptions	237 (82%)	246 (84%)
AEs leading to death	14 (5%)	17 (6%)

Overall, patients in the HCX/F arm experienced slightly more AEs than patients in the CX/F arm [redacted] However, these differences are minimal given that patients in the trastuzumab-containing arm had a longer treatment duration (including a longer duration of chemotherapy) as a result of improved survival outcomes (OS and PFS) and not all of the AEs were treatment related. The AEs considered related to study treatment occurring at a similar frequency in both arms; 63% in the CX/F arm and 65% in the HCX/F arm

All Grade AEs which occurred at an incidence of at least 5% in either treatment arm are presented in the table below (Table 9).

Table 9: Safety impact of addition of trastuzumab to chemotherapy in the ToGA study by trial treatment (FAS): All Grade AEs (incidence at least 5%) and Grade ≥ 3 AEs (incidence at least 1%)
Note: Frequencies in bold are >5% higher in absolute terms than for other group

Body system / Adverse event	All grade		Grade ¾	
	Treatment allocation			
	Fluoropyrimidine / ciplatin N = 290 No. (%)	Trastuzumab / Fluoropyrimidine / ciplatin N = 294 No. (%)	Fluoropyrimidine / ciplatin N = 290 No. (%)	Trastuzumab / Fluoropyrimidine / ciplatin N = 294 No. (%)
Gastrointestinal disorders				
Nausea	184 (63)	197 (67)	21 (7)	22 (7)
Vomiting	134 (46)	**147 (67)**	22 (8)	18 (6)
Diarrhoea	80 (28)	**109 (37)**	11 (4)	27 (9)
Constipation	**93 (32)**	75 (26)	5 (2)	2 (<1)
Stomatitis	43 (15)	**72 (24)**	6 (2)	2 (<1)
Abdominal pain	42 (14)	46 (16)	4 (1)	4 (1)
Blood and lymphatic system disorders				
Neutropenia	165 (57)	157 (53)	88 (30)	79 (27)
Anaemia	61 (21)	**81 (28)**	30(10)	36 (12)
Thrombocytopenia	33 (11)	47 (16)	8 (3)	14 (5)
Febrile neutropenia	8 (3)	15 (5)	8 (3)	15 (5)
General disorders and administration site conditions				
Fatigue	82 (28)	**102 (35)**	7 (2)	12 (4)
Asthenia	53 (18)	55 (19)	10 (3)	14 (5)
Pyrexia	36 (12)	54 (18)	-	3 (1)
Mucosal inflammation	18 (6)	**37 (13)**	2 (<1)	6 (2)
Metabolism and nutrition disorders				
Anorexia	133 (46)	135 (46)	18 (6)	19 (6)
Skin and subcutaneous tissue disorders				

Palmar-plantar erythrodysaesthesia	64 (22)	75 (26)	5 (2)	4 (1)
Alopecia	27 (9)	32 (11)	-	-
Nervous system disorders				
Dizziness	28 (10)	31 (11)	-	-
Dysgeusia	14 (5)	28 (10)	-	-
Lethargy	-	-	1 (<)	3 (1)
Investigations				
Weight decreased	40 (14)	**69 (23)**	7 (2)	6 (2)
Respiratory, thoracic and mediastinal disorders				
Hiccups	28 (10)	34 (12)	-	-
Dyspnoea	16 (6)	9 (3)	5 (2)	1 (<1)
Pulmonary embolism	-	-	4 (1)	4 (1)
Renal and urinary disorders				
Renal impairment	39 (13)	47 (16)	3 (1)	2 (<1)
Infections and infestations				
Nasopharyngitis	17 (6)	**37 (13)**	-	-
Septic shock	-	-	5 (2)	1 (<1)

Investigator text for Adverse Events encoded using MedDRA version 11.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Fluoropyrimidine: Investigator preference of Capecitabine or 5-FU

A review of Table 9 shows that there was a slight excess of AEs in the trastuzumab arm, (ie events, the frequency of which was greater in the trastuzumab arm than in the comparative arm by more than 5%) namely vomiting, diarrhoea, stomatitis, anaemia, fatigue, mucosal inflammation, weight decrease, and nasopharyngitis. Importantly, the excess was generally small and most cases were of mild-moderate severity so that there were very few additional cases of Grade 3-4 events. The most common Grade ≥ 3 AEs reported were blood and lymphatic system disorders, gastrointestinal disorders and, metabolism and nutrition many of which may be attributable to longer chemotherapy duration rather than trastuzumab itself.

It is not unreasonable to expect patients in the trastuzumab plus chemotherapy arm to experience slightly more AEs due to the additional agent and extended duration of chemotherapy as a result of more successful treatment, specifically in terms of delaying disease progression. Critically, the addition of trastuzumab to CX/F did not adversely affect the safety profile with regards to the frequency or severity of discontinuations due to AEs, SAEs, dose modifications and AEs leading to death.

Similar to the FAS population, almost all patients included in the high HER2 expressing subgroup experienced at least one adverse event (98% in CX/F, 99.6% in HCX/F for the high HER2 expressing group). The nature and pattern of adverse events in both arms of the subgroup was consistent with the study safety population.

6.7.4 Adverse events of special interest

There are very few adverse events clearly associated with trastuzumab as discussed in 6.7.3. However, infusion reactions and cardiac dysfunction have been associated with trastuzumab treatment in studies conducted in breast cancer patients. Therefore it is of interest to look at these more closely. It can be seen that what was been observed in the mGC setting in the ToGA study is consistent with the data in the breast cancer setting, as observed over the past 10 years.

6.7.4.1 Infusion reactions

[redacted] none of the events were fatal.

The incidence of patients exhibiting at least one infusion-related AE gradually decreased with cycle after cycle 1 (41% cycle 1, 2% cycle 8) [redacted]

6.7.4.2 Cardiac safety

As pre-specified in the protocol, a baseline LVEF value of 50% or more (measured by ECHO or MUGA) was an eligibility criteria of study entry. At screening, the median LVEF value was 64% (range 48-90) in the CX/F arm and 65% (range 50-86) in the HCX/F arm. The incidence of cardiac failure was minimal and similar between the two treatment arms and is summarized in Table 10. Of note, more patients in the trastuzumab arm experienced asymptomatic reductions in LVEF. The decrease in asymptomatic LVEF function in the trastuzumab arm was predictable from the known pharmacology of trastuzumab and clinical experience with the drug in breast cancer studies. Importantly, this did not translate to an increase in cardiac adverse events related to treatment or leading to death and can be regarded as a laboratory finding with little clinical significance to the patient.

Table 10: Cardiac adverse events

Cardiac event, n (%)	CX/F (n=290)		CX/F + trastuzumab (n=294)	
	All	Grade 3/4	All	Grade ¾
Cardiac AEs, total	18 (6)	9 (3)	17 (6)	4 (1)
Cardiac failure	2 (<1)	2 (<1)	1 (<1)	1 (<1)
Asymptomatic LVEF drops[a]				
<50% <50% and by ≥10%	2 (1.1) 2 (1.1)		14 (5.9) 11 (4.6)	
Cardiac AEs leading to death	2 (<1) Cardiac arrest; cardio-respiratory arrest		2 (<1) Acute MI; angina unstable and cardiac failure	
Cardiac AEs related to treatment	2 (<1)		2 (<1)	

[a]Measured at baseline and every 12 weeks; MI, myocardial infarction

6.7.5 Clinical impact of treatment toxicity

As demonstrated above, the addition of trastuzumab to chemotherapy had minimal impact on the overall number of treatment-related adverse events (including SAEs) experienced by patients or on the frequency of severe and life-threatening events.

One measure of the impact of treatment toxicity on patients is the extent to which it interferes with the ability to deliver treatment because it causes treatment delays, treatment interruptions or dose reductions. In this respect, more patients in the trastuzumab arm completed the defined six cycles of chemotherapy compared with patients in the chemotherapy alone arm (see 6.7.2). Time delays between treatment cycles remained relatively constant in both treatment arms. Dose modifications due to AEs (any grade), where a successful strategy as the rates of treatment discontinuation for safety reasons was comparable in both study arms (17% and 18% for CX/F and HCX/F, respectively).

The longer duration of chemotherapy in the trastuzumab arm may explain the slight increase in AEs experienced but this was minimal. Moreover, the AEs considered related to study medication occurred at a similar frequency in both arms indicating that the main cause of AEs was chemotherapy and trastuzumab made very little difference to patients in terms of AEs.

6.8 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available.

Inferences about relative treatment effects drawn from non-RCT evidence will necessarily be more circumspect than those from RCTs with properly controlled evidence. The bias that may be present in non-randomised data means the results should be interpreted cautiously. When possible, the use of more than one independent source of such evidence needs to be examined to gain some assurance of the validity of any conclusions drawn.

6.8.1 Details of how the relevant non-RCTs have been identified and selected

None identified.

6.8.2 Summary of methodology of relevant non-RCTs

N/A

6.8.3 Critical appraisal of relevant non-RCTs

N/A

6.8.4 Results of the relevant non- RCTs

N/A

6.9 Interpretation of clinical evidence

6.9.1 Provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

In the palliative chemotherapy of advanced and metastatic gastric cancer, overall survival and preventing symptomatic deterioration are the twin aims. Since the introduction of chemotherapy in the late 1980s/early 1990s, it has become well established that chemotherapy improves survival compared with best supportive care (Wagner 2005). However, advances in efficacy have subsequently been limited and prognosis remains poor, under 12 months, for these patients.

In the phase III trial, ToGA, the addition of trastuzumab to chemotherapy extended median overall survival by a significant 4.2 months to 16 months versus from 11.8 months with chemotherapy alone (HR of 0.65; 95% CI 0.51-0.83; [redacted]) in the EMEA approved high HER2 expressing subgroup (Trastuzumab SmPC 2010; Van Cutsem ASCO 2009a). This is at least 4 months longer than observed with any doublet or triplet chemotherapy regimen (Wagner 2005, 2006) even in patients unselected for HER2 overexpression.

The trial also measured PFS and ORR which were all significantly improved in the trastuzumab plus chemotherapy arm (Van Cutsem 2009a). Patients free of progression and tumour shrinkage can reasonably be expected to be free of worsening disease symptoms and the psychological benefit to patients of knowing that their cancer is not growing is important. As such, PFS and ORR are also clinically important end-points.

Furthermore, patients in both arms of the ToGA study had improved QoL over time, particularly at the end of chemotherapy indicating that the addition of trastuzumab does not have a negative impact on patients QoL (Satoh 2010). This is of particular importance given the poor prognosis of this patient group in whom it has been recommended that treatment strategies be conducted according to the principles of palliative care (Wagner 2005, 2006defined as ‘an approach that improves the quality of life of patients and their families facing the problems associated with life threatening illness’ by the World Health Organisation.(Wagner 2005, 2006).

The ToGA trial collected comprehensive safety data which showed that the addition of trastuzumab to CX/F did not adversely affect the safety profile with regards to the frequency or severity of discontinuations due to AEs, SAEs, dose modifications and AEs leading to death. A similar percentage of AEs were considered related to study medication in both arms (63% in the CX/F arm and 65% in the HCX/F arm), indicating the main cause of AEs was chemotherapy. Moreover, the

addition of trastuzumab to CX/F had minimal impact on the burden of AEs caused by cytotoxic chemotherapy which is already accepted as offering an acceptable balance in terms of harms and benefits.

Patients eligible for trastuzumab would be spared the epirubicin-related toxicities as these two agents should not be administered in combination due to the effect of both agents on cardiac tissue. Extensive experience in the breast cancer setting during the past 10 years suggests that cardiac dysfunction associated with trastuzumab manifests as a reduction in LVEF which tends to be transient and often resolves when treatment with trastuzumab is interrupted/stopped (Guarneri 2006; Suter 2007; Perez 2008). In contrast, the cardiac damage caused by anthracyclines is more likely to be irreversible and can manifest many years after treatment (Ewer 2005). The risk of trastuzumab-related cardiac dysfunction is more than off-set by the cardiotoxicity benefits of dropping epirubicin and the prolonged survival, beyond 12 months, and increased progression-free interval associated with the addition of trastuzumab to cisplatin and a fluoropyrimidine.

In short, the results of the ToGA study represent a significant advance to patients diagnosed with high HER2 expressing (IHC3+ or IHC2+/FISH+) mGC in terms of dramatically extending overall survival to beyond 12 months without negatively impacting on tolerability or the patients' QoL. The outcomes assessed in the trial are of greatest relevance to clinical practice, and show that trastuzumab is effective and well tolerated in combination with chemotherapy (CX/F) in this setting, providing a 35% increase in OS for the subgroup of patients diagnosed with HER2 positive mGC, as defined by the EMEA license (Van Cutsem ASCO 2009a; Tratuzumab SmPC 2010). The fact that the EMEA assessment of the license was expedited through the 60 day rather than the 90 day process reinforces the clinical significance of these data in terms of the dramatic increase in OS for this highly selected HER2 positive patient subgroup. The magnitude of benefit seen with the addition of trastuzumab to CX/F has not been demonstrated by any other single agent or combination regimen in this disease setting.

6.9.2 Identify any factors that may influence the applicability of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select suitable patients based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the Summary of Product Characteristics?

The ToGA study describes a very significant advance in outcomes in a group of patients that can readily be identified in clinical practice – those with inoperable mGC requiring platinum-based palliative chemotherapy and whose tumours overexpress HER2. Although HER2 is not currently tested for, this can readily be done as previously described using techniques that have been applied in the diagnosis of breast cancer for a number of years.

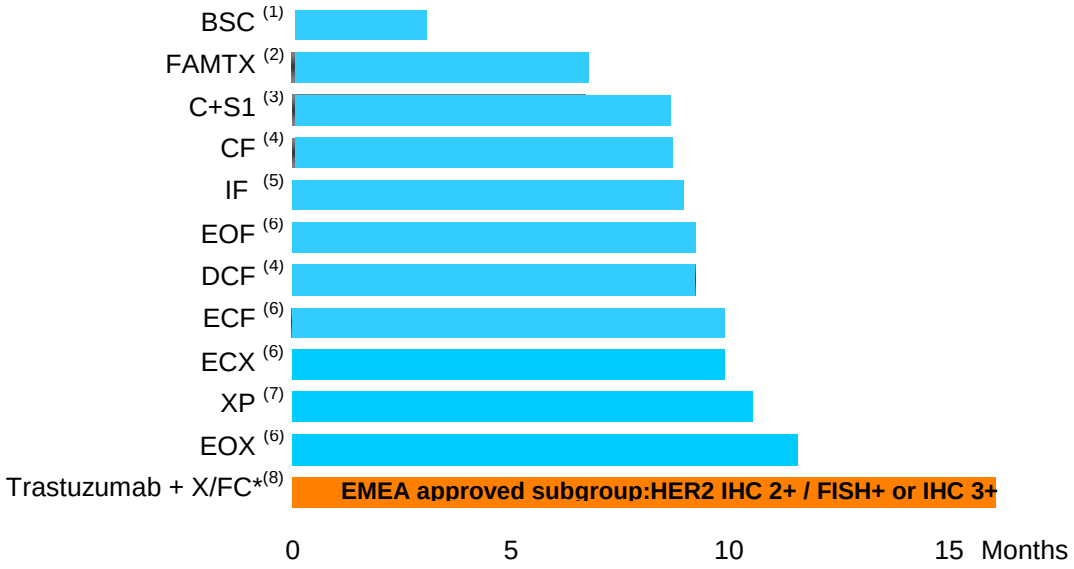
There is no reason to suppose that the survival benefits demonstrated by the addition of trastuzumab to platinum based chemotherapy in the ToGA study would not be achieved if these treatments were administered in routine UK clinical practice.

Although 56% patients in both arms of the ToGA trial were from Asian countries, the point estimate in the preplanned subgroup analysis suggest that the treatment effect is at least the same, if not better, for the European population (HR 0.63; 95%CI 0.44-0.89) versus the overall trial population (HR 0.74; 95%CI 0.6-0.91).

One issue that does arise is that the base regimen (cisplatin and a fluoropyrimidine) was not the most widely used chemotherapy regimen in UK clinical practice (more often epirubicin, cisplatin, and a fluoropyrimidine). Though as has already been discussed (section 4 and 6.6), the three drug combination does not appear to offer efficacy benefits when directly compared with cisplatin plus capecitabine (CX) in a randomised trial (Yun 2010, PFS HR: 0.96, 95%CI: 0.58-1.57).Furthermore, the addition of epirubicin to CF has been shown to provide no statistically significant overall survival benefit in two trials (Tobe 1992, OS HR: 0.57, 95%CI:0.27-1.20; Kim 2001, OS: 0.83, 95%CI: 0.42-1.61). Given that all the randomised clinical trials identified reported no significant benefit of a triplet versus doublet treatment regimen (Yun 2010, Kim 2001, Tobe 1992) and the lack of evidence to the contrary, it is reasonable to assume that epirubicin in combination with cisplatin and either capecitabine or 5-FU offers comparible efficacy to cisplatin in combination with capecitabine or 5-FU alone in the HER2 positive patient population. As shown in Figure 17 the combination of trastuzumab, cisplatin and a fluoropyrimidine produces by far the best survival outcomes ever reported in the

chemotherapy of mGC, breaking the 1 year barrier for the first time and dramatically extending overall survival by 35% to a median of 16 months, without negatively impacting on tolerability or the patients QoL.

Figure 17: Median overall survival for best supportive care, current chemotherapy treatment, and chemotherapy plus trastuzumab



*87.1% patients received capecitabine

BSC, best supportive care; FAMTX, methotrexate, 5-FU and doxorubicin;
C+S1, cisplatin plus S1; CF, cisplatin plus 5-FU; IF, irinotecan plus 5-FU;
EOF, epirubicin, oxaliplatin and 5-FU; DCF, docetaxel, cisplatin and 5-FU;
ECF, epirubicin, cisplatin and 5-FU; ECX, epirubicin, cisplatin and Xeloda;
XP, Xeloda plus cisplatin; EOX, epirubicin, oxaliplatin and Xeloda;
X/FC, Xeloda or 5-FU plus cisplatin.

References

1. Murad 1993.
2. Vanhoefer 2000.
3. Ajani 2009; Abstract 8.
4. Van Cutsem 2006.
5. Dank 2008.
6. Cunningham 2008.
7. Kang 2009
8. Van Cutsem 2009.

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

7.1.1 Identification of studies

Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided in appendix 3, section 9.3.

MEDLINE, EMBASE, MEDLINE in process, NHS EED and HEED were searched for cost effectiveness studies on the use of trastuzumab in advanced gastric cancer (as per the decision problem).

Table 11: Economic evaluation search inclusion criteria

Population:	Any aGC patients
Intervention:	Trastuzumab
Comparators:	Any
Outcomes:	All health economic outcomes
Study Design:	Economic evaluation

Keyword strategies were developed using key references retrieved through initial scoping searches. Search strategies did not include search terms or filters that would limit results to specific publication types. Each search result's title and abstract were assessed for relevance according to the pre-defined inclusion criteria. Studies identified as being potentially relevant were retrieved for full assessment.

The above methodology is robust and founded on the methods outlined in the CRD's 'Guidance for undertaking reviews in health care' (2008). The objective of the search, and the inclusion criteria defined as a product of that objective, was clearly aligned with the decision problem. Full details of the search strategy, date of search and service provider used are detailed in section 9.10.

7.1.2 Description of identified studies

Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. Where studies have been identified and not included, justification for this should be provided.

No economic evaluations of trastuzumab in advanced gastric cancer were identified through searching. As trastuzumab is early in it's aGC life-cycle this lack of economic analysis is not surprising. In light of the absence of existing published economic analysis a de novo approach is fully justified.

7.2 De novo economic evaluation(s)

In the absence of a relevant published economic evaluation, manufacturers or sponsors should submit their own economic evaluation. When estimating cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal'). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	Reference case	Section in 'Guide to the methods of technology appraisal'
Defining the decision problem	The scope developed by the institute	5.2.5 & 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 & 5.2.6
Perspective costs	NHS and Personal Social Services	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10

Type of economic evaluation	Cost-effectiveness analysis	5.2.11 to 5.2.12
Synthesis of evidence on outcomes	Bases in a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12

HRQL, health related quality of life; NHS, National Health Service; QALYs, quality-adjusted life years

7.2.1 Technology

7.2.1.1 How is the technology (assumed to be) used within the economic evaluation? For example, give indications, and list concomitant treatments, doses, frequency and duration of use.

Trastuzumab is assumed to be used in accordance with the recent license extension for metastatic gastric cancer. As such we have evaluated the following trastuzumab containing combinations:

- Trastuzumab in combination with cisplatin and capecitabine (HCX)
- Trastuzumab in combination with cisplatin and 5-FU (HCF)

Trastuzumab is administered as an intravenous infusion of an initial infusion of 8 mg/kg of body weight followed by 6mg/kg every 3 weeks.

The summary of product characteristics states that the initial dose should be delivered over 90 minutes. If the first infusion is well tolerated, the subsequent infusions may be administered over 30 minutes.

Table 12 and Table 13 below describe the interventions of interest and Figure 18 and Figure 19 illustrates this same information as a schema.

Table 12: HCX treatment regimen as per ToGA protocol

given every 21 days	Day 1 (Immediately after trastuzumab infusion)	Days 2 to 14	Days 15 to 21
Trastuzumab* Infusion over 90 minutes 1st dose and over 30 minutes for subsequent doses if well tolerated	8mg/kg loading dose for first cycle 6mg/kg subsequent cycles	-	No Treatment
Cisplatin Pre-hydration over 2 hours Infusion over 120 minutes Post hydration over 6 hours	80 mg/m2	-	
Capecitabine Oral therapy	*Days 1-14* Capecitabine 1000 mg/m^2 by mouth, twice daily, within 30 minutes of the end of breakfast and dinner.		

*Trastuzumab infusion can be given during hydration period of cisplatin

Table 13: HCF treatment regimen per the ToGA protocol

given every 21 days	Day 1 (Immediately after trastuzumab infusion)	Day 2 to 5	Day 6 to 21
Trastuzumab* Infusion over 90 minutes 1st dose and over 30 minutes for subsequent doses if well tolerated	8mg/kg loading dose for first cycle 6mg/kg subsequent cycles	-	No Treatment
Cisplatin Pre-hydration over 2 hours Infusion over 120 minutes Post hydration over 6 hours	80 mg/m2	-	
5-FU Continuous infusion	800 mg/m² daily for 5 days via continuous infusion		

*Trastuzumab infusion can be given during hydration period of cisplatin

Figure 18: Schema of per protocol treatment schedule for regimens HCX

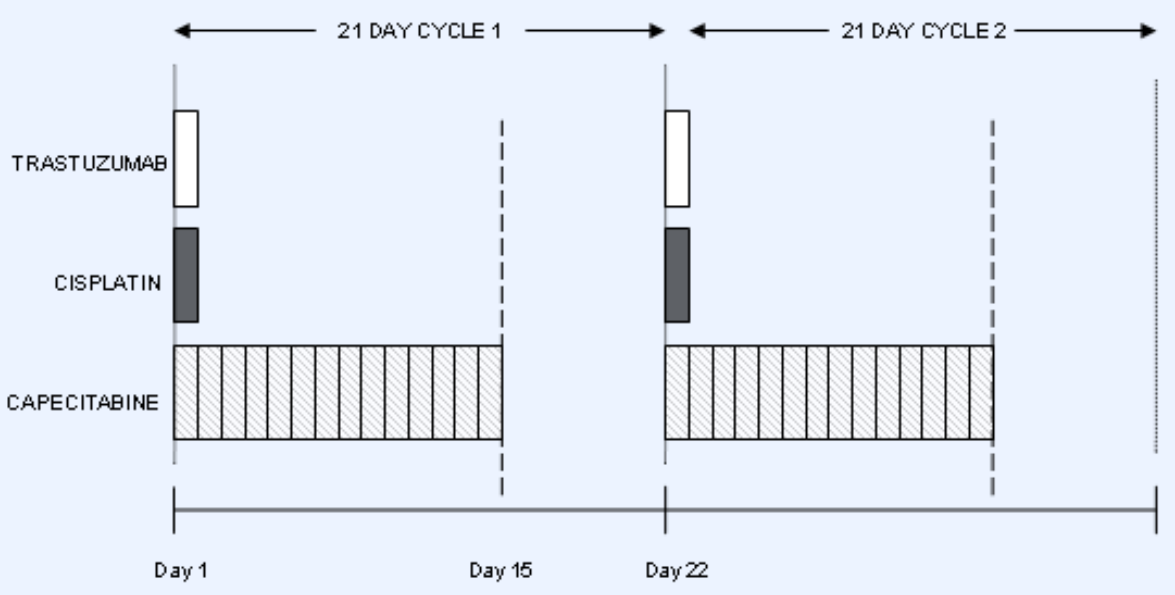
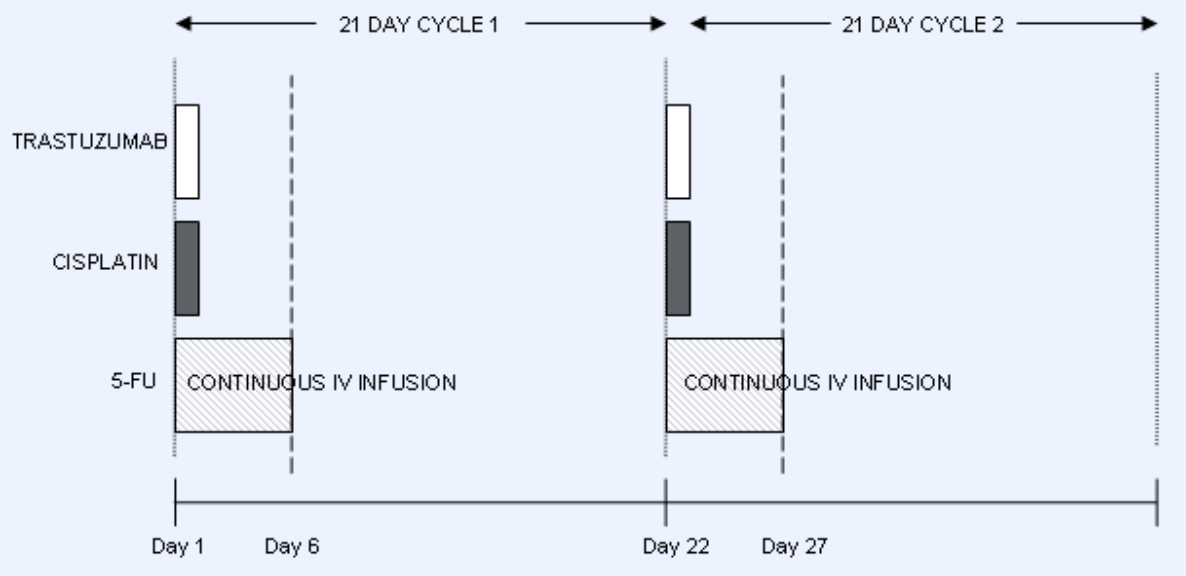


Figure 19: Schema of per protocol treatment schedule for regimens HCF



Concomitant treatments

There are no concomitant treatments required for treatment with HCX or HCF above those required for the comparator regiments (Expert Opinon, see Appendix E2).

7.2.1.2 Has a treatment continuation rule been assumed? Where the rule is not stated in the SmPC this should be presented as a separate scenario, by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- the costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required)
- the robustness and plausibility of the endpoint on which the rule is based
- whether the 'response' criteria defined in the rule can be reasonably achieved
- the appropriateness and robustness of the time at which response is measured
- whether the rule can be incorporated into routine clinical practice
- whether the rule is likely to predict those patients for whom the technology is particularly cost effective
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

The economic analysis is based on the observed treatment duration in the ToGA study to ensure that the cost of treatment match the clinical outcomes conferred from this expenditure.

7.3 Patients

7.3.1.1 What group(s) of patients is/are included in the economic evaluation? Do they reflect the licensed indication? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem?

The patients included in the economic evaluation reflect those of the licensed population. I.e. the subgroup of the ToGA study that had metastatic disease and were classed as HER2 positive (IHC2+ with FISH+ or IHC3+)

7.3.1.2 Was the analysis carried out for any subgroups of patients? If so, how were these subgroups identified? If subgroups are based on differences in relative treatment effect, what clinical information is there to support the biological plausibility of this approach? For subgroups based on differences in baseline risk of specific outcomes, how were the data to quantify this identified? How was the statistical analysis undertaken?

As per the final scope, analysis was not performed for any subgroups aside from that defined by the license which represents a significant sub-group of the advanced gastric population .

7.3.1.3 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Refer to the subgroups identified in the scope.

As per the final scope, analysis was not performed for any subgroups.

7.3.1.4 At what points do patients 'enter' and 'exit' the evaluation? Do these points differ between treatment regimens? If so, how and why?

All patients enter the economic evaluation at the point of commencement of first-line treatment. HER2 testing is a relevant cost to the decision problem that would have occurred prior to commencing treatment; this cost was assumed be incurred at time zero of the economic analysis.

Patients entered into the arm in the economic analysis as per the arm in which they were randomised in the ToGA study and remained in the economic model for the remainder of their life.

7.3.2 Comparator technology

What comparator(s) was/were used and why was it/were they chosen? The choice of comparator should be consistent with the summary of the decision problem (Section A).

The inclusion criteria for comparators were as follows:

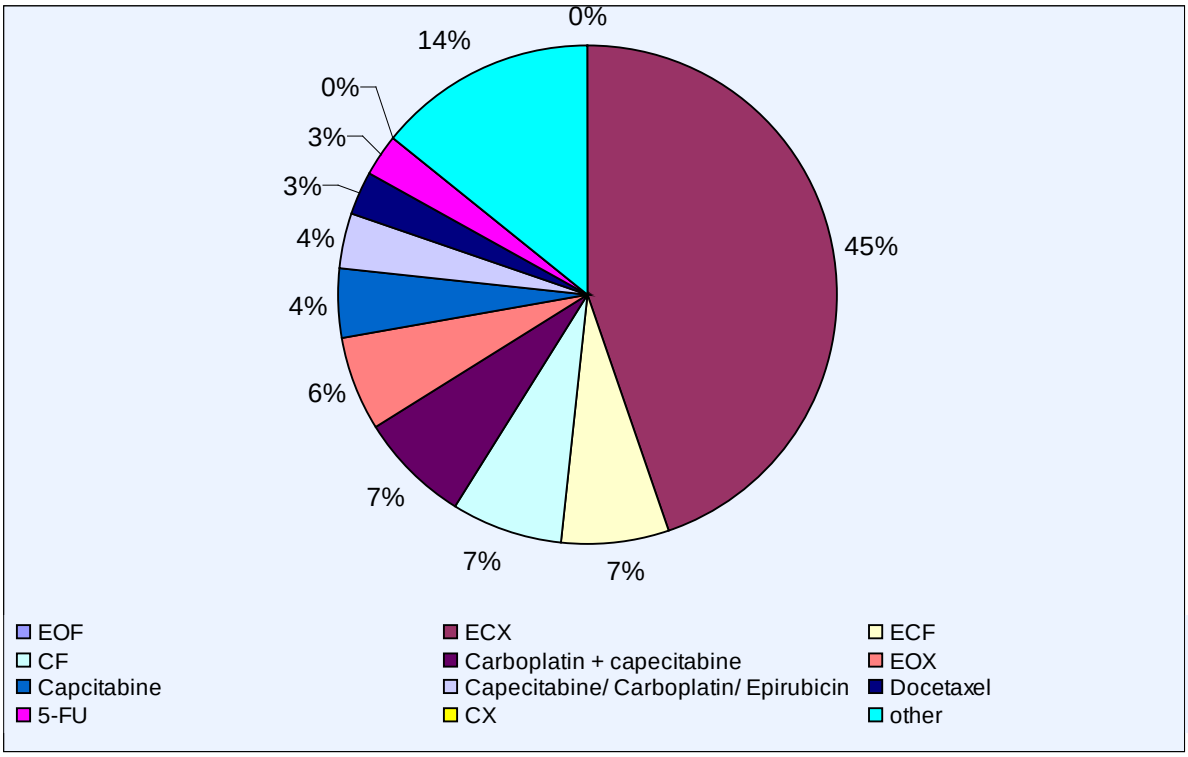
- The therapy is routinely used in the NHS (>10% usage)
- The therapy is within the final scope of the appraisal

Therapies were considered to be used routinely if it was estimated, based on market research, that they were used to treat greater than 10% of mGC patients that are treated with first-line chemotherapy in the NHS in England and Wales.

Usage data was purchased from a syndicated study that tracks usage of chemotherapy as well as supportive care agents across all cancer types (Synovate Market Research 2). This research had been performed independently from Roche by Synovate Healthcare. In the study representative panels of cancer treating physicians complete forms directly from reviewing patients' charts. The latest estimates for mGC available to Roche represent a moving average total (sample size =112) for the year up to September 2009. The results of this research are displayed in Figure 20 below.

The results indicate that by far the most used regimen in the UK is ECX. Patients not treated with ECX appear to be treated with a wide variety of regimens, none of which are used in more than 10% of patients. This result is supported in part by previous market research (Synovate Market Research 2) based on clinician perception, which also suggested ECX was the most used regimen. However there was a disparity between the two studies in that the perception of clinicians was that there was greater use of ECF and EOX than suggested by the chart review. A further detail of each of these studies is provided in appendix E6.

Figure 20: Estimated usage of chemotherapy by regimen in the NHS



Abbreviations and synonyms: *C, cisplatin; E, epirubicin; 5FU/ F, 5-fluorouracil X/Xeloda, capecitabine.* ***Notes****: The number of patient records sampled was 112. (see appendix E6 for further details)*

It was confirmed by clinical experts as part of a recent Roche advisory board (see Appendix E3) that ECX is the dominant regimen in England and Wales, however it was also noted that some patients may not be able to receive capecitabine and that these patients would most like be treated with ECF. It was also mentioned that in a minority of centres EOX was used as an alternative to ECX. Based on this the comparisons considered of most relevance to England and Wales was HCX compared to ECX, and HCF versus ECF for patients not suitable for treatment with capecitabine. As a secondary analysis HCX was compared to EOX.

The dose schedules for ECX, ECF and EOX are shown below. It is worth noting that the double regimens used a reference in the ToGA study contain a 33% higher dose of cisplatin than the triplet regimens typically used in the UK. In addition the triplet therapy involves treatment with capecitabine or 5-FU throughout the 21 day cycle.

ECX

Components: Epirubicin (E), cisplatin (C) and capecitabine (X)

Source of regimen details: REAL-2 Study (Cunningham 2008)

Dosing and Administration:

Patients receive ECX over a 21 day cycle. Epirubicin and cisplatin are administered on the first day of each cycle whilst capecitabine is administered on each day of the cycle. This 21 day cycle is repeated until disease progression or unacceptable toxicity. A schema of the regimen is shown below.

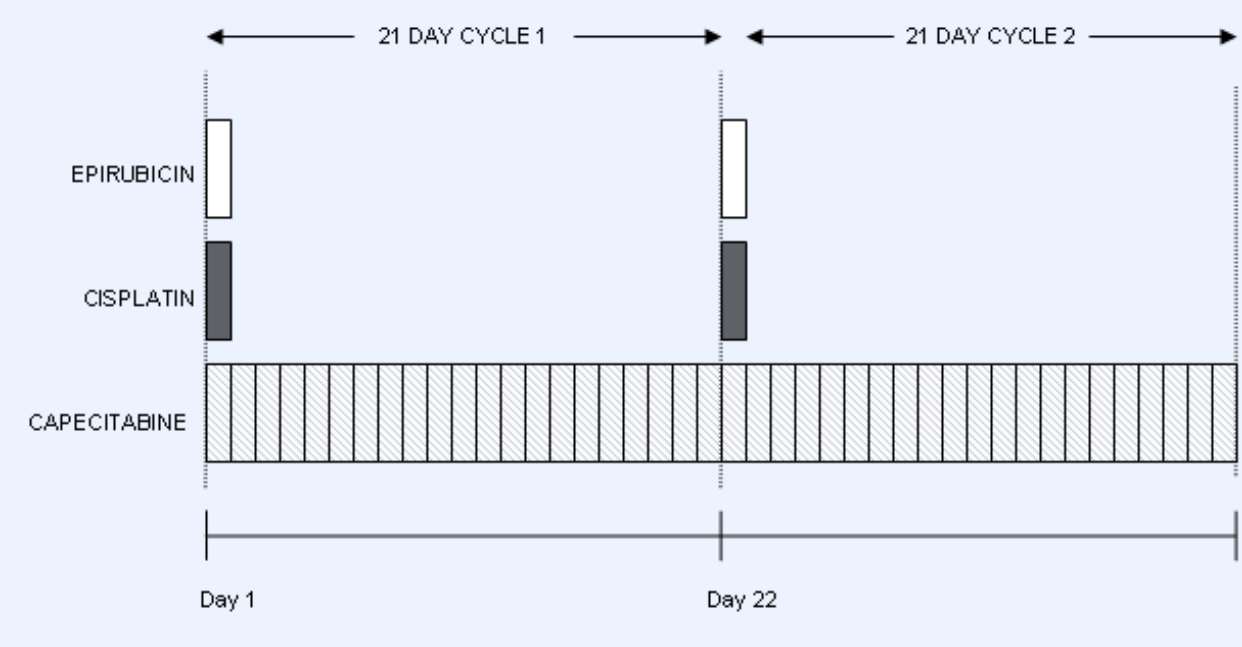


Table 14 ECX components (frequency and dosing)

Regimen	Epirubicin dose and frequency	Cisplatin dose and frequency	Fluoropyrimidine dose and frequency
ECX	50mg/m^2 Day 1 of each 21 day-cycle	60mg/m^2 Day 1 of each 21 day-cycle	Day 1-21. Oral capecitabine 625mg/m^2 twice per day for all 21 days of each cycle

On day 1 the following medication is administered in hospital on a day case basis:

- epirubicin bolus injection,
- cisplatin infusion, and
- Commencement of oral capecitabine therapy.

Patients receiving the ECX regimen are discharged after day 1 of the cycle. On days 2-21 patients they receive oral capecitabine therapy at home with no further resource required until day 1 of the next cycle.

ECF

Components: Epirubicin (E), cisplatin (C) and 5-FU (F)

Source of regimen details: REAL-2 Study (Cunningham 2008)

Dosing and Administration:

The ECF regimen has two of the same components as the ECX regimen with the substitution of one fluoropyrimidine (capecitabine) for another (5-FU). The regimen is given over a 21 day cycle with epirubicin and cisplatin are administered on day 1 in the same dose as in the ECX regimen. Whilst in the ECX regimen the fluoropyrimidine component is administered orally in the ECF regimen the 5-FU is administered by continuous infusion via a central venous access line. A schema of the regimen is shown below.

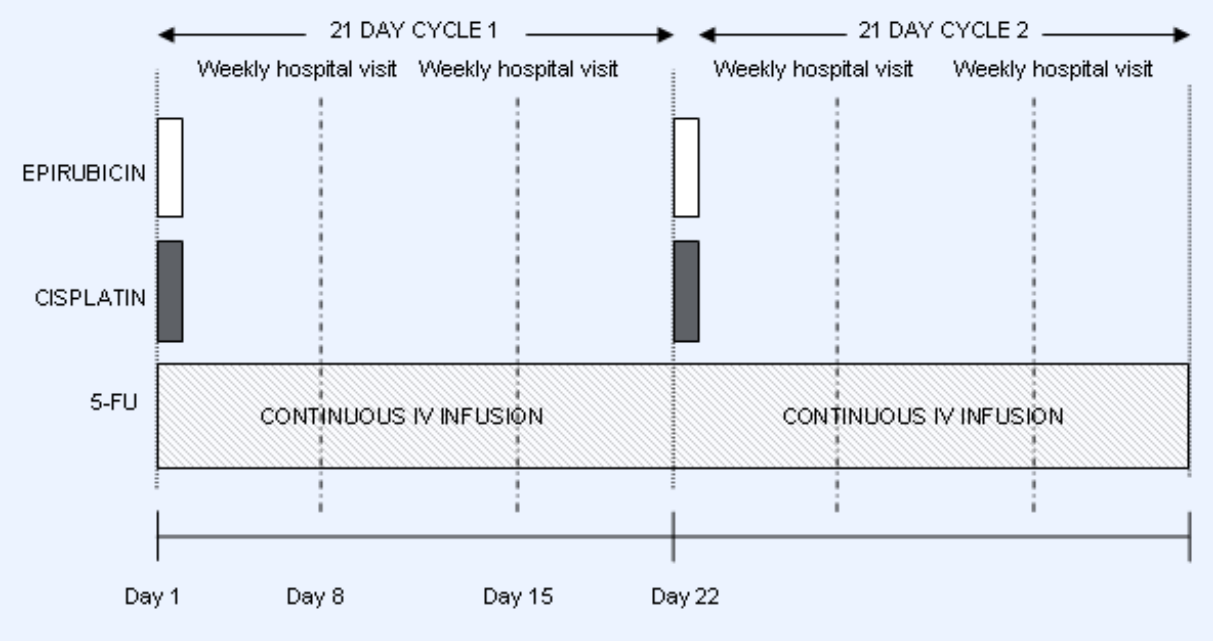


Table 15: ECF components (frequency and dosing)

Regimen	Epirubicin dose and frequency	Cisplatin dose and frequency	Fluoropyrimidine dose and frequency
ECF	50mg/m^2 Day 1 of each 21 day-cycle	60mg/m^2 Day 1 of each 21 day-cycle	Day 1-21. IV 5-FU 200mg/m^2 per day for all 21 days of each cycle, as a continuous infusion

One day prior to the commencement of ECF therapy patients visit hospital to have a central venous access line inserted to facilitate continuous 5-FU infusion for the duration of treatment.

On day 1 the following medication is administered in hospital on a day case basis:

- epirubicin bolus injection,
- cisplatin infusion, and
- commencement of IV 5-FU continuous infusion via the central venous access line

Patients are then discharged home and receive continuous IV 5-FU infusion until day 21 of the cycle. On days 8 and 15 hospital or district nurse visits are required to enable weekly replacement of the pump required for continuous IV 5-FU infusion. Every week of every cycle a pharmacist must prepare the 5-FU for IV administration.

EOX

Components: Epirubicin (E), oxaliplatin (O) and capecitabine (X)

Source of regimen details: REAL-2 Study (Cunningham 2008)

Dosing and Administration:

Patients receive EOX over a 21 day cycle. Epirubicin and oxaliplatin are administered on the first day of each cycle whilst capecitabine is administered on each day of the cycle. This 21 day cycle is repeated until disease progression or unacceptable toxicity. A schema of the regimen is shown below.

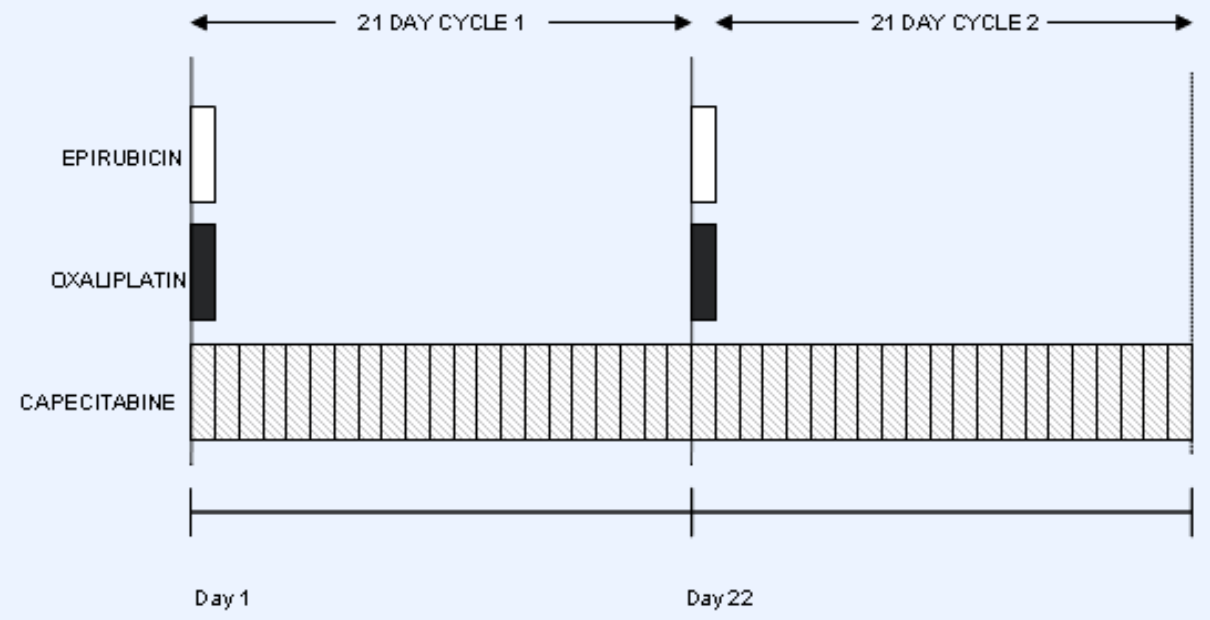


Table 16: EOX components (frequency and dosing)

Regimen	Epirubicin dose and frequency	Oxaliplatin dose and frequency	Fluoropyrimidine dose and frequency
EOX	50mg/m^2 Day 1 of each 21 day-cycle	130mg/m^2 Day 1 of each 21 day-cycle	Day 1-21. Oral capecitabine 625mg/m^2 twice per day for all 21 days of each cycle

On day 1 the following medication is administered in hospital on a day case basis:

- epirubicin bolus injection,
- oxaliplatin infusion, and
- commencement of oral capecitabine therapy.

Patients receiving the ECX regimen are discharged after day 1 of the cycle. On days 2-21 patients they receive oral capecitabine therapy at home with no further resource required until day 1 of the next cycle.

7.3.3 Study perspective

If the perspective of the study did not reflect NICE's reference case, provide further details and a justification for the approach chosen.

The economic analysis reflects the perspective of the NHS and Personal Social Services.

7.3.4 Time horizon

The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared.
What time horizon was used in the analysis, and what was the justification for this choice?

An 8 year time horizon was used; equivalent to a life-time time horizon in the population of interest. Virtually all patients within the economic model were followed to death (only <0.01% of the cohort are estimated to survive past this period).

7.3.5 Framework

The purpose of this section is to provide details of the framework of the analysis. Section a) below relates to model-based evaluations, and section b) below relates to evaluations conducted alongside clinical trials. Please complete the section(s) relevant to the analysis.

a) Model-based evaluations

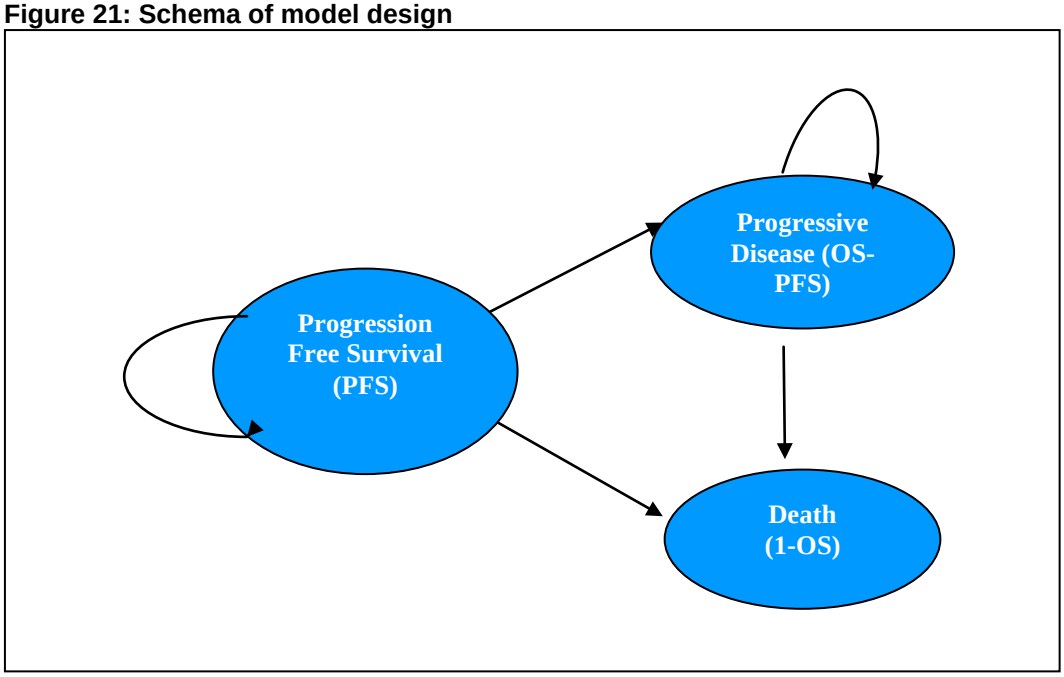
7.3.5.1 Please provide the following.

- A description of the model type.
- A schematic of the model. For models based on health states, direction(s) of travel should be indicated on the schematic on all transition pathways.
- A list of all variables that includes their value, range (distribution) and source.
- A separate list of all assumptions and a justification for each assumption.

Model Structure

A 3 stage, Excel based, area under the curve model was designed to estimate the disease progression of HER2-positive metastatic gastric cancer patients and the subsequent total direct costs and QALYs for each intervention. The model had a cycle length equal to one month. The definition of the 3 selected health states were aligned with the respective phase III RCT (ToGA). The health states are typical of previous economic evaluations of metastatic oncology interventions, progression-free survival (PFS), progressive disease (PD) and death.

Figure 21: Schema of model design



All patients were assumed to start in the PFS health state, consistent with the ToGA study.

For the interventions included in the ToGA study (HCX/F and CX/F) the Kaplan-Meier data from the ToGA RCT for PFS, and overall survival (OS) were extrapolated using parametric survival analysis in order to estimate the proportion of patients in the PFS and death health states for the expected lifetime of the patient. The most appropriate parametric function was selected following extensive statistical analysis of each function's goodness of fit and a visual inspection of the plausibility of longer term outcomes. Further details on these extrapolation methods are provided in section 7.3.5.8.

Since 87% of patients in ToGA received capecitabine based therapy the HCX/F survival curves were used to represent the survival outcome of HCX. The survival curves estimated from the reference arm in ToGA were used also to represent the survival outcomes of the capecitabine based comparator regimens used in the UK (ECX and EOX). The risk of death with 5-FU regimens, HCF and ECF, was assumed to be increased by 15% (HR taken from Okines 2009) over that of HCX and ECX respectively. The rational for these assuptions are provided in section 6.6 above.

The proportion of patients in PFS was derived directly from the extrapolated PFS curve for each cycle of the model. The proportion of patients who were in the health state of death was also derived directly from the extrapolated overall survival curves and calculated as [1-OS]. The proportion of patients within the progressive disease health state was then calculated as the residual of the PFS and Death health states (1 – [PFS+death]). Parametric extrapolation of the Kaplan-Meier curves allowed the proportions of patients in each health state to be estimated for the period beyond the trial follow-up, where no data from the RCT on disease progression or survival is known.

Kaplan-Meier survival analysis was used to calculate the mean treatment duration for each drug based on the time from first dose to the time until cessation of treatment as recorded in the ToGA study. Monthly drug acquisition and administration costs were applied to these treatment durations to estimate the total drug acquisition and administration cost for each of the regimens.

Utility scores were applied to each health state in each cycle of the model to adjust for the patient's health related quality of life. Direct healthcare costs associated with each health state (excluding death) were also applied in each cycle of the model along with the standard discount rate (3.5% pa) for both costs and benefits. A half-cycle adjustment was applied in the model to account for the fact that not all costs and outcomes occur at the end of each cycle.

The model was then able to produce estimates of each intervention's life expectancy, QALYs and direct NHS costs for each intervention along with the subsequent ICER.

Below is a table summarising the model parameters and values used in the model.

Table 17: Model Parameters and Values

Model Variable	Value	Source
Time in each health state		
1st line treatment Duration	Proportion of patients on treatment at month t out of proportion of patients in PFS at month t taken from each drug of each regimen and applied to the parametric PFS curve as described in section 7.3.8 Treatment durations of epirubicin, cisplatin and oxaliplatin in the triplet regimens were assumed to be the same as observed for cisplatin in the comparator arm of the ToGA study. Likewise the duration of duration of 5-FU and capecitabine observed in the comparator arm of the ToGA were applied to the 5-FU and capecitabine treatment durations for the triplet regimens	ToGA
PFS	Weibull extrapolation of the ToGA PFS data.	
Progression to Death (Progressive Disease)	OS-PFS	

OS	Weibull extrapolation of trial data. In accordance with the result from Okines et al a hazard ratio of 1.15 is applied to ECF vs. ECX and HCF vs. HCX	ToGA Okines 2009
Costs		
HER2 Testing	IHC test £68 FISH test £133 17.8% of mGC patients are estimated to be eligible for trastuzumab (IHC2+ FISH+ or IHC3+) 66% of eligible patients are IHC2+ and thus require a FISH test Hence per Trastuzumab patient • 5.61 IHC tests are performed • 0.66 FISH tests are performed Total cost per patient = £466.67	Bang ASCO 2009 Cost of testing: Source Biomedical and UCL
Supportive-care costs		
Monthly PFS health state supportive care • Consultations • Cardiac Monitoring • CT scans	£352 during treatment with epirubicin for comparator regimens £225 during treatment with trastuzumab £91 post treatment cessation Assumptions: One consultation visit per 3 weeks during treatment with cisplatin and every 6 weeks after Cardiac monitoring as per SmPC (every dose with Epirubicin; every 3 months with trastuzumab) whilst on treatment. CT scan at diagnosis and then at signs of progression so is assumed to cancel out comparing across the regimens	Expert Opinion; NHS reference costs, 2008/9
Monthly PD costs	£542 as per PFS supportive care cost 2nd line treatments were similar between arms in the ToGA trial and thus the cost of these is assumed to cancel out. (see Appendix E4). Verified by expert opinion (Appneix E2)	CG81: Advanced breast cancer guideline: diagnosis and treatment, February 2009 ToGA
End of life costs	£4,000	TA179 2009

Treatment cycles per month (as part of intervention regimen / comparator regimen)		
5-FU	1.32 / 1.29	*ToGA*
Capecitabine	1.27 / 1.25	
Cisplatin	1.28 / 1.26	
Epirubicin	NA / 1.26 assumed to be the same as cisplatin	
Oxaliplatin	NA / 1.26 assumed to be the same as cisplatin	
Trastuzumab	1.34 / NA	
Drug acquisition costs per treatment cycle†		
5-FU	£0.0128/mg * protocol dose * RDI	Price from latest BNF as of Jan 2010 (BNF58) Capecitabine price changed from Jan 2010 HCX and HCF dose from ToGA ECX, ECF, and EOX dose from REAL-2
Capecitabine	£0.004429/mg * protocol dose * RDI	
Cisplatin	£0.5036/mg * protocol * RDI	
Epirubicin	£1.6133/mg * protocol * RDI	
Oxaliplatin	£2.995/mg * protocol * RDI	
Trastuzumab	£2.726/mg * protocol * RDI	
Drug acquisition costs per month	Per cycle cost * observed mean number of cycles per month in trial	
Drug administration and pharmacy and transport costs per cycle (per month cost[T])		
ECF	£500 (£644)	ToGA; ref cost 2008/9 (see section 7.3.8 for more details)
HCF	£383 (£494)	
HCX	£305 (£393)	
ECX	£305 (£393)	
EOX	£305 (£393)	
Trastuzumab + 5-FU	£267 (£344)	
Trastuzumab + capecitabine	£162 (£209)	
5-FU monotherapy	£231 (£297)	
Trastuzumab maintenance	£153 (£197)	
Capecitabine monotherapy	£18 (£24)	
Utilities		
PFS	0.7292 at baseline increasing by 0.0043 per month during PFS	EQ-5D results from ToGA
Post progression	0.577	Sunitinib NICE STA for GIST
Discount rates		
Costs	3.5%	Guide to Methods, NICE
QALYs	3.5%	Guide to Methods, NICE

[T]per cycle costs multiplied by observed mean number of cycles in the ToGA study. (see section 7.3.8)

The calculation of parameter estimates as well as further detail on the references is provided in the appropriate sections below. The assumed ranges for each model parameter are listed in Section 7.3.10.4 and Appendix E3 when describing the probabilistic sensitivity analysis (PSA). Further details on the calculation of costs are provided in Section 7.3.8.

Main Assumptions in the economic model

CX, ECX, EOX are equivalent in terms of efficacy. There is a paucity of evidence directly comparing ECX and CX however the one RCT identified (Yun, 2010) did not show a significant difference between these regimens. Likewise the one identified study comparing cisplatin with oxaliplatin based triple therapy suggests these regimens are comparable. (see section 6.6). This assumption was further supported by clinical experts in a recent advisory board meeting (See appendix E2), with particular refernce to the variation in the administred dose of C and X across the doublet and triple therapy regimens.

Capecitabine containing regimens are superior in terms of OS to 5-FU regimens. The available evidence, from both the Real-2 study (Cunningham 2008) and patient level meta-analysis (Okines 2009) showed a marginal but statistically significant difference between capecitabine-based therapy and 5-FU-based therapy. Given the evidence it was considered unreasonable to assume equivalence between these regimens in the analysis. (see section 6.6)

Second-line treatment costs post progression are equivalent across all the interventions / comparators. The proportion and mix of anti-cancer treatments given post progression were very similar across all of the treatment arms of the ToGA study (see Appendix E4). It was therefore assumed that there was no difference between the arms in terms of second- and third-line treatment costs and thus these costs have been excluded from the analysis. Monthly supportive care costs were applied to the PD health state to account for any additional costs incurred through increased survival times within this health state. Sensitivity to variation in this monthly cost was explored in the sensitivity analysis. Clinical experts (Appendix E2) confirmed that second-line therapy selection was not based on first-line treatment and therefore it would be expected that the choice of second-line therapy would not be influenced by the use of trastuzumab.

Quality of life whilst in each health state is not affected by which regimen a patient is treated with. There was a comparable improvement in quality of life (QoL) in both arms of the study as measured by the EORTC-QLQ-C30 and QLQ-ST022 instruments (Satoh 2010) as well as the EQ-5D. (see section 6.4.7). It is assumed that utility during PFS is also similar for the comparators of relevance to the UK (ECX, ECF, and EOX). This assumption was validated by clinical experts (Appendix E2)

Due to the volume of trastuzumab utilisation within the breast cancer indication, it was assumed that the majority of centres will vial share and thus keep wastage of drugs to a minimum. Trastuzumab received positive guidance from NICE for use in breast cancer in TA34 and TA107. Discussions with clinical experts indicates many centres currently used vial sharing practices to eliminate wastage. Given the current economic pressures facing the NHS it is anticipated that these vial sharing programs will continue to expand as PCTs and hospital trusts seek to make the efficiency savings required of them. In order to maximise the efficiency of service delivery Roche anticipate that

patients receiving trastuzumab for gastric cancer will vial share in tandem with those patients currently receiving trastuzumab for breast cancer.

The clinical experts attending a recent Roche advisory board (appendix E2) expected that the majority of centres are currently vial sharing and that centres that are not are likely to adopt this practice in the future. The clinicians were unable to provide a precise estimate however indicated that assuming 80% would not be an unreasonable assumption. It was therefore assumed for the base case analysis that 80% of centres in the UKI currently vial share. The sensitivity of the ICER to uncertianty in the assumed estimate was tested in sensitivity analysis.

7.3.5.2 Why was this particular type of model used?

Some form of modelling exercise was required as not all patients were followed until death therefore extrapolation of the clinical trial data was required for PFS and OS. The median follow-up period of the ToGA study on which the analysis is based was sufficiently long to follow the majority of patients until disease progression and then until death. Given survival time did not greatly exceed the time frame of the main clinical trial an area under the curve model was considered appropriate.

7.3.5.3 What was the justification for the chosen structure? How was the course of the disease/condition represented? Please state why any possible other structures were rejected.

The structure of stratifying the clinical outcomes of oncology patients into progression-free, progression, and death is consistent with previous health technology assessment of therapies for first-line metastatic cancer. The health states align with the key objectives of treatment within this disease area: to increase the length of time patients remain alive and increase the duration of time spent in the progression-free health state. Furthermore, the main outcomes of the clinical trial could be stratified into one of these 3 heath states: progression-free survival, progressed patients and death.

7.3.5.4 What were the sources of information used to develop and inform the structure of the model?

The model was structured around the ToGA RCT. This trial provided the proportion of time a patient spent in each of the health states before death as well as time to treatment cessation.

7.3.5.5 Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?

The 3 health states within the model capture all conditions relevant to the decision problem.

7.3.5.6 For discrete time models, what was the model's cycle length, and why was this length chosen? Does this length reflect a minimum time over which the pathology or symptoms of a disease could differ? If not, why not?

The cycle length of the model is monthly. Clinical assessment is not performed on a more regular basis than every month. Therefore it is reasonable to assume that costs or clinical outcomes would not change on a more frequent basis than every month for the purpose of the model.

7.3.5.7 Was a half-cycle correction used in the model? If not, why not?

A half-cycle correction was applied to the model.

7.3.5.8 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer-term difference in effectiveness between the technology and its comparator?

Despite there being a relatively mature follow-up of patient outcomes (median of 17.1 and 18.6 months for CX/F and HCX/F respectively) at the time of the latest data cut there was still a proportion of patients that were still alive or who had not progressed. 24.9% and 19.5% of patients remained in PFS for the trastuzumab+chemotherapy and chemotherapy-alone arms respectively; 43.2% and 37.2% of patients were still alive in the trastuzumab-containing arms and chemotherapy alone arms respectively. Consequently as is common practice within economic evaluation a parametric extrapolation of the survival data was performed in order to estimate the longer term outcomes for those patients not having experienced the endpoints of interest within the study.

The parameters for the endpoints PFS and OS, under the assumption of a parametric survival function, were estimated using the clinical data. Gompertz, Weibull, Log Logistic, Log Normal and Exponential survival functions were estimated based on the data and then assessed for goodness of fit. To assess goodness of fit the Akaike (AIC) and Bayesian Information Criteria (BIC) statistics were utilised along with a graphical inspection of the fit of the data and plausibility of longer term predictions, before selecting the most appropriate curve for the final model.

Whilst the time to treatment cessation Kaplan-Meier curves are almost complete (see Figure 28 section 7.3.8) some extrapolation of the dose curve for trastuzumab was required. A linear regression of the proportion of patients on treatment out of those remaining progression free over time was used to extrapolate the remainder of the dose curve.

Progression Free Survival

Extrapolation of the progression free data was carried out under the assumption that the data followed a parametric model structure. The parameters were estimated using the available clinical data.

Table 18: Summary of Parametric Functions' Goodness of Fit for PFS

Parametric Model	AIC	BIC
llogistic	978.35786522	966.15954095
lnormal	985.22067161	973.02234734
Weibull	1004.7883717	988.52393934
Gompertz	1055.4603357	1043.2620114
exponential	1052.8417241	1044.7095079

The parametric function with the lowest AIC and BIC value and subsequently representing the best statistical goodness of fit was the Log Logistic function.

However, graphical examination ruled the log logistic function and the next best statistical fit, the log normal function out, as they appeared to severely over-estimate the tail of the survival curves leading to implausibly long survival outcomes for some patients (see Figure 22 and Figure 23 below).

Finally given the completeness of the survival curves, the Kaplan-Meier PFS curves were used up to the end of month 12. The tails of the Kaplan-Meier curves become erratic beyond 12 months as they are subject to an increased level of uncertainty due to decreasing patient numbers. Hence from month 13 the Weibull function (with parameters estimated based on all data from i.e. from time 0) was used to extrapolate the data as this was the 3rd best fitting curve in terms of statistical fit and unlike the log logistic and log normal functions did not result in implausible maximum durations of PFS. The resulting PFS curves used in the base case are shown in Figure 24 below.

Figure 22: Extrapolated Progression-Free Survival data from ToGA using the Log Logistic Survival Function (IHC2+/FISH+ or IHC3+ metastatic patients only)

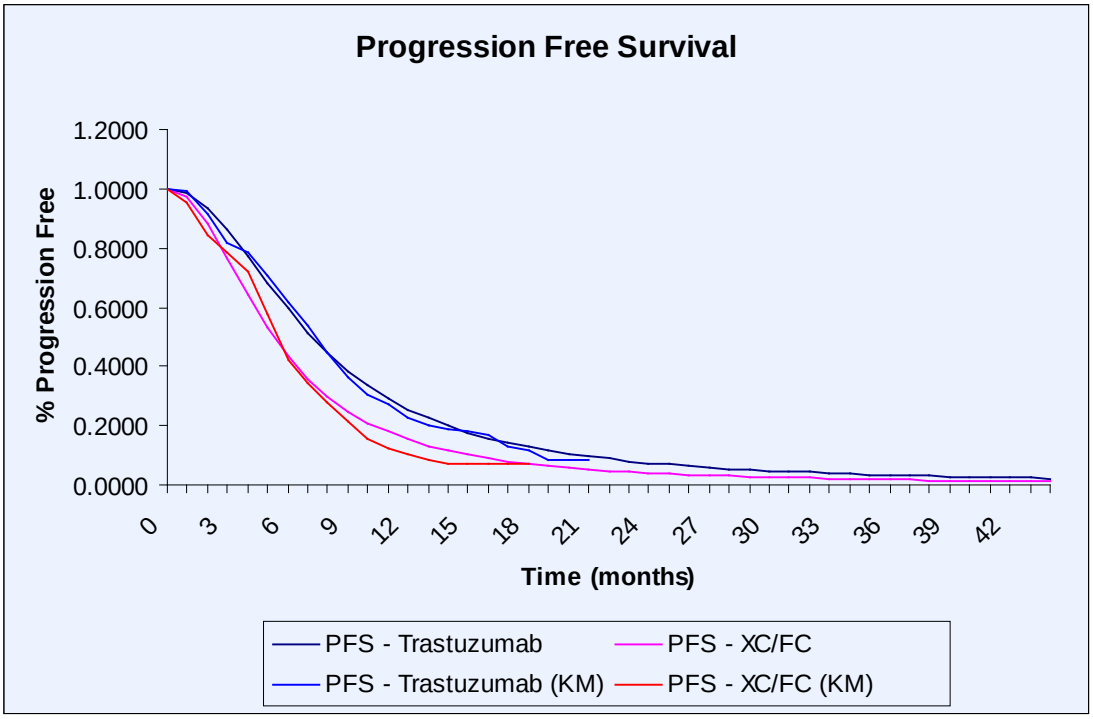


Figure 23: Extrapolated Progression-Free Survival data from ToGA using the Log Normal Survival Function (IHC2+/FISH+ or IHC3+ metastatic patients only)

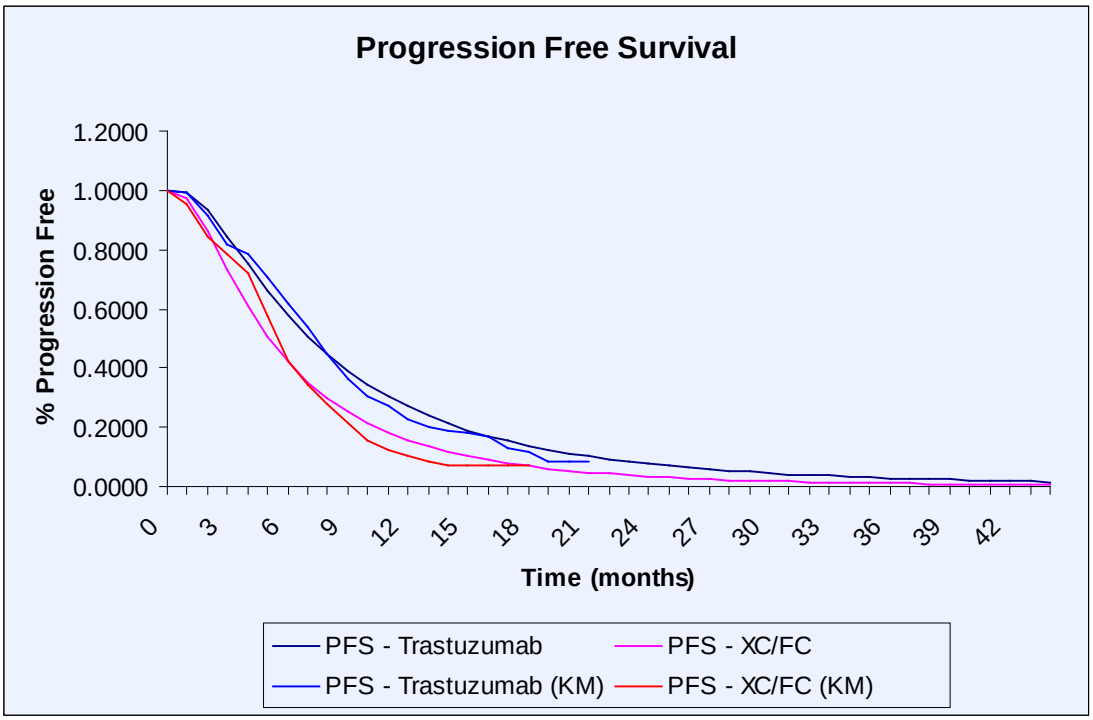
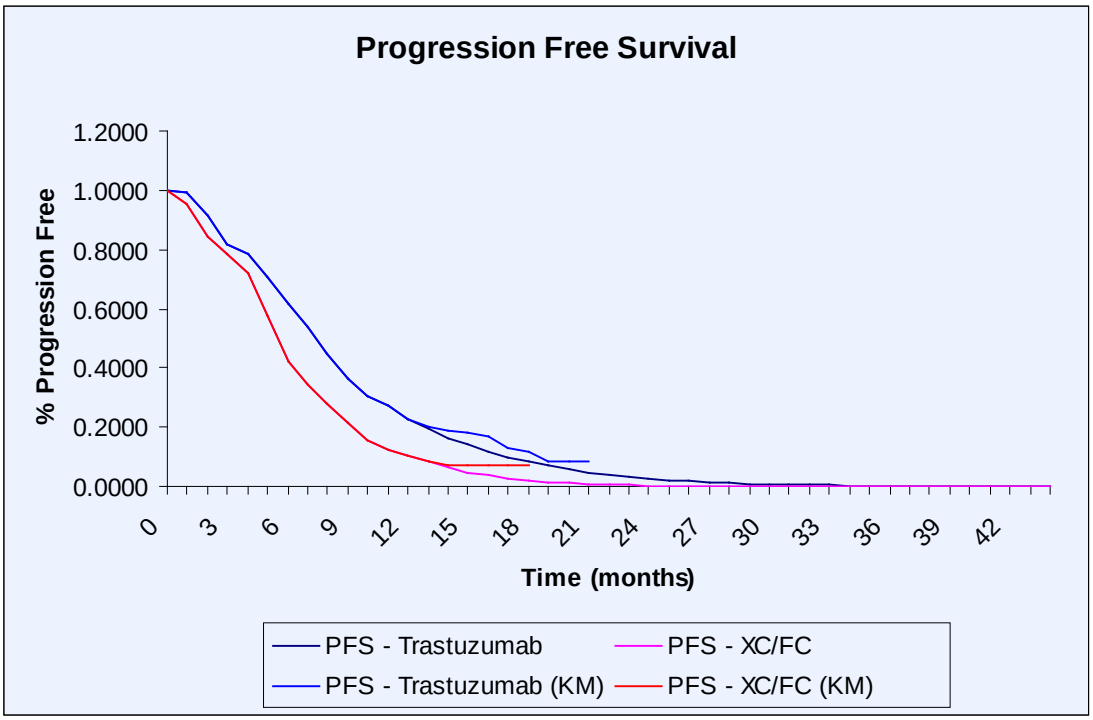


Figure 24: Extrapolated Progression-Free Survival data of ToGA using the KM estimates up to the end of month 12 and extrapolated using the Weibull function from this point on (IHC2+/FISH+ or IHC3+ metastatic only)



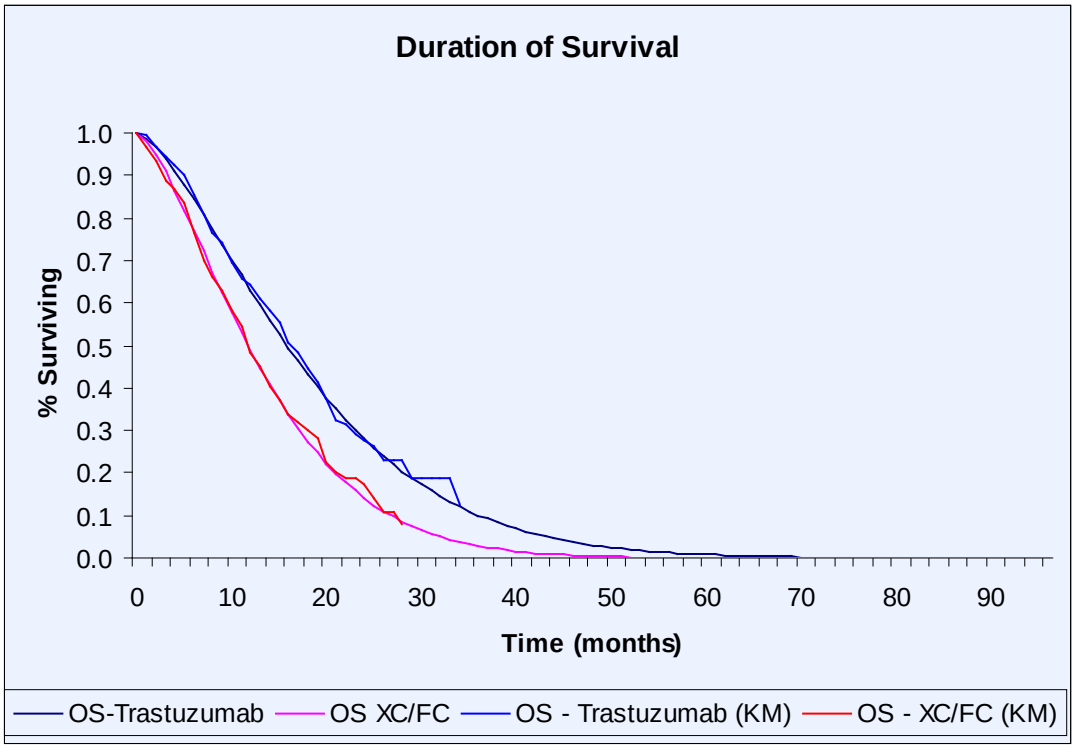
Overall Survival

As per the PFS extrapolation, Gompertz, Weibull, Log Logistic, Log Normal and Exponential survival functions were estimated based on the data and assessed for their fit to the OS data with the Weibull function being selected as the best fit to model the data. The goodness of fit results are presented in the table below:

Table 19: Summary of Parametric Functions' Goodness of Fit for OS

Parametric Model	AIC	BIC
Weibull	909.9214657	893.65703334
llogistic	914.44613306	902.24780879
lnormal	926.0578762	913.85955193
exponential	944.29294009	936.16072391
Gompertz	983.41152063	971.21319636

Figure 25: Extrapolated overall survival from ToGA using the Weibull survival function (IHC2+/FISH+ or IHC3+ metastatic only)



Parameter estimates for the Weibull function in OS and PFS are shown in the table below.

Table 20: Weibull Parameter Estimates for OS and PFS by Treatment Arm

Efficacy Endpoint	Trastuzumab + Chemotherapy	Chemotherapy alone
Overall Survival (OS)		
Lambda	0.012383713	0.019144391
Gamma	1.457504857	1.457504857
Progression Free Survival (PFS)		
Lambda	0.036642015	0.061428405
Gamma	1.424785732	1.424785732

The PFS Weibull survival function is defined as

$$\text{with } \lambda = \exp\left(\frac{-(\mu+\delta)}{\sigma}\right) \text{ and } \gamma = \frac{1}{\sigma}$$

and δ representing the treatment covariate and the model μ intercept.

$$S(t) = \exp(-\lambda t^{\gamma}) \qquad \text{with } \lambda = \exp\left(\frac{-(\mu+\delta)}{\sigma}\right) \text{ and } \gamma = \frac{1}{\sigma}$$

7.3.6 Clinical evidence

Where relevant, answers to the following questions should be derived from, and consistent with, the clinical evidence section of the submission (section 6). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided and a justification for the approach provided

7.3.6.1 How was the baseline risk of disease progression estimated? Also state which treatment strategy represents the baseline.

An “area under the curve” model design was utilised. The risk for disease progression and death was derived from the ToGA study by fitting the Weibull parametric function to the subgroup of patients that are within trastuzumab’s license. Therefore the Weibull curves for the comparator arm within this subgroup provides the baseline risk. The protocol for the ToGA study allowed clinicians to opt to use either capecitabine or 5-FU. Given the vast majority of patients (87%) received CX as opposed to CF in the comparator arm, for the purposes of the indirect comparisons and to help simplify the analysis,

it is assumed that the baseline risk observed in the ToGA trial represents the outcomes of patients receiving CX.

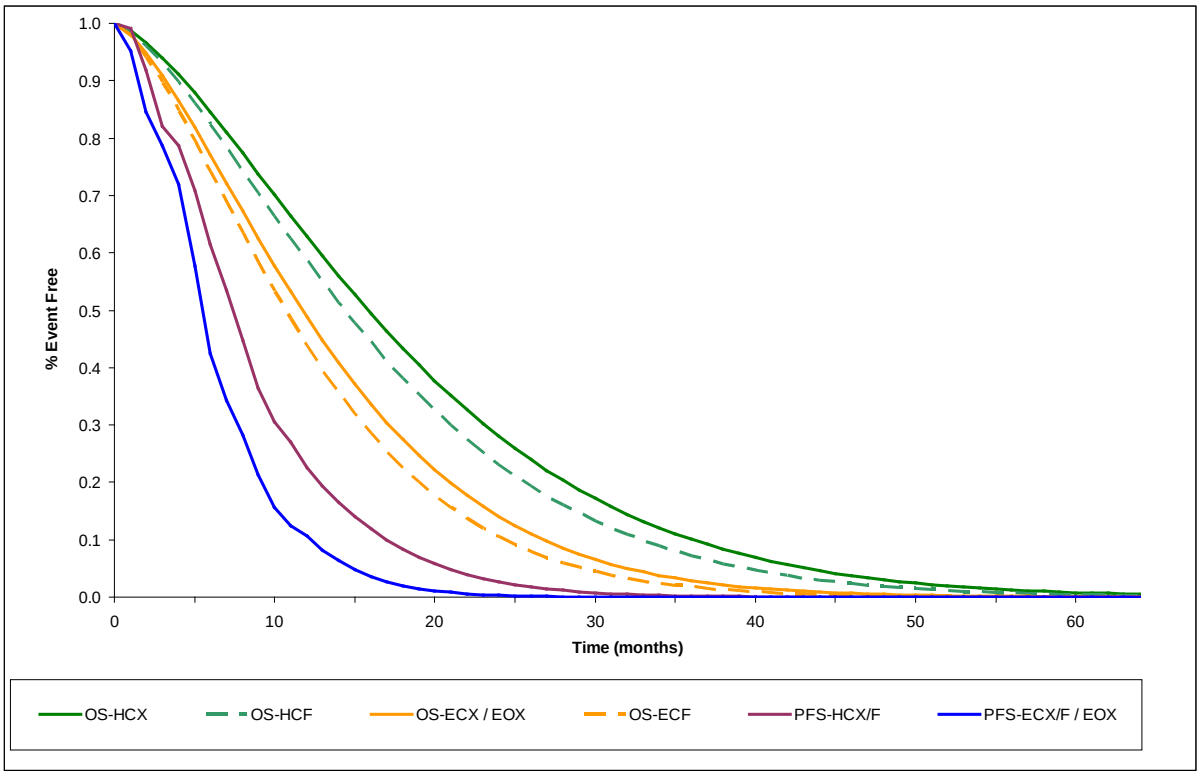
7.3.6.2 How were the relative risks of disease progression estimated?

It was assumed that CX, ECX, and EOX offer equivalent efficacy (see section 4 and 6.6). The relative risk of progression and death for patients receiving HCX relative to CX (and thus also the treatment effect of HCX relative to ECX and EOX) was estimated by fitting Weibull parametric curves to the data from the ToGA trial. Only data from patients that fall within the license of trastuzumab were included in this analysis. Please see section 6.3.5.8 above for more details of the selection the chosen parametric function.

Real-2 (Cunningham 2008) and meta-analysis (Okines 2009) demonstrated that capecitabine based regimens confer an overall survival advantage over 5-FU based regimens. The hazard ratio from the meta-analysis was applied to the extrapolated ECX and HCX OS survival curves to derive the survival curves for ECF and HCF respectively. This implicitly assumes that the CX/F and HCX/F arms of ToGA represent a reasonable reflection of the outcomes of CX and HCX respectively. The justification for this assumption is that the vast majority of patients (87%) received capecitabine based therapy in ToGA. It also assumes that the treatment effect of adding trastuzumab is the same when added to either CF or CX. This assumption is supported by there being no significant interaction observed in the ToGA study between the base chemotherapy and treatment (p-value: 0.6328)

The resulting OS curves used in the base case analysis are shown in Figure 26 below. Sensitivity of the ICER to changes in the relative efficacy of the comparator regimens and to the survival function employed to extrapolate the data was explored in the sensitivity analysis.

Figure 26: Extrapolated Survival Curves used in the Base Case Analysis



7.3.6.3 Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years [QALYs])? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

The health states of progression free survival and progressive disease were linked to the final outcome of QALYs in the model. The utility scores for PFS were estimated based on the EQ-5D results of the trial for PFS. As EQ-5D data was not captured for the duration of post progression in the ToGA trial, utility scores were informed by estimates from the literature for the PD health state (see section 7.3.6.4 for more details).

7.3.6.4 Were the health effects or adverse effects associated with the technology included in the economic evaluation? If not, would their inclusion increase or decrease the estimated cost effectiveness of this technology?

The frequency and type of adverse events observed in the ToGA trial were comparable between the arms and consistent with those observed from treatment with the triplet therapies used in the UK (based on comparison with the results REAL-2; Cunningham 2008 see Table 31 section 7.3.8.1. However the cost of treating adverse events of grade 3 and above was included in the analysis for

completeness. The details of how these costs were estimated and applied in the model are provided in section 7.3.8.1

Any disutility of receiving first-line chemotherapy is assumed to have been captured in the utility value for the PFS health state. There was a comparable improvement in quality of life (QoL) in both arms of the study as messured by the EORTC-QLQ-C30 and QLQ-ST022 instruments (Satoh 2010) and the EQ-5D (see section 7.3.7). In addition clinical experts (Appendix E2) indicated they would not expect a difference in utility for patients receiving the triplet therapy typically used in the UK compared to the doublet regimens used in ToGA. Thus it was assumed that the Quality of life whilst in each health state is not affected by which regimen a patient is treated with.

7.3.6.5 Was expert opinion used to estimate any clinical parameters? If so, how were the experts identified, to which variables did this apply, and what was the method of elicitation used?

Phase III clinical trial data was predominantly the source used to provide values for clinical parameters. Expert opinion was used to inform the following clinical practice assumptions:

- Most relevant comparators to the UK NHS
- The frequency of visits to disconnect the ambulatory pump and flush the CVAD.
- Frequency of consultations during PFS
- Type and frequency of tests during PFS
- The percentage of patients that received the 5-FU infusions via an ambulatory pump as opposed to receiving these infusions via a hospital based pump as an inpatient.
- The proportion of patients requiring NHS funded transport to attend hospital.
- The use of vial sharing to minimise wastage of trastuzumab

In addition to advising on clinical practice the follow assumptions were validated with clinical experts:

- Equivalent efficacy across the doublet therapy used in ToGA and the triplet therapy used typically in the UK.
- There is a modest reduction in the risk of death for patients treated with capecitabine based therapy
- The choice of 2nd line treatment is not based on which 1st line treatment patients receive.
- Utility values in each health state are the same across all the regimens being compared

Expert opinion was initially provided via telephone conversation by 2 experts to inform the model structure and clinical assumptions employed in the economic analysis. After which validation of these assumptions was provided during a Roche advisory board meeting attended by 8 clinical experts and an expert health economist. All the clinical experts were oncologist highly experienced in the treatment of gastric cancer.

Uncertainty around these clinical practice assumptions was explored in the one-way sensitivity analysis.

7.3.6.6 What remaining assumptions regarding clinical evidence were made? Why are they considered to be reasonable?

All assumptions relating to clinical evidence have been previously described.

7.3.7 Measurement and valuation of health effects

The value of health effects should be expressed in terms of QALYs for the appropriate time horizon. For the reference case, the measurement of changes in HRQL should be reported directly from patients and the value of changes in patients' HRQL (that is, utilities) should be based on public preferences using a choice-based method. The EQ-5D is the preferred measure of HRQL in adults. The methods to elicit EQ-5D utility values should be fully described. When EQ-5D data are not available or are inappropriate for the condition or effects of treatment, the valuation methods should be fully described and comparable to those used for the EQ-5D. Data collected using condition-specific, preference-based measures may be presented in separate analyses. The use of utility estimates from published literature must be supported by evidence that demonstrates that they have been identified and selected systematically.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

7.3.7.1 If health effects were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?

For the purpose of the economic analysis health effects have been expressed using QALYs

7.3.7.2 Which health effects were measured and valued? Health effects include both those that have a positive impact and those with a negative impact, such as adverse events.

The health effect associated with PFS and progressed states were measured via survival analysis and valued via utility scores. This allowed for different health benefits to be calculated for patients in the intervention and comparator arms by taking into account the difference in life expectancy and the duration of time spent in each of these states. It is assumed that any disutilities associated with treatment related adverse events are included within the utilities collected within the trial.

7.3.7.3 How were health effects measured and valued? Consideration should be given to all of the following:

- State whether the EQ-5D was used to measure HRQL or provide a description of the instrument/s used.

- Provide details of the population in which health effects were measured. Include information on recruitment of sample, sample size, patient characteristics and response rates.
- Were the data collected as part of a RCT? Refer to section 5.3 as necessary and provide details of respondents.
- How were health effects valued? If taken from the published literature, state the source and describe how and why these values were selected. What other values could have been used instead?
- Was a mapping mechanism (or 'cross-walk') generated to estimate health-related utilities of patients in the trials? Provide details of the rationale for the analysis, the instruments used, the sample from which the data were derived and the statistical properties of the mapping mechanism.
- Were health states directly valued? If so, provide details of the rationale for the analysis, the HRQL measures that were valued, the population who produced the values and full details of the methods used. Explain the rationale for the analysis and the choice of instruments used.

Literature search for PFS and PD utility values

No utilities conforming to the NICE guide to methods are available in the literature (see section 10.8, Appendix 3) Those values that have been used in economic evaluations in, or related to, gastric cancer (Glimelius et al. and Dan et al.) stem from the 1995 Glimelius paper in which an extremely primitive method of utility elicitation was utilised in a very small number of patients. The two values produced by Glimelius are listed below:

Primary Chemotherapy = 0.75

Best Supportive Care = 0.58

Whilst these values were not obtained using methods recommended in the NICE guide to methods it is encouraging that they are roughly equivalent to the values obtained through EQ-5D collection in ToGA and those utilised in the economic evaluation (see table below).

Utility values during PFS

In ToGA the EQ-5D utility questionnaire was completed at baseline, then 3-weekly until disease progression. The EQ-5D results from patients in the study who fall within the license of trastuzumab were valued using the UK tariff reported by Dolan (Dolan 1997). A statistical model (mixed model) was then fitted to these utility values. Initially time from baseline, and treatment were included as co-variates in this model. A positive effect of trastuzumab on utility was estimated, however treatment was dropped from the base case model as it was not a statistical significant predictor of outcome (p-value: 0.1429). The results of the final model can be seen below.

Effect	Estimate	Error	DF	t Value	Pr > |t|
Intercept	0.7292	0.01087	421	67.11	<.0001
DAY	0.000142	0.000057	388	2.48	0.0135

Table 21: Goodness of fit EQ-5D mixed model

2 Res Log Likelihood	79.9
AIC (smaller is better)	81.9
AICC (smaller is better)	81.9
BIC (smaller is better)	84.7

Inclusion of treatment and removal of time as co-variates was explored in sensitivity analysis.

A total of 431 patients were used in the analysis with a 3'256 data points used to estimate the PFS utility estimates. 9 patients did not have sufficient information in order to estimate their impact to the utilities.

Utility values during Progression

The ToGA protocol only required the administration of the EQ-5D questionnaire until disease progression. The mean utility scores recorded during the final completed EQ-5D, where the visit was on the day of first recorded progression or after, were 0.7088 (n=77) and 0.7172 (n=91) for trastuzumab + chemotherapy and chemotherapy alone arm respectively.

In the absence of post progression utility values for metastatic gastric cancer being identified in the literature a utility value of 0.577, taken from a recent NICE appraisal of sunitinib in the 2nd line treatment of gastrointestinal stromal tumours (NICE TA179, 2009) was used as a proxy. Whilst this is a different disease area and line of treatment the utility estimates for 2nd line PFS in this study (0.73) were consistent with those of 1st line PFS in the ToGA. We note the assumption of transferability of disutility associated from moving from stable disease to progressive disease from one tumour type to another has been used previously (NICE TA91).

Table 22: Utility values used in base case analysis

Heath state	Utility weight	Source	Comments and assumptions
PFS	0.7292 at baseline Increasing by 0.000142 daily during PFS	ToGA	EQ-5D results from ToGA for population valued using the York tariff
PD	0.577	TA179 2009	Utility weights taken from a phase III study using EQ-5D in patients with GIST after progression on 2nd line treatment.

7.3.7.4 Were any other generic or condition-specific preference based measures used in the clinical trials? Provide a description of the data below. The results should be considered in a sensitivity analysis (see Section 6.2.11).

No

7.3.7.5 Were any health effects excluded from the analysis? If so, why were they excluded?

No

7.3.8 Resource identification, measurement and valuation

For the reference case, costs should relate to resources that are under the control of the NHS and PSS when differential effects on costs between the technologies under comparison are possible. These resources should be valued using the prices relevant to the NHS and PSS. Evidence should be presented to demonstrate that resource use and cost data have been identified systematically.
Some technologies may have a substantial impact on the costs (or cost savings) to other government bodies. In these exceptional circumstances, costs to other government bodies may be included if this has been specifically agreed with the Department of Health, usually before referral of the topic. When non-reference-case analyses include these broader costs, explicit methods of valuation are required. In all cases, these costs should be reported separately from NHS/PSS costs. These costs should not be combined into an incremental cost-effectiveness ratio (ICER; where the QALY is the outcome measure of interest).
All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

7.3.8.1 What resources were included in the evaluation? (The list should be comprehensive and as disaggregated as possible.)

1) Drug acquisition costs
2) Drug administration costs
    a) Pharmacy preparation and dispensing
    b) Administration day case appointments
    c) District nurse visits
    d) Acquisition cost of ambulatory pumps
3) Monitoring
    a) Face to Face consultations
    b) CT scans
    c) Blood tests
    d) Cardiac Monitoring
4) Installation and replacement of central venous access devices (CVADs)
5) Treatment of Adverse Events
6) Supportive care costs post progression in first line
7) HER2 testing

Methods used for estimating costs per patient

Overview

A cost per treatment cycle for each regimen, which included drug acquisition, pharmacy, drug administration, and monitoring, was calculated. A monthly cost of treatment was then calculated based on the average treatment duration observed in the ToGA study. These monthly costs were then multiplied by the mean number of months on treatment. Kaplan-Meier survival analysis was used to calculate the mean treatment duration based on the time from first dose to the time until cessation of treatment (end of last cycle i.e. 21 days after the last dose). A monthly cost of supportive care was applied for the remainder of PFS post cessation of first line treatment (cessation of cisplatin for comparator regimens and trastuzumab for intervention regimens).

Average Adverse event and CVAD costs per patient were applied to month one of the PFS health state and thus no discounting was applied to this cost.

Given the very similar proportion of patients that received each of the 2nd line treatments recorded in the ToGA study (see appendix E4), it was assumed there is no differences in costs for second-line treatment between the different interventions/comparators. Hence no cost for second-line treatments has been applied in the model. Instead a monthly supportive care cost of £542 was applied for each of the interventions for the duration of post progression survival.

Consistent with the recent appraisal of sunitinib for the treatment of GIST (TA179 2009), a cost associated with death of £4,000 was included within the analysis, to reflect end of life costs associated with intensive palliative and hospice related care. This cost was based on an estimate from the literature (Coyle et al, 1999) and represents the average cost of hospital and hospice stays inflated to 2010 costs. As a sensitivity analysis no cost of death was assumed.

Drug acquisition costs per cycle

Drug acquisition unit costs

All drug acquisition costs were taken from the most recent version of the BNF (BNF58) as summarised below, with the lowest cost generic version selected where both branded and generic presentations were available. Where the cost per mg differed depending on the vial size the weighted average price per mg was used. A full list of drug prices is included in Appendix E1.

Table 23: Unit costs of evaluated drugs (BNF58 accessed Jan 10)

Product	£/mg
Trastuzumab	2.7160
Oxaliplatin non proprietary	2.9950
5FU non proprietary	0.0128
Capecitabine	0.0044
Cisplatin non-proprietary	0.5036
Epirubicin non-proprietary	1.6133

Drug utilisation

The duration of treatment, average dose and subsequent total cost of each of the trastuzumab containing regimens was based upon that observed within the ToGA study. This provides an empirical basis for the assumptions and also is consistent with the observed and modelled health benefits of the interventions. The table below shows the mean per cycle dose in the ToGA study for each regimen by drug.

Table 24: Mean dose (mg) per cycle observed in ToGA study by arm (IHC2+ FISH+ or IHC3+ subgroup)

Study Arm (ITT)	Trastuzumab 1st cycle	Trastuzumab subsequent cycles	5-FU	Capecitabine	Cisplatin
Trastuzumab + 5-FU/ Cisplatin	490	377	6,415	39,274	118
5-FU + Cisplatin	N/A	N/A	6,230	40,041	120

The data in the table above was used to calculate the relative dose intensity per cycle ($Actual\_dose\_per\_cycle / protocol\_dose\_per\_cycle$) that was applied in the model.

Relative dose intensity per cycle for the comparator regimens was obtained from the appendix of the REAL-2 study paper (Cunningham, 2008).

Table 25: Relative dose intensity per cycle used in the model

	ECX	EOX	ECF	HCX	HCF
5-FU			93%		93%
Capecitabine	88%	88%		82%	
Cisplatin	92%		91%	86%	86%
Epirubicin	89%	89%	93%		
TrastuzumabLD				98%	98%
Trastuzumab				100%	100%
Oxaliplatin		93%			

Table 26: Dose per cycle (mg) used in the model

	ECX	EOX	ECF	HCX	HCF
5-FU	-	-	6,674	-	6,415
Capecitabine	39,818	39,818	-	39,274	-
Cisplatin	95	-	93	118	118
Epirubicin	77	77	79	-	-
TrastuzumabLD	-	-	-	490	490
Trastuzumab	-	-	-	377	377
Oxaliplatin	-	207	-	-	-

As can be seen from the table above the dose per cycle of 5-FU and Capecitabine is similar between the regimens, whilst cisplatin is approximately 26% greater in the intervention regimens. This disparity is a result of the triplet regimens used typically in the UK using a lower protocol dose of cisplatin (60mg/m^2) compared with the double regimens upon which HCX and HCF are based which use a protocol dose of 80mg/m^2.

Drug administration and pharmacy costs per cycle

The combined pharmacy and drug administration costs assumed in the model are shown below

Table 27: Combined drug administration (inc. patient transport) pharmacy, and monitoring costs per cycle / month

Regimen	Cost per cycle (per month)
ECF	£500 (£644)
HCF	£383 (£494)
HCX	£305 (£393)
ECX	£305 (£393)
EOX	£305 (£393)
Trastuzumab + 5-FU	£267 (£344)
Trastuzumab + capecitabine	£162 (£209)
5-FU monotherapy	£231 (£297)
Trastuzumab maintenance	£153 (£197)
Capecitabine monotherapy	£18 (£24)

A table showing a breakdown of the resource use by regimen is presented in Appendix E1.

Drug administration costs

Table 28: Drug administration delivery costs per hospital visit, excluding district nurse, pharmacy and patient transport and ambulatory pump costs (inflated to 2010 costs) per cycleTable 28 below lists the administration costs used in the model. These costs were sourced from previous NICE appraisals and from the NHS reference costs 2008/9. Other treatment costs (i.e. chemotherapy drugs including any pharmacy dispensing on-costs and associated drugs to deal with the symptoms or side effects of the chemotherapy drugs themselves) are excluded from NHS reference costs associated with the delivery of chemotherapy and thus were included separately. Monitoring is also not included in the

chemotherapy delivery costs listed in the 2008/9 references costs and thus was also costed separately.

Administration of HCF involves a continuous infusion over 5 days whereas ECF requires a 21 day continuous infusion. These infusions can be delivered either through an ambulatory pump where the patient spends the nights after day 1 at home or though a hospital-based pump where the patient is required to stay in the hospital for the duration of the infusion. It is understood that the vast majority of patients receive treatment via an ambulatory pump and that the decision to keep a patient in the hospital is determined by the health of the patient and not which 5-FU based regimen they are treated with. (Expert Opinion see Appendix E2). Hence it has been assumed that all patients receiving 5-FU do so via an ambulatory pump and go home over night.

The unit cost for hospital administration of trastuzumab was also taken from Ward and colleagues (Ward 2006) and inflated to 2010 costs.

Below are the delivery costs per visit applied in the base case analysis. For the HCX and HCF regimens, consistent with its licensed indication and the ToGA trial, trastuzumab is continued as a maintenance therapy beyond cessation of chemotherapy. In addition in ToGA not all chemotherapy drugs were stopped at the same time and thus administration costs for not only trastuzumab maintenance but also trastuzumab in combination with 5-FU (HF) and 5-FU monotherapy were needed to be estimated.

It was assumed that the delivery cost per visit of 5-FU monotherapy would be the same as for trastuzumab and that the combination of trastuzumab and 5-FU would cost 20% more than this. The affect on the ICER to changes in these assumed costs was explored in the sensitivity analysis.

Table 28: Drug administration delivery costs per hospital visit, excluding district nurse, pharmacy and patient transport and ambulatory pump costs (inflated to 2010 costs) per cycle

Regimen	Delivery costs inflated to 2010 costs	Reference cost HRG code / reference
HCX ECX EOX HCF ECF	£268	SB14Z: Deliver complex Chemotherapy, including prolonged infusional treatment at first attendance.
Trastuzumab + 5FU	£159	Trastuzumab maintenance * 1.2 (modelling assumption)
Trastuzumab maintenance 5-FU monotherapy	£133	Ward and colleagues: ERG report Trastuzumab Early Breast Cancer STA

Ambulatory Pump costing

It was assumed that a disposable 5 day elastomeric 'balloon' pumps are used for the delivery of 5FU. The cost of the pump was estimated to be £38.50, based on the average of the pumps provided by a large medical supplier (Baxter UK website, FOLFusor SV1 nominal flow rate 1ml/h and the FOLFusor SV0.5 nominal flow rate 0.5ml/h single pack; http://www.ecomm.baxter.com/ecatalog/browseList.do?key=17cd8cf0d04f79333274eea7f0ce892a&pageNr=1&lid=10011&hid=10000&cid=10001)

This cost was assumed to be part of the pharmacy on-costs and therefore in addition to the HRG reference costs used to calculate the cost of a hospital visit for drug administration.

Regular district nurse visits

The HCF regimen involves a 5 day continuous infusion via an ambulatory pump. A district nurse would visit the patient at there home at the end of the infusion to disconnect the pump and flush the CVAD.

The ECF regimen involves a 21 day continuous infusion via an ambulatory pump. However as the pumps are only designed to work over a 7 day period they must be replaced weekly. At the beginning and the end of the 21 day cycles this will be performed in the hospital however the 2 replacements required mid cycle are either performed by a district nurse at the patients home or by a nurse in the hospital (Expert opinion Appendix E2). The cost of a district nurse visit of £39 was applied in the model based on the HRG: CN301AF District Nursing Services : Adult : Face To Face (NHS reference costs 2008/9) inflated to 2010 costs. It was assumed that the cost of removing the pump would be same irrespective of the whether this is done in the hospital or by a district nurse.

Pharmacy costing

Pharmacy costs are not included within the drug delivery reference costs and therefore were costed separately.

A prospective time-and-motion study was conducted in two UK secondary care NHS Trusts to quantify, in terms of time, the secondary care NHS resource use associated with the preparation and administration of XELOX (capecitabine in combination with oxaliplatin) and FOLFOX-6 (5-FU in combination with folinic acid and oxaliplatin) in metastatic colorectal cancer (Millar 2008). The results of the study indicated that dispensing of capecitabine (Xeloda) and preparation of oxaliplatin required an average of 12 minutes each. It was assumed for the base case analysis that each of the component medicines in the regimens of interest to this appraisal would also take 12 minutes to prepare.

One hour of a pharmacist time performing patient related activities (accounting for overheads, qualifications, and salary on costs) costs £45 (PSSRU, 2009); £47 when inflated to 2010 costs. It was therefore estimated in the base case that the cost of preparing one infusion or dispensing capecitabine costs £9.40 (47*12/60).

Sensitivity of the ICER to changes to the assumed cost of pharmacy preparation were explored in the sensitivity analysis by applying costs reported by the SCHARR in there evaluation of bevacizumab (Tappenden 2007). In table 43 of this paper the cost of dispensing capecitabine is stated as £12 and a single infusion as £23.

Treatment cycles per patient

Mean number of cycles per month

As illustrated by the table below, the cycle duration observed in ToGA was longer than that stipulated in the protocol.

Table 29: Mean number of cycles per month observed in ToGA

	Trastuzumab	5-FU	Capecitabine	Cisplatin
Per Protocol (days)	21	21	21	21
Actual Cycle duration (days) HCX/F	22.7	23.1	24.0	23.9
Actual Cycle duration (days) CX/F		23.3	24.3	24.2
Cycles per month used in model HCX, HCF	1.34	1.32	1.27	1.28
Cycles per month used in model ECX, EOX, ECF		1.31	1.25	1.26

The average number of cycles per month for each drug was used to calculate monthly treatment costs for each drug separately. It was assumed that the average cycle duration of drugs in CX/F would apply to the equivalent drugs in ECX, ECF and EOX and that epirubicin and oxaliplatin would have the same average cycle duration as cisplatin in the CX/F regimen. This assumption was validated by clinical experts (Appendix E2)

Mean treatment duration per patient in the ToGA

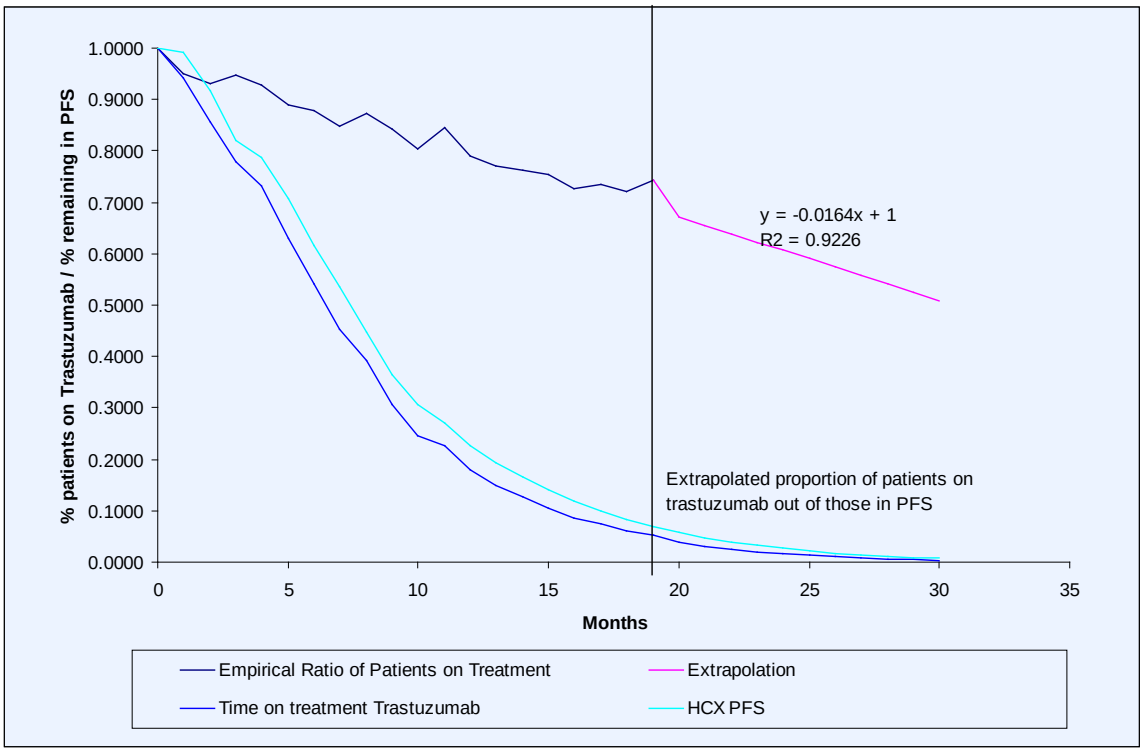
The protocol for the ToGA trial specified treatment of trastuzumab in combination with cisplatin and either 5-FU or capecitabine for the earlier of 6 cycles or disease progression followed by trastuzumab maintenance therapy until disease progression. In the ToGA trial, not all patients were treated until progression and some patients continued chemotherapy for longer than 6 cycles and some less.

Kaplan-Meier survival analysis was used to calculate the mean treatment duration based on the time from first dose to the time until cessation of treatment as recorded in ToGA. The Kaplan-Meier curves (see Figure 28 below) were sufficiently complete, for all the drugs bar trastuzumab, not to require extrapolation. Whilst almost complete, the treatment duration curve for trastuzumab required some

extrapolation. This was achieved by extrapolating the change in the ratio of the proportion of patients on treatment out of those in PFS with time using linear regression. (see figure Figure 27 below)

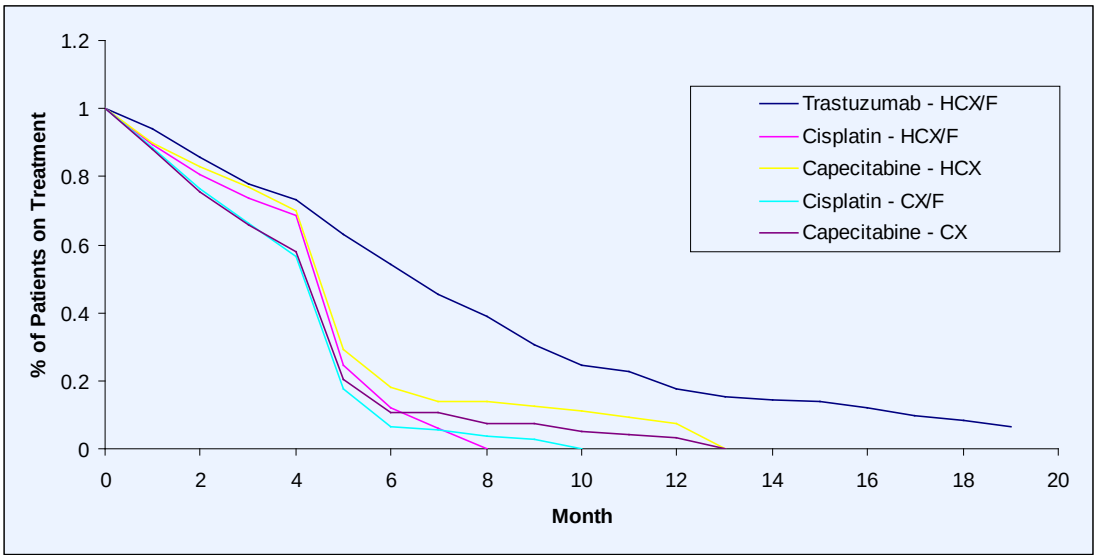
The mean duration of treatment of CX/CF and thus that assumed for ECX and ECF and EOX are consistent with estimates of average treatment duration obtained from UK market research (Synovate market research). This market research indicated clinicians (n=25) expected to deliver 4.9 cycles when using ECF and 4.6 cycles when with ECX. This compares with a mean of 4.7 cycles of cisplatin / oxaliplatin in the ECF, ECX and EOX arms of the economic analysis.

Figure 27: Trastuzumab treatment duration



It was assumed that the time on treatment is correlated to the duration of PFS. Therefore rather than using the Kaplan-Meier curves directly in the model the proportion of patients on treatment out of those still in PFS was applied to the extrapolated PFS curves used in the model.

Figure 28: Kaplan-Meier plot of time to treatment cessation in ToGA by regimen



It was assumed that the relative treatment duration (treatment duration / PFS) is the same for ECX, EOX, and ECF as observed for the CX/F regimen in ToGA. Epirubicin and oxaliplatin were assumed to have the same relative treatment duration as cisplatin.

Supportive care, monitoring, adverse events and CVAD costs

Monthly progression free survival monitoring costs

Consultations with an oncologist were assumed to take place approximately every 3 weeks during treatment with chemotherapy and every 6 weeks after including during whiles on maintenance trastuzumab therapy (Expert Opinion). The cost of each visit applied in the model was £125.49 (2008/9 reference costs: 370; Consultant Led: Follow Up Attendance Non-Admitted Face to Face inflated to 2010 costs).

Unit costs for cardiac monitoring for patients receiving either trastuzumab or Epirubicin were based on the ERG report by Ward and colleagues on trastuzumab for early breast cancer (Ward 2006) in this report it was hypothesised that 33% of patients receive a MUGA scan costing £258 and rest are monitored via echocardiogram costing £120. The same assumptions were used for the base case except the cost of an echocardiogram was taken from the latest NHS reference costs of £76 (HRG: DA02)

Clinical experts (Appendix E2) indicated that patients would receive a CT scan at the start of treatment and then again at signs of progression irrespective of the regimen they were receiving. Hence in the base case it was assumed that there was no marginal cost of CT scans when using

HCX/F over the comparators. The affect on the ICER of including a regular 3 monthly CT scan was explored in the sensitivity analysis.

Adverse Events

The costs of the treatment related adverse events, as observed in the ToGA study and REAL-2 (Cunningham 2006) were incorporated into the economic model.

Adverse events (AEs) included within the economic model for costing purposes had to meet the following selection criteria:

- Grade 3 or 4 AEs (no grade 5 events in study ToGA or REAL-2)
- An incidence equal to or greater than 5% was observed in any of the arms of the trials

The expected cost per episode of each individual adverse event was calculated as follows: Number of events / the number treated * the estimated cost of treating the event.

The sum of the expected cost for each adverse event then generated the total expected cost of adverse events for each arm in the model. This total cost of adverse events is included within the model as a lump sum in the first model cycle. The subsequent total expected average cost of treating grade 3 and 4 adverse events for each intervention are presented in the results section.

Table 30: Unit cost for treatment of adverse events

Adverse event	Unit cost (£'s) inflated to 2010 costs	Reference / comment
Anaemia	582	Agrawal 2006
Anorexia	132	LRIG 2006 Erlotinib
Diarrhoea	237	LRIG 2006 Erlotinib
Febrile Neutropenia	3,272	Ref costs 2008/9
Neutropenia / granulocytopenia	140	LRIG 2006 Erlotinib
Palmar-plantar erythrodysaesthesia syndrome (Hand and Foot)	156	York CRD 2004, September 2004
Vomiting / Nausea	728	Ref costs 2008/9

Published NHS reference costs were used were available, otherwise adverse event costs were sourced from the literature. The safety population (patients having received at least one administration of study drug) from the ToGA study was utilised for the purposes of adverse event data. Treatment costs taken from the reference costs were a weighted average of the most applicable HRG's (see Appendix E1 for HRG's included)

The frequency and type of adverse events included in the model, according to the selection criteria above, are summarised in the following table:

Table 31: Incidence (%) of adverse events costed in the model from ToGA and REAL-2

Adverse event	HCX/F	ECX	ECF	EOX
Anaemia	12.24	10.50	13.10	8.60
Anorexia	6.46	-	-	-
Diarrhoea	9.18	5.10	2.60	11.90
Febrile neutropenia	5.10	6.70	9.30	7.80
Hand-foot syndrome	1.36	10.30	4.30	3.10
Nausea and vomiting	13.61	7.70	10.20	11.40
Neutropenia	26.87	51.10	41.70	27.60

Central Venous Access Device (CVAD) costing

Consistent with the assumption that all patients receiving 5-FU did so via an ambulatory pump it was assumed that 100% of patients receiving 5-FU would required a CVAD to be installed. Insertion of a CVAD was assumed to require a separate hospital visit, consistent with current clinical practice. The cost of a CVAD insertion of £487 was taken from reference costs 2008/9 HRG QZ14A (Day Case): "Vascular Access except for Renal Replacement Therapy with CC" and inflated to 2010 costs.

Cost for removal of the CVAD was estimated to be minimal and therefore excluded as the CVAD is often left installed after treatment and if removal is required, it was assumed this would happen during the last chemotherapy administration.

Progressive Disease health state cost

As displayed in Appendix E4, 2nd line treatments in ToGA were similar across both arms of the study, both in terms of the total proportion of patients receiving 2nd line treatments, and also the mix of drugs used. It was therefore assumed that there was no difference in treatment cost between the interventions post progression on first-line. However monthly supportive care costs, sourced from the NICE Advance breast cancer guideline were applied as the model predicted a differential time spent in the PD health state across the various interventions evaluated within the model. Details of the estimation of this monthly cost are supplied in the table below.

Source	Progressive Disease cost	Comments/Reference
CG81: Advanced breast cancer guideline: diagnosis and treatment, February 2009	£542 per month (calculated based on 4.33 weeks per month)	Resource source: NICE CG81. Costing source: PSSRU (2009). Community nurse: home visit 20 min., once a week. £65 per hour = £21.67 per week Clinical nurse specialist: 1hr contact time, once a week. £55 per hour = £55 per week per week GP contact: 1 home visit, every fortnight £57 per visit including direct care staff costs Therapist: 1 hour, every fortnight. £40 per visit for NHS therapist. TOTAL= (£24*4.33) + (£55*4.33) + (£28.5*4.33) + (£20*4.33) = £541.99

HER2 Testing

To ensure that only patients that overexpress HER2 are treated with trastuzumab any patient being considered for treatment that is otherwise eligible would required a HER2 test.

Initially patients would be tested using the IHC test which costs £68 per test (average of Source Biomedical and UCL price) and then for those that are classed as IHC2+ a further confirmation of HER2 status would be required using the FISH test, which costs £133 per test (average of Source Biomedical and UCL price).

For the purpose of the economic evaluation for patients treated with trastuzumab we need to factor in not only the cost of the test which they had but also the other tests that would be performed which would result in patients not being deem eligible for treatment with trastuzumab. Hence we need a cost of IHC and FISH testing per patient treated with trastuzumab.

17.8% of mGC patients are estimated to be eligible for trastuzumab (IHC2+ FISH+ or IHC3+) (Table 3, Bang 2009). The proportion of mGC patients eligible is not reported however it is assumed that this proportion applies equally to locally advanced patients and metastatic patients. Based on this it is estimated that 5.61 (1/17.8%) IHC tests would be performed for every mGC patient treated with trastuzumab.

66% of eligible patients are IHC2+ (Table3, Bang 2009) and thus require a FISH test (Table 3, Bang 2009)
Hence the cost per patient that is used in the economic analysis is £542.49 (5.61*£77 + 0.66*£167)

7.3.8.2 How were the resources measured?

See section above

7.3.8.3 Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?

See section above

7.3.8.4 Were resources used to treat the disease/condition included for all relevant years (including those following the initial treatment period)? Provide details and a justification for any assumptions that were made (for example, assumptions regarding types of subsequent treatment).

As displayed in Appendix E4 2nd line treatments in ToGA were similar across all of the arms of the study both in terms of the total proportion of patients receiving 2nd line treatments and also the mix of drugs used. It was therefore assumed that there was no difference in treatment cost between the interventions post progression. This assumption was validated by clinical experts (Appendix E2). However to capture the cost associated with extended time in the PD health state a monthly supportive care costs of £542 for the duration of time spent in this health state. (see section 7.3.8.1 above for details)

7.3.8.5 What source(s) of information were used to value the resources? Were alternative sources of information available? Provide a justification for the preferred source and explain any discrepancies between the alternatives.

The majority of the costs were sourced from the recently published reference costs 2008/9 or from previous NICE appraisals.

See section 7.2.8.1 for more detailed information on estimation of cost.

7.3.8.6 What is the unit cost (excluding VAT) of the intervention(s) included in the analysis? Does this differ from the (anticipated) acquisition cost reported in section 1? If price discounts are presented in sensitivity analyses provide details of formal agreements regarding the discount including the period over which the discount is agreed and confirmation of national organisations with which the discount has been agreed for the whole of the NHS in England and Wales.

The currently list price of the intervention drugs were used for the evaluation. No price discounts are anticipated or explored within the analysis. Further details on the unit costs are provided in section 7.2.8.1 above.

7.3.8.7 Does the technology require additional infrastructure to be put in place? Provide details of data sources used to inform resource estimates and values.

No additional infrastructure would be required for the administration of trastuzumab.

7.3.8.8 Were the resources measured and valued in a manner consistent with the reference case? If not, how and why do the approaches differ?

Only costs relating to resources under control of the NHS and PSS were included. Prices were taken from National reference costs 2008/2009, BNF 58, and PSSRU 2009. Only when costs could not be identified from these sources were alternative sources from the literature utilised to inform the model.

7.3.8.9 Were resource values indexed to the current price year?

Costs were inflated to 2010 costs based on the PSSRU 2009 cost index.

7.3.8.10 Provide details of and a justification for any assumptions that were made in the estimation of resource measurement and valuation.

The monthly resource costs of patients in the progressive health state were assumed equal regardless of whether the patient received trastuzumab or not due to the relatively equal balance observed in the 2nd-line treatments utilised in the ToGA trial (see Appendix E4).

Further details of the methods used for estimating resource use are described in section 7.2.8.1

7.3.9 Time preferences

Were costs and health benefits discounted at the rates specified in NICE's reference case?

Both costs and health benefits were discounted monthly at a rate equivalent to 3.5% annual discount rate.

7.3.10 Sensitivity analysis

7.3.10.1 Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.
All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

7.3.10.2 For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Not applicable

7.3.10.3 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated including a description of alternative scenarios included in the analysis.

Selection of the correct parametric function to inform the survival analysis may be considered a source of structural uncertainty and therefore alternative functions were evaluated. The following scenarios were explored:

- The log logistic function was used to extrapolate the PFS survival curves
- The log logistic function was used to extrapolate the OS survival curves
- The Weibull was used in its entirety and not only the post 12 months section of the curve
- The extrapolation of the trastuzumab dose curve performed based on the assumption that there was no decrease in the ratio of patients on treatment out of those in PFS

The results are reported along with the results of the one-way sensitivity analysis.

7.3.10.4 Which variables were subject to sensitivity analysis? How were they varied and what was the rationale for this?

The Table below lists the all the variables subject to one-way sensitivity analysis along with the range over which the parameter values were varied and the rational for this.

Table 32: Univariate sensitivity conducted

Parameter modified	Base value	Low value	High value	
Utility Values				
PFS Utility value	0.73	0.66	0.80	The values were altered by 10% up and down from the base case this translates into a substantial change in the assumed average utility for the health state and any larger divergence seemed implausible given utility values used in previous nice appraisals in metastatic cancer.
Include increase in utility with trastuzumab in PFS	No	No	Yes	The EQ-5D results of ToGA suggested a non-significant benefit in utility during PFS for HCX/F over CX/F
Include increase in utility over time during PFS	Yes	No	Yes	The EQ-5D results of ToGA showed that time was significant predictor of utility during PFS with utility increasing over time.
Progression Utility Value	0.58	0.52	0.63	As above
Survival Analysis				
PFS survival Function Weibull or Log Logistic PFS or KM				For the base case due to the completeness of the data the KM curves were used until month 12 and then extrapolated using the Weibull curve. The Log Logistic represented offered the best statistical fit to the data but appeared to severely over estimate the tail of the PFS curve which then overlapped the OS curve. However for completeness the ICER was calculated using the Log logistic
OS Survival Function	KM+Weibull Weibull	Full Weibull Log Logistic	Log Logistic Log Normal	The ICER with the Weibull full curve was also explored. The Weibull offered both a good statistical and graphical fit and so was used for the base case

Weibull or Log Logistic OS or KM				The next two best fitting curves were the Log Logistic and the Log normal and thus the sensitivity of the ICER to changes in the assumed function were explored based on using these two alternatives
PFS HR (ECX vs. CX)				The base case assumes that the CX regimen is equivalent in terms of PFS and OS to the ECX regimen (the rational for this is discussed in Section 4 and 6.6) This analysis was performed to see the effect of relaxing that assumption. There is only one RCT identified that investigated ECX vs. CX (Yun 2010). This study which failed to show a significant difference between the regimens however reported a HR for ECX vs. CX was 0.96. Hence this was used to explore the impact on the ICER of assuming a difference between the regimens.
OS HR (ECX vs. CX)				As above. OS was not reported in the Yun study so it was assumed for the purpose of the sensitivity analysis that ECX also reduced the risk of death by the same amount as reported for PFS.
PFS HR (EOX vs. ECX)	1	0.96	1	The base case assumes that the EOX regimen is equivalent in terms of PFS and OS to the ECX regimen (the rational for this is discussed in Section 4 and 6.6) This analysis was performed to see the effect of relaxing this assumption on the ICER. There is only one RCT identified replacing cisplatin with oxaliplatin (Cunningham 2008). This study which did not show a significant difference reported a HR for oxaliplatin (EOX and EOF) vs. cisplatin (ECX and ECF) of 0.92 (OS). Hence this was used to explore the impact on the ICER of assuming a difference between the regimens.
OS HR (EOX vs. ECX)	1	0.92 0.92	1	As above
Clinical Practice Assumptions				
% pts requiring hospital transport	30%	0%	50%	Assumption

Proportion of centres vial sharing	80%	50%	100%	This sensitivity analysis explores the assumed proportion of centres that adopt the practice of vial sharing
Extrapolation of trastuzumab treatment duration KM assuming either: the number treated at time t / number in PFS is constant or based on linear regression decreases over time	Reduces over time	Constant	Reduces over time	The KM curve for treatement duration of trastuzumab terminates ends at month 19. Beyond this point the ratio of patients on treatment out of those remaining in PFS is assumed to reduce over time based on linear regression of the KM curve. This alternative scenario assumes that the ratio remains constant from month 19 onwards.
Unit Costs				
Cost of hospital funded transport per visit	£30	£18	£42	Varied up and down by 40%
Cost of 5-FU pump	£39	£23	£54	Varied up and down by 40%
Cost per consultation with oncologist	£125	£75	£176	Varied up and down by 40%
CT scan every 3 months	£0	£0	£106	Varied up and down by 40%
End of life cost	£4,000	£0	£4,000	Varied up and down by 40%
Cost of Cardiac Monitoring	£133	£80	£186	Varied up and down by 40%
Cost of administration day 1 of cycle	£268	£161	£376	Varied up and down by 40%
Cost of administration of Trastuzumab monotherapy	£133	£80	£186	Varied up and down by 40%
Pharmacy cost infusion	£9	£9	£23	The base case used the results of a time and motion study multiplied by PSSRU costs to calculate the cost of pharmacy In a previous appraisal it was estimated that the cost of a preparation of a single infusion cost £23 (Tappenden 2007)
Pharmacy cost oral	£9	£9	£12	The base case used the results of a time and motion study multiplied by PSSRU costs to calculate the cost of pharmacy In a previous appraisal it was estimated that the cost of a preparation of a single infusion cost £12 (Tappenden 2007)
Cost of Progressive Disease Health State	£542	£325	£759	Varied up and down by 40%
Total Comparator Adverse Event costs	£245	£147	£344	Varied up and down by 40%
Total ECX Adverse Event costs	£354	£212	£496	Varied up and down by 40%
Total Trastuzumab Adverse Event costs	£328	£197	£460	Varied up and down by 40%

7.3.10.5 Was probabilistic sensitivity analysis (PSA) undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated; including the derivation and value of 'priors'.

PSA was undertaken. The sample size was set at 500 and then the PSA was re-run at a sample size of 1,000; no meaningful difference was seen between the two results. Distributions were applied around the following parameters to reflect parameter uncertainty in the model:

- Utilities values
- Unit costs
- Monthly supportive care costs
- Adverse event probabilities
- Survival curves parametric parameters
- PFS monthly Kaplan-Meier estimates

A list of all parameters included in the PSA along with assumed distributions and the value of priors is provided in Appendix E3

7.3.11 Statistical analysis

7.3.11.1 How were rates or probabilities based on intervals transformed into (transition) probabilities?

Transition probabilities were not calculated as the model was based on an area under the curve design. The derivation of the survival curves is described in section 7.3.5.8.

7.3.11.2 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

The transition probabilities implicit in the PFS and OS curves used in this area under the curve do vary over time.

7.3.12 Validity

7.3.12.1 Describe the measures that have been undertaken in order to validate and check the model.

The internal validation and debugging of the model was performed by a health economist who had not been involved in the development of the model. The following validation procedures were performed:

- Execution of selected extreme tests to check the plausibility of model outcomes. Extreme testing was applied to the following parameters: treatment efficacy, adverse event costs, cost of study drugs and administration, discount rates, and health utilities.

7.4 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following:

7.4.1 Base-case analysis

7.4.1.1 What were the results of the base-case analysis?

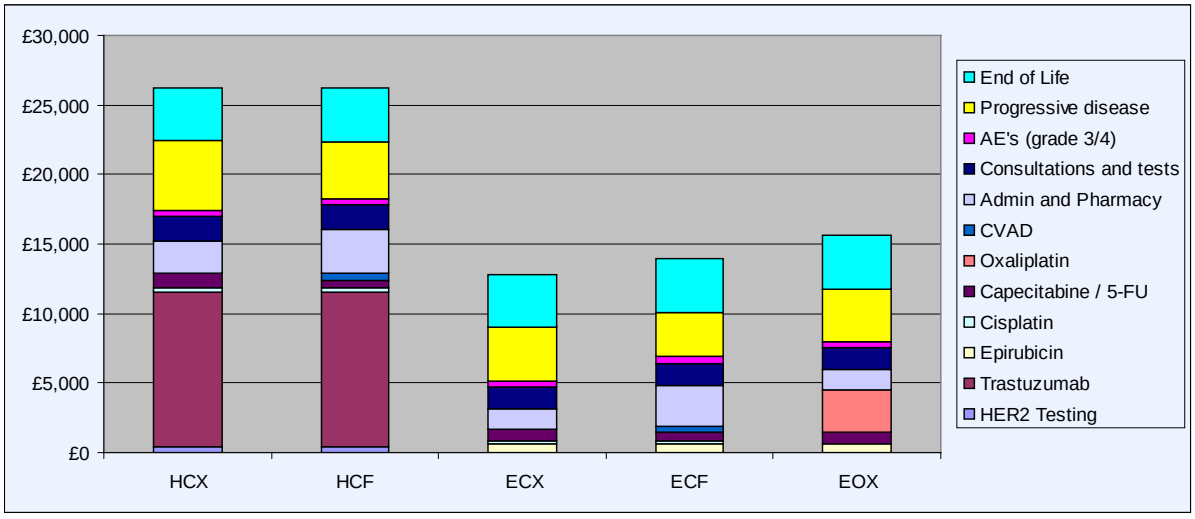
First-line analysis

The results of the base-case analysis are provided below. The mean results of the probabilistic sensitivity analysis (PSA) (see section 7.4.3) were virtually identical to the deterministic results; hence all the figures presented in this section (7.4.1.1) represent the deterministic results. The PSA means are provided alongside the scatter plots in the sensitivity analysis (section 7.4.3)

Costs

The figure below shows the total cost per patient for each of the interventions / comparators by category of cost.

Figure 29: Mean total costs per patient



It can be seen that the drug acquisition, administration and post progression health state cost are the main drivers of cost variance between the regimens.

ECX resulted in the lowest total cost of all the regimens with a total cost per patient of £12,820. HCX and HCF cost approximately the same at £26,000.

The data displayed above in Figure 29 is represented in tabular format below.

Table 33: Total cost for each intervention per patient

	HCX	HCF
HER2 Testing	£467	£467
Trastuzumab	£11,029	£11,029
Epirubicin		
Cisplatin	£305	£305
Capecitabine / 5-FU	£1,091	£567
Oxaliplatin		
CVAD		£505
Admin and Pharmacy	£2,277	£3,082
Consultations and tests	£1,782	£1,782
AE's (grade 3/4)	£407	£407
Progressive disease	£5,003	£4,157
End of Life	£3,794	£3,812
Total Direct Costs	**£26,156**	**£26,113**

Table 34: cost for each comparator per patient

	ECX	ECF	EOX
Epirubicin	£582	£599	£582
Cisplatin	£226	£222	
Capecitabine / 5-FU	£911	£599	£911
Oxaliplatin			£3,021
CVAD		£505	
Admin and Pharmacy	£1,471	£2,879	£1,471
Consultations and tests	£1,542	£1,542	£1,542
AE's (grade 3/4)	£436	£527	£463
Progressive disease	£3,803	£3,163	£3,803
End of Life	£3,848	£3,861	£3,848
Total Direct Costs	**£12,820**	**£13,899**	**£15,641**

Mean time in each health state and Quality-Adjusted Life Years

Table 35 shows that the combination of HCX results in a mean gain of 4.8 months of life compared with ECX / EOX. HCF results in a mean gain of 4.3 months of life compared with ECF.

Approximately half of the extension in life resulted from an extension of PFS. The remaining benefit therefore resulting from increased time in post progression survival. This is consistent with the median results from the study.

Table 35: Time (months) spent in each health state till death per patient (undiscounted)

	HCX	HCF	ECX	ECF	EOX
PFS post treatment	8.68	8.68	6.36	6.36	6.36
Progressive Disease	9.76	8.08	7.31	6.07	7.31
Total	**18.44**	**16.76**	**13.67**	**12.43**	**13.67**

When the mean extension in each health state was weighted to account for quality of life it was seen that HCX results in an increased QALY per patient of 0.25 over ECX/EOX and 0.31 for HCX over ECF.

Table 36: QALYs per patient

	HCX	HCF	ECX	ECF	EOX
PFS	0.54	0.54	0.39	0.39	0.39
Progressive Disease	0.44	0.37	0.34	0.28	0.34
Total QALY's	**0.98**	**0.91**	**0.73**	**0.67**	**0.73**

Table 37: Incremental QALYs per patient

	ECX	ECF	EOX
HCX			
PFS	0.15	0.15	0.15
Progressive Disease	0.11	0.16	0.11
Total QALY's	**0.25**	**0.31**	**0.25**
HCF			
PFS	0.15	0.15	0.15
Progressive Disease	0.03	0.09	0.03
Total QALY's	**0.18**	**0.23**	**0.18**

Incremental cost effectiveness results

The mean incremental cost and QALY for each therapy option is displayed on the cost-effectiveness plane below HCX resulted a greater number of QALYs for approximately the same overall cost as HCF and thus was the dominant trastuzumab containing regimen. ECX was the dominant comparator regimen as it offered equivalent efficacy at a reduced cost to the other comparators. Hence ECX and HCX make up the efficiency frontier (see Figure 30 below).

Figure 30: Simultaneous incremental results

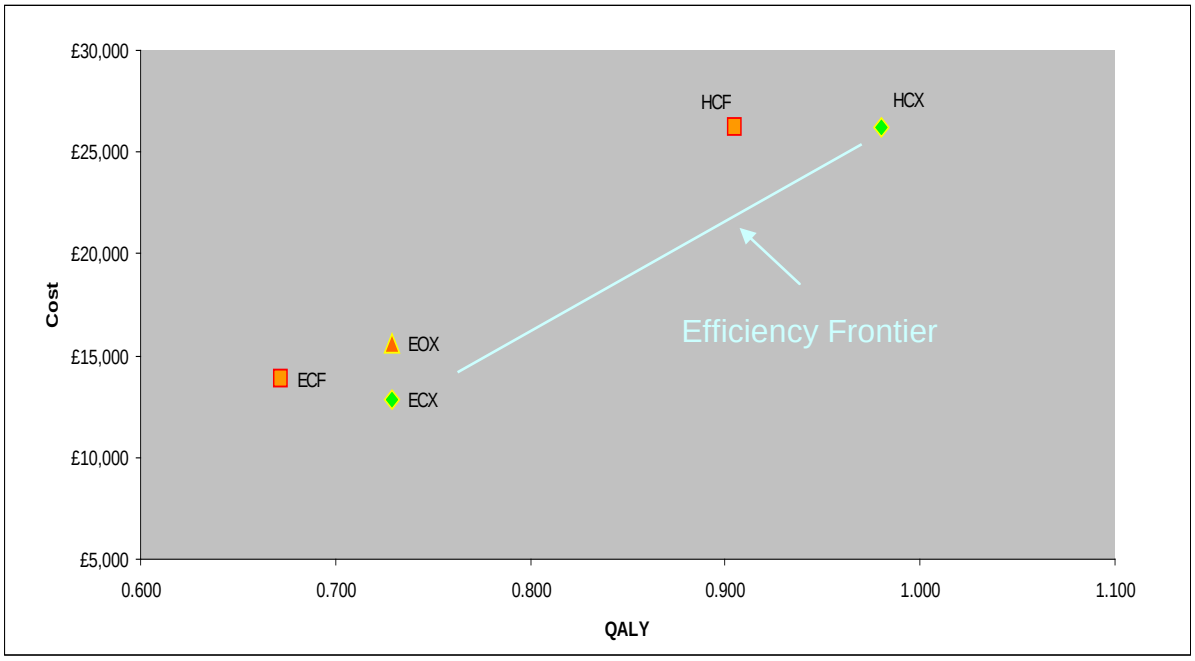


Table 38: Mean Incremental cost per patient

HCX vs ECX	**£13,336**
HCF vs ECF	**£12,214**
HCX vs EOX	**£10,515**

Table 39: Mean ICERs (£/LY) per patient

HCX vs ECX	**£34,774**
HCF vs ECF	**£34,722**
HCX vs EOX	**£25,433**

Table 40: Mean ICERs (£/QALY) per patient

HCX vs ECX	**£53,010**
HCF vs ECF	**£52,363**
HCX vs EOX	**£41,795**

The incremental cost effectiveness ratios (£/QALY) for each of the interventions compared to each of the comparators is provided in Table 38 above. Highlighted in the table are the ICER's that are of most relevance to the decision problem.

Comparing the two regimens on the efficiency frontier (see Figure 30 above) HCX and ECX results in an incremental cost per QALY of £53,010.

A small number of patients may not be suitable for capecitabine making the incremental cost effectiveness of HCF vs. ECF also of relevance, which results in a cost per QALY of £52,363.

Replacing the 3rd most used regimen within the NHS, EOX, results in a cost per QALY of £41,795.

7.4.2 Subgroup analysis

7.4.2.1 What were the results of the subgroup analysis/analyses if conducted?

As per the final scope no sub-group analysis was performed.

7.4.3 Sensitivity analyses

7.4.3.1 What were the main findings of the sensitivity analyses?

HCX vs. ECX

One way sensitivity analysis

The effect of changes in parameter values for the comparison HCX with ECX is shown below.

Table 41: One-way sensitivity analysis of HCX vs. ECX to changes to mean parameter estimates (base case £53,297)

Parameter modified	Base value	Low value	High value	ICER Low	ICER High
Utility Values					
PFS Utility value	0.73	0.66	0.80	£56,047	£50,286
Include increase in utility with trastuzumab in PFS	0.00	0.00	1.00	£53,010	£49,346
Include increase in utility over time during PFS	1.00	0.00	1.00	£54,936	£53,010
Progression Utility Value	0.58	0.52	0.63	£55,353	£50,858
Survival Analysis					
Weibull or Log Logistic PFS	7	1	3	£53,739	£55,324
Weibull or Log Logistic OS	1	3	1	£47,882	£53,010
OS HR (ECX vs CX)	1	0.96	1.04	£56,175	£50,328
Clinical Practice Assumptions					
% pts requiring hospital transport	30%	0%	50%	£52,852	£53,116
Proportion of centres vial sharing	0.8	50%	100%	£55,517	£51,340
Extrapolation of trastuzumab (number treated at time t / number in PFS) 0 = constant, 1= fit linear regression	1	0	1	£53,010	£53,297
Unit Costs					
Cost of CVAD installation	£505	£303	£707	£53,010	£53,010
Cost of hospital funded transport per visit	£30	£18	£42	£52,947	£53,074
Cost of 5-FU pump	£39	£23	£54	£53,010	£53,010
Cost per consultation with oncologist	£125	£75	£176	£52,142	£53,879
CT scan every 3 months	£0	£0	£106	£53,010	£53,324
End of life cost	£4,000	£0	£4,000	£53,223	£53,010
Cost of Cardiac Monitoring	£133	£80	£186	£53,499	£52,522
Cost of district nurse visit	£39	£24	£55	£53,010	£53,010
Cost of administration day 1 of cycle	£268	£161	£376	£52,843	£53,178
Cost of administration of Trastuzumab monotherapy	£134	£81	£188	£52,052	£53,969
Cost of administration of Trastuzumab in combination with 5-FU	£161	£97	£226	£53,010	£53,010
Pharmacy cost infusion	£9	£9	£23	£53,010	£53,297
Pharmacy cost oral	£9	£9	£12	£53,010	£53,021
Cost of Progressive Disease Health State	£542	£325	£759	£51,102	£54,918
Total Comparator Adverse Event costs	£321	£192	£449	£53,010	£53,010
Total ECX Adverse Event costs	£436	£262	£611	£53,704	£52,317
Total ECF Adverse Event costs	£527	£316	£738	£53,010	£53,010
Total EOX Adverse Event costs	£463	£278	£648	£53,010	£53,010
Total trastuzumab Adverse Event costs	£407	£244	£570	£52,363	£53,658

Figure 31: Tornado diagram for HCX vs. ECX

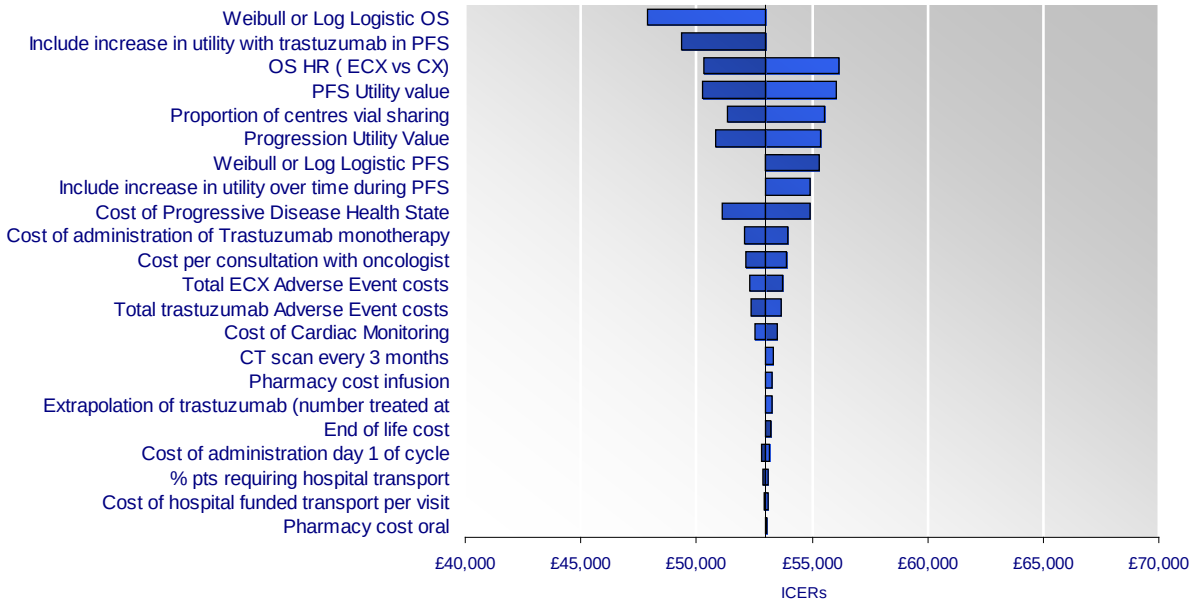
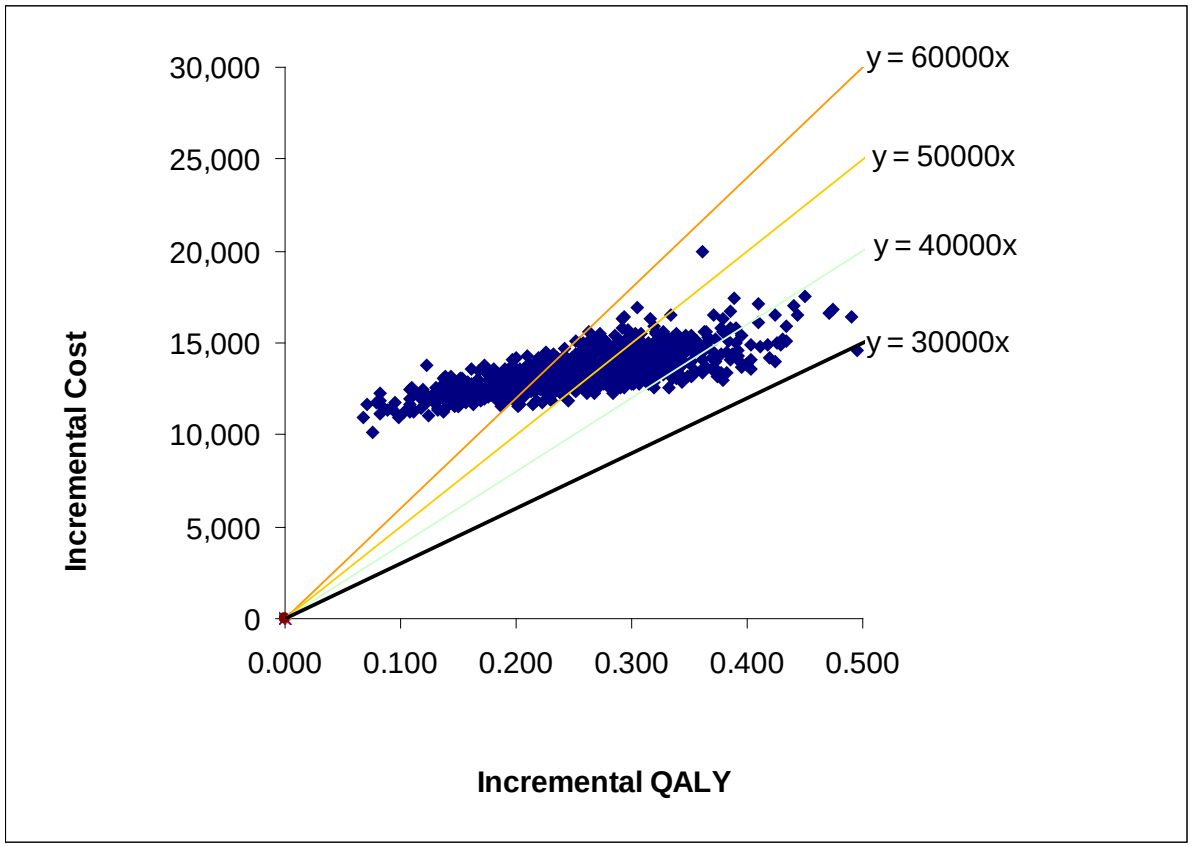
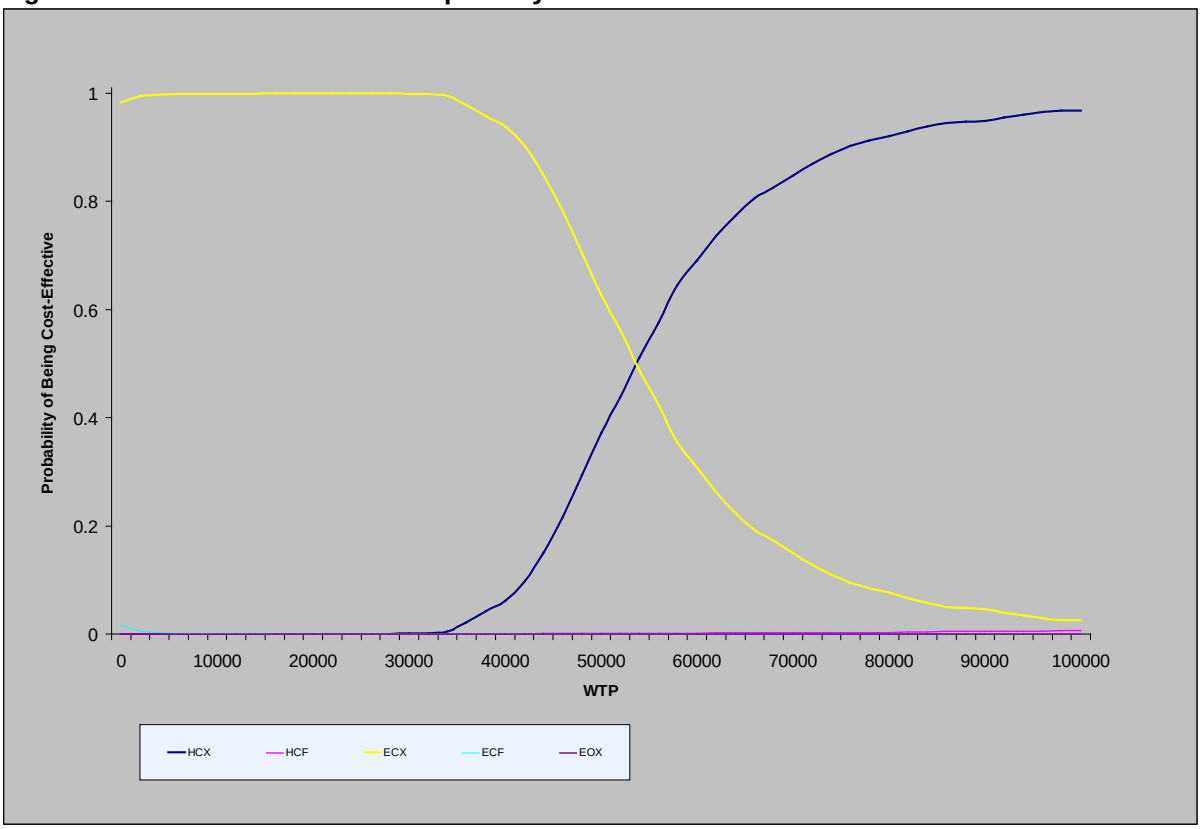


Figure 32: Scatter plot HCX vs. ECX



Mean ICER = 53,352

Figure 33: Cost Effectiveness Acceptability Curve



HCF vs. ECF

Table 42: One-way sensitivity analysis of HCF vs. ECF to changes to mean parameter estimates (base case £ 52,363)

Parameter modified	Base value	Low value	High value	ICER Low	ICER High
Utility Values					
PFS Utility value	0.73	0.66	0.80	£55,612	£49,472
Include increase in utility with trastuzumab in PFS	0.00	0.00	1.00	£52,363	£48,479
Include increase in utility over time during PFS	1.00	0.00	1.00	£54,420	£52,363
Progression Utility Value	0.58	0.52	0.63	£54,419	£50,456
Survival Analysis					
Weibull or Log Logistic PFS	7	1	3	£54,143	£58,925
Weibull or Log Logistic OS	1	3	1	£47,680	£52,363
Clinical Practice Assumptions					
% pts requiring hospital transport	30%	0%	50%	£52,197	£52,473
Proportion of centres vial sharing	0.8	50%	100%	£55,039	£50,578
Extrapolation of trastuzumab (number treated at time t / number in PFS) 0 = constant, 1= fit linear regression	1	0	1	£52,363	£52,672
Unit Costs					
Cost of CVAD installation	£505	£303	£707	£52,363	£52,363
Cost of hospital funded transport per visit	£30	£18	£42	£52,296	£52,429
Cost of 5-FU pump	£39	£23	£54	£53,007	£51,718
Cost per consultation with oncologist	£125	£75	£176	£51,425	£53,300
CT scan every 3 months	£0	£0	£106	£52,363	£52,701
End of life cost	£4,000	£0	£4,000	£52,572	£52,363
Cost of Cardiac Monitoring	£133	£80	£186	£52,889	£51,836
Cost of district nurse visit	£39	£24	£55	£52,698	£52,027
Cost of administration day 1 of cycle	£268	£161	£376	£52,181	£52,544
Cost of administration of Trastuzumab monotherapy	£134	£81	£188	£51,389	£53,336
Cost of administration of Trastuzumab in combination with 5-FU	£161	£97	£226	£51,938	£52,788
Pharmacy cost infusion	£9	£9	£23	£52,363	£52,752
Pharmacy cost oral	£9	£9	£12	£52,363	£52,363
Cost of Progressive Disease Health State	£542	£325	£759	£50,659	£54,066
Total Comparator Adverse Event costs	£321	£192	£449	£52,363	£52,363
Total ECX Adverse Event costs	£436	£262	£611	£52,363	£52,363
Total ECF Adverse Event costs	£527	£316	£738	£53,267	£51,458
Total EOX Adverse Event costs	£463	£278	£648	£52,363	£52,363
Total trastuzumab Adverse Event costs	£407	£244	£570	£51,664	£53,061

Figure 34: Tornado diagram for HCF vs. ECF

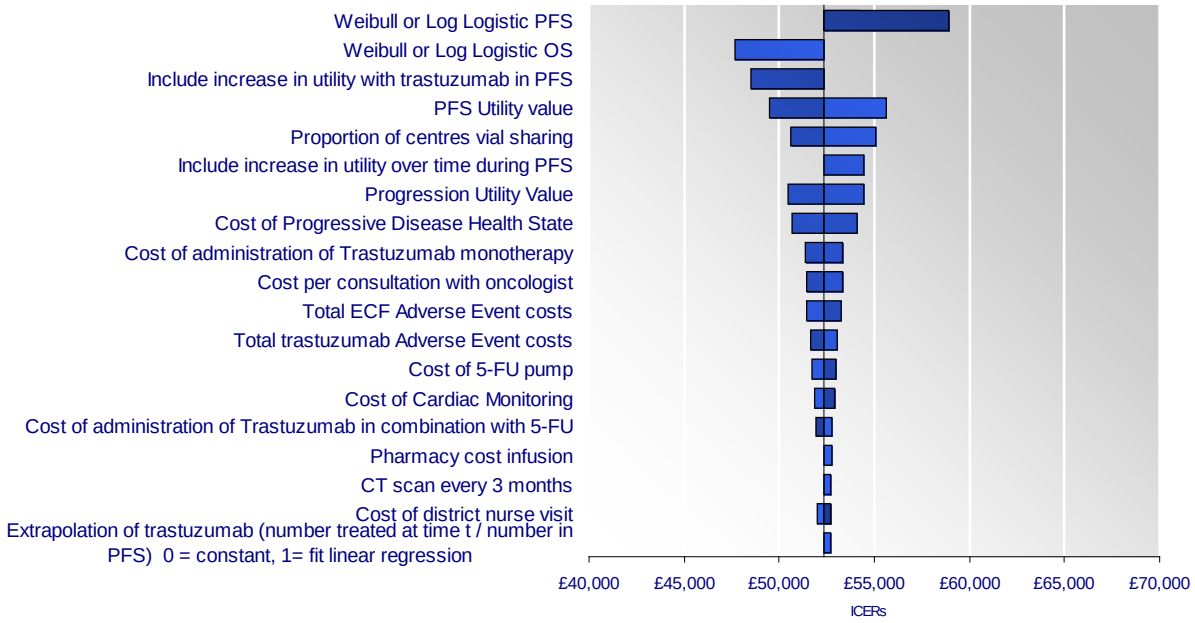
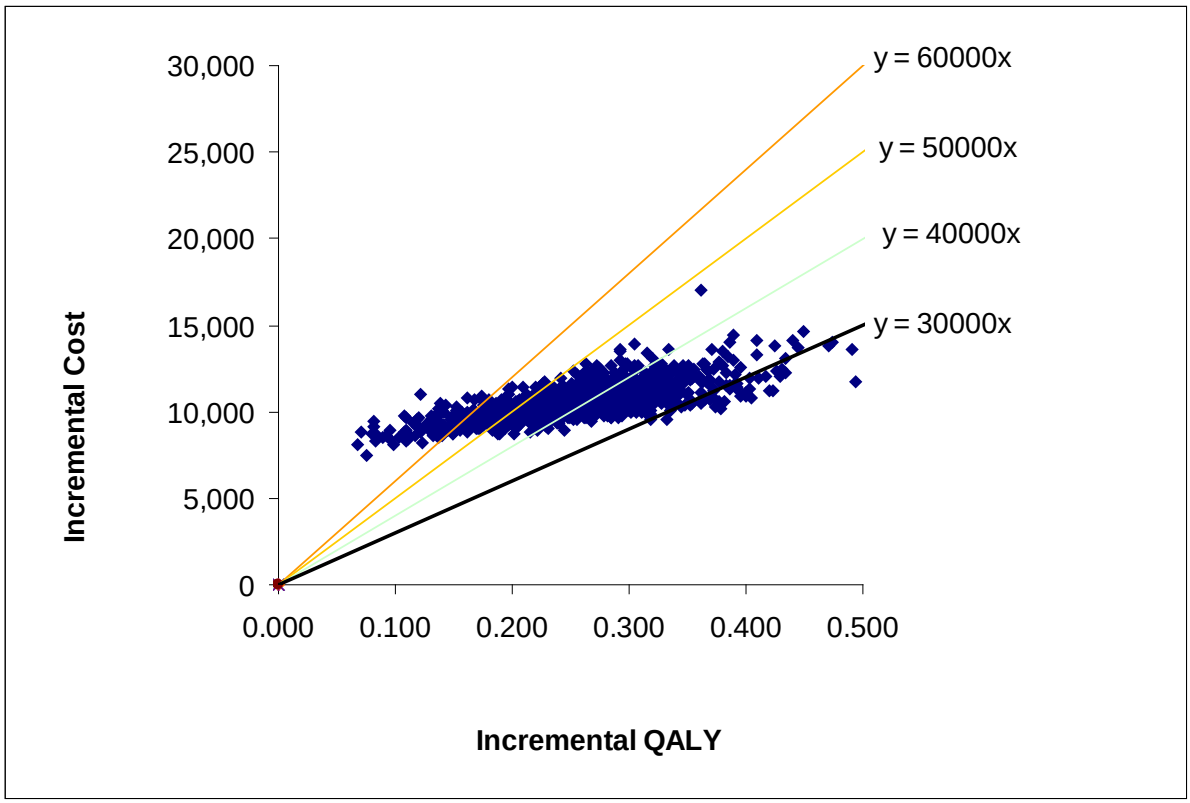


Figure 35: Scatter plot HCF vs. ECF



Mean ICER = £52,031

HCX vs. EOX: *Base case = £41,795*

Parameter modified	Base value	Low value	High value	ICER Low	ICER High
Utility Values					
PFS Utility value	0.73	0.66	0.80	£44,189	£39,647
Include increase in utility with trastuzumab in PFS	0.00	0.00	1.00	£41,795	£38,906
Include increase in utility over time during PFS	1.00	0.00	1.00	£43,313	£41,795
Progression Utility Value	0.58	0.52	0.63	£43,642	£40,098
Survival Analysis					
Weibull or Log Logistic PFS	7	1	3	£43,159	£44,605
Weibull or Log Logistic OS	1	3	1	£38,086	£41,795
OS HR (EOX vs ECX)	1.00	0.92	1.09	£47,020	£38,075
Clinical Practice Assumptions					
% pts requiring hospital transport	30%	0%	50%	£41,636	£41,901
Proportion of centres vial sharing	0.8	50%	100%	£43,606	£40,588
Extrapolation of trastuzumab (number treated at time t / number in PFS) 0 = constant, 1= fit linear regression	0	0	1	£41,795	£42,082
Unit Costs					
Cost of CVAD installation	£505	£303	£707	£41,795	£41,795
Cost of hospital funded transport per visit	£30	£18	£42	£41,732	£41,859
Cost of 5-FU pump	£39	£23	£54	£41,795	£41,795
Cost per consultation with oncologist	£125	£75	£176	£40,926	£42,664
CT scan every 3 months	£0	£0	£106	£41,795	£42,109
End of life cost	£4,000	£0	£4,000	£42,008	£41,795
Cost of Cardiac Monitoring	£133	£80	£186	£42,283	£41,307
Cost of district nurse visit	£39	£24	£55	£41,795	£41,795
Cost of administration day 1 of cycle	£268	£161	£376	£41,627	£41,963
Cost of administration of Trastuzumab monotherapy	£134	£81	£188	£40,837	£42,753
Cost of administration of Trastuzumab in combination with 5-FU	£161	£97	£226	£41,795	£41,795
Pharmacy cost infusion	£9	£9	£23	£41,795	£42,082
Pharmacy cost oral	£9	£9	£12	£41,795	£41,806
Cost of Progressive Disease Health State	£542	£325	£759	£39,887	£43,703
Total Comparator Adverse Event costs	£321	£192	£449	£41,795	£41,795
Total ECX Adverse Event costs	£436	£262	£611	£41,795	£41,795
Total ECF Adverse Event costs	£527	£316	£738	£41,795	£41,795
Total EOX Adverse Event costs	£463	£278	£648	£42,531	£41,060
Total trastuzumab Adverse Event costs	£407	£244	£570	£41,148	£42,443

Figure 36: HCX vs. EOX tornado diagram

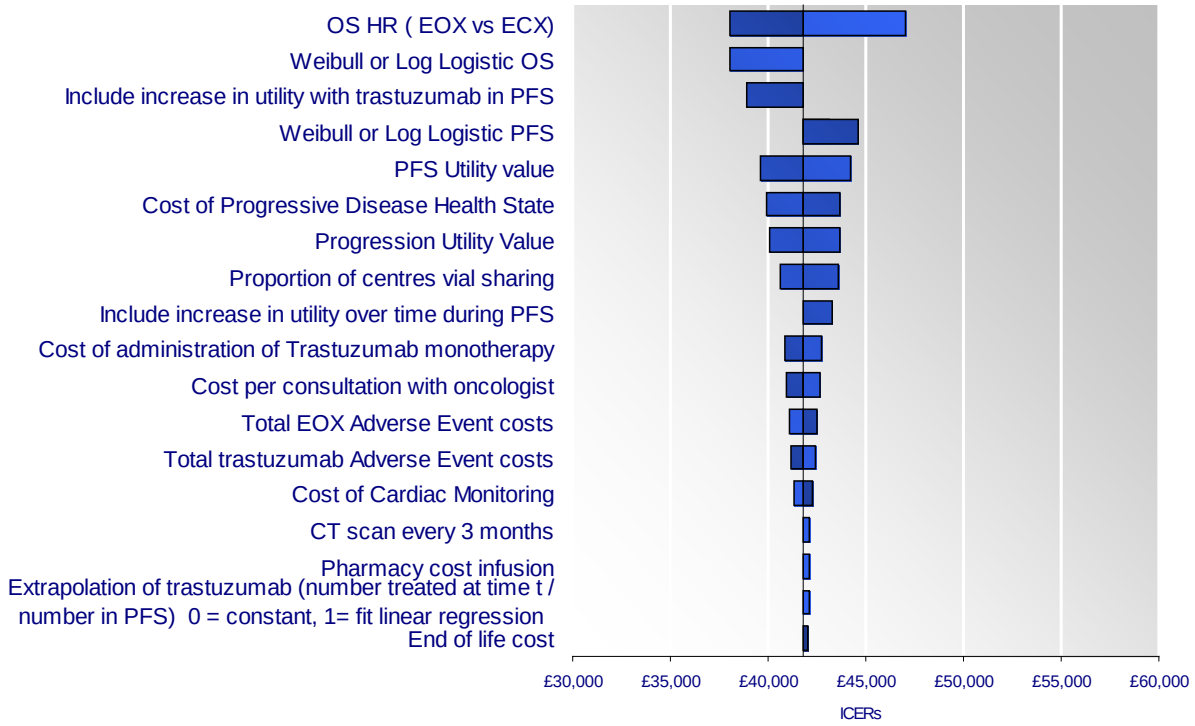
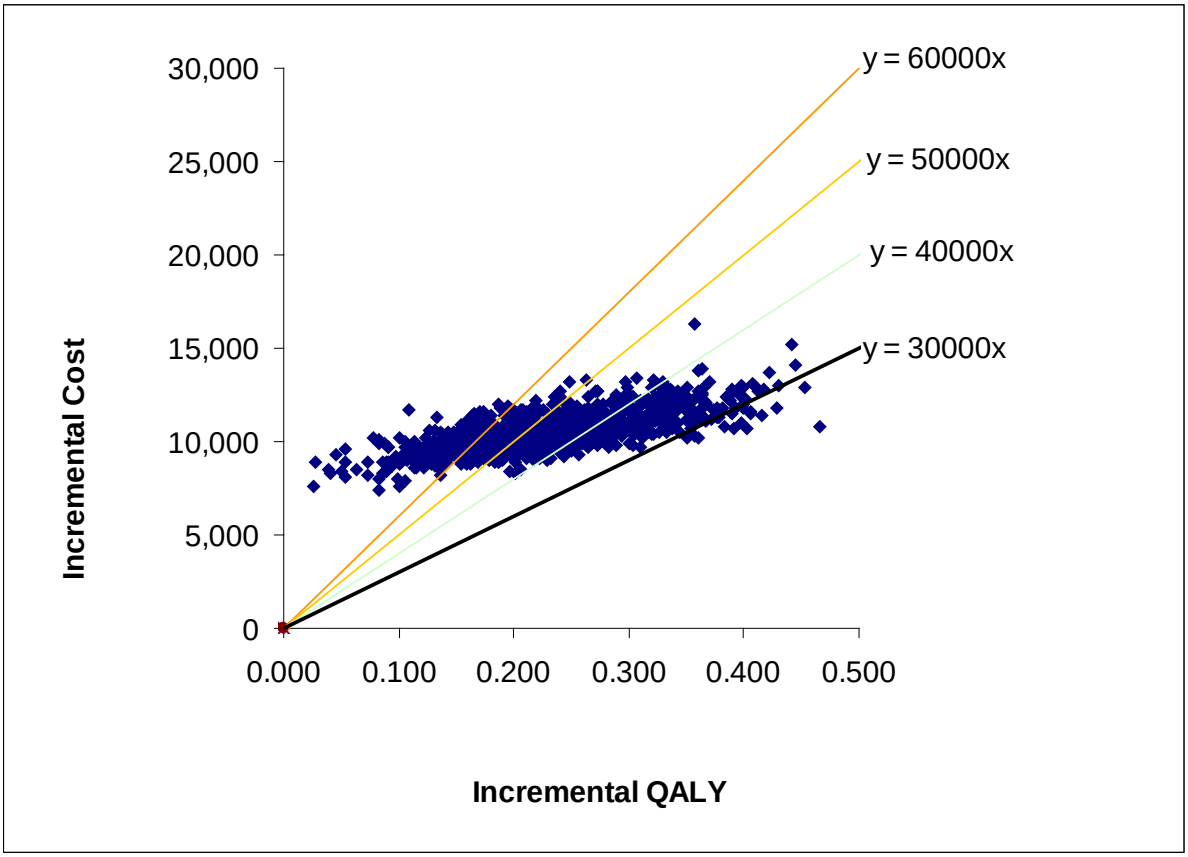


Figure 37: HCX vs. EOX scatter plot



7.4.3.2 What are the key drivers of the cost effectiveness results?

The results of the sensitivity analysis suggest that the results are not influenced greatly by changes to clinical practice assumptions, resource unit costs or changes to utility values. This is not that surprising as these changes are applied to both arms of the model.

Generally the ICER estimates did not vary greatly in response to the tested one-way sensitivity analysis.

The model is most sensitive to the use of the log logistic parmetric function for OS over the use of the Weibull function as used in the base case. The log logistic was seen to overestimate the time patients spent in each health state. When using log logistic with PFS the ICER is increase by approximately 10%.

Inclusion of Hercptin treatment effect in PFS ustility had the next most effect reducing the ICER for the primary analysis HCX vs ECX to £49,346

Relaxing the assumption of equal efficacy across double and triple regimens and cisplatin and oxaliplatin based therapy had the next most substantial effect on the results for the HCX vs. ECX and vs. EOX comparisons. Comparing HCX vs. EOX the deviation from the base case was approximately £4k when one assumes an OS hazard ratio of 0.92 for EOX vs. CX, however this was insufficient for EOX to become part of the efficiency frontier as it was still extendedly dominated by ECX and HCX. Hence relaxing this assumption does not alter the cost effectiveness of HCX. When comparing HCX and the most used regimen ECX the variance around the base case ICER was only £3k (6% of base case ICER) when one assumes an OS hazard ratio of 0.96 for ECX vs. CX.

Adjusting the utility values by 10% in each direction for the PFS and PD health states changed the ICER by around £2k-£3k from the base case in each of the comparisons. This only represents less than a 6% variation from the base case.

7.4.4 Interpretation of economic evidence

7.4.4.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

Not applicable. No previous economic analysis was identified to compare with.

7.4.4.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology?

The base case of the economic evaluation is relevant to HER2 positive patients in first line mGC who would be considered suitable for cisplatin-based combination chemotherapy. The economic evaluation is therefore of particular relevance to patients that would currently receive cisplatin based regimens. As discussed under section 7.3.2 above the most used regimen is ECX. After that there appears to be great variation in therapies used however the economic analysis explores the cost effectiveness of replacing the next most likely regimens to be replaced.

7.4.4.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

Strengths

a) The incremental clinical effects of HCX/F and CX/F are based upon a large randomised head to head phase III study, which demonstrated a significant treatment effect of adding trastuzumab to chemotherapy. Consequently the certainty of the treatment effect of trastuzumab and the subsequent incremental clinical advantages of adding trastuzumab to either chemotherapy is strong.

b) Very little extrapolation of the primary endpoint, PFS, was required due to the maturity of follow-up in the ToGA RCT, helping to reduce uncertainty in treatment effect.

c) A very mature and detailed dataset was available for first-line treatments in the ToGA study therefore the mean dose, treatment frequency, and duration of treatment could be estimated with a high level of certainty for trastuzumab containing regimens directly from the relevant RCT.

d) The utilities used in the PFS health state are based on EQ-5D data collected in the pivotal trial (ToGA) and thus represent the gold standard approach of valuing the health state as per the NICE guide to methods.

Weaknesses

a) No head-to-head data is available for comparison with the triplet therapy standard of care regimens in the UK. There is insufficient data to perform a robust formal indirect comparison especially given that treatment of this specific sub population has never been investigated using the comparator regimens. Therefore there is a lack of certainty around the relative effectiveness of ECX, ECF, and EOX compared to the comparators used in the ToGA study.

b) Utility values for patients in the PD health state were based on patients who had progressed after 2nd line therapy with GIST. However adjustment either side of the base case within a plausible range only affected the ICER by around 4%

c) The aggregated nature of the progressed health state may appear an over-simplification of the natural disease progression of mGC patients.

7.4.4.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

We have not identified any further analysis that would enhance the completeness of the results. The approach that is considered to be most likely to enhance the robustness of the results would be to collect further empirical data to inform the head to head comparison of the regimens used as comparators in ToGA and those typically used in the UK in the population of relevance. However such a trial would be unethical given the known benefits of trastuzumab in this patient population.

8 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will facilitate the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

It is estimated that NICE approval of trastuzumab in gastric cancer would have a budget impact of in £2.56m 2010, £3.86m in 2011, £5.19m in 2012, £5.88m in 2013 and £5.92m in 2014.

Table 43. Budget impact of NICE approval

Year	Administration Budget Impact	Drug Budget Impact	Total Budget Impact*
2010	£0.17m	£2.05m	£2.56m
2011	£0.32m	£3.10m	£3.86m
2012	£0.41m	£4.15m	£5.19m
2013	£0.45m	£4.70m	£5.88m
2014	£0.45m	£4.73m	£5.92m

*Total budget impact incorporates numerous factors not captured in the 'administration' and 'drug' headings (including the cost of supportive care, adverse events etc). Therefore total budget impact is not equivalent to administration budget impact + drug budget impact.

8.2 What number of patients were assumed to be eligible? How was this figure derived?

The estimated number of patients eligible for treatment with trastuzumab for gastric cancer was calculated individually for both England and Wales and then combined to estimate the total number of eligible patients.

England:

The gastric cancer incidence rate in England in 2006 was 0.0122% (Cancer Research UK, February 2006). This incidence rate was based upon those patients conforming to ICD-10 code C16 (malignant neoplasm of the stomach) which includes cancer of the GOJ in sub classification C16.0.

For the purposes of this evaluation it is assumed that this rate is representative of the incidence rate in 2010-2014. This incidence rate was applied to ONS 2008-based mid-year principal population figures for England in order to determine the number of patients expected to have gastric cancer in

the time-period of interest. It was assumed that 80% of patients presenting with gastric cancer would have a metastatic form of the disease (Cancer Research UK).

The ToGA trial was utilised to determine the proportion of these patients that would have IHC2+/FISH- or IHC3+ HER2 over-expressing disease (16.88%). This figure was derived in the following way:

Proportion of patients entering Toga with 'HER2 over-expressing' disease (as defined in the trial) multiplied by the proportion of those patients which are IHC2+/FISH- or IHC3+. Or numerically:

22.1% x 76.4% = 16.88%

On the basis of market research commissioned by Roche (Synovate Healthcare 2009) it was assumed that 53% of patients with this form of disease would receive first line chemotherapy. The remaining patients formed the population eligible to receive trastuzumab in this budget impact assessment.

Table 44. Estimated number of patients eligible to receive treatment in England

Assumptions	%	**Value 2010**	**Value 2011**	**Value 2012**	**Value 2013**	**Value 2014**
Local population		52,198,207	52,577,102	52,953,960	53,331,991	53,709,928
Gastric Cancer Incidence	0.0122%	6,368	6,414	6,460	6,507	6,553
Proportion of patients with metastatic disease	80%	5,095	5,132	5,168	5,205	5,242
Proportion IHC2+/FISH+ or IHC3+	16.88%	860	866	873	879	885
Proportion receiving chemotherapy	53%	458	462	465	468	472
Eligible population		458	462	465	468	472

Wales

The above procedure was repeated for Wales with application of the same data sources and assumptions.

Table 45. Estimated number of patients eligible to receive treatment in Wales

Assumptions	%	**Value 2010**	**Value 2011**	**Value 2012**	**Value 2013**	**Value 2014**
Local population		3,010,623	3,024,218	3,039,845	3,055,659	3,071,554
Gastric Cancer Incidence	0.0165%	497	499	502	504	507
Proportion of patients with metastatic disease	80%	397	399	401	403	405
Proportion IHC2+/FISH+ or IHC3+	16.88%	67	67	68	68	68
Proportion receiving chemotherapy	53%	36	36	36	36	36
Eligible population		36	36	36	36	36

England and Wales

Predicted eligible population in England and Wales:

2010: 458 + 36 = **494**
2011: 462 + 36 = **498**
2012: 465 + 36 = **501**
2013: 468 + 36 = **505**
2014: 472 + 36 = **508**

8.3 What assumption(s) were made about current treatment options and uptake of technologies?

It was assumed that in the absence of NICE approval for trastuzumab in gastric cancer 80% of patients would be treated with ECX, 10% would be treated with ECF and 10% would be treated with EOX. This was a simplifying assumption made as it was not considered particularly informative, to cost the numerous licensed, and unlicensed, monotherapies and doublet regimens currently being used in small numbers in the NHS (as identified in market research).

The proportions assumed were applied to the eligible population figures calculated in section 8.2 to determine the number of patients likely to receive each treatment regimen each year in the absence of NICE approval.

Table 46. Number of patients receiving each regimen, each year in the absence of NICE approval of trastuzumab combination therapy

Treatment Regimen	Value 2010	Value 2011	Value 2012	Value 2013	Value 2014
ECF	395	398	401	404	407
ECX	49	50	50	50	51
EOX	49	50	50	50	51

8.4 What assumption(s) were made about market share (where relevant)?

On the basis of Roche internal forecasting it was assumed that trastuzumab based triplet regimens would hold 40% of the market in 2010, 60% of the market in 2011, 80% of the market in 2012 and 90% in 2013 and 2014. Of these it was assumed 80% of trastuzumab based regimens were HCX and 20% were HCF.

It was assumed that remaining non-trastuzumab held market would be split between ECX (80%), ECF (10%) and EOX (10%).

Table 47. Assumed proportion of patients receiving each regimen, each year given NICE approval of trastuzumab combination therapy

Treatment Regimen	Value 2010	Value 2011	Value 2012	Value 2013	Value 2014
ECX	48%	32%	16%	8%	8%
ECF	6%	4%	2%	1%	1%
EOX	6%	4%	2%	1%	1%
HCF	32%	48%	64%	72%	72%
HCX	8%	12%	16%	18%	18%

These assumed future market share estimates were multiplied by the population figures from section 8.2 to calculate the number of patients expected to be treated with each regimen over the next 5 years (see Table 48).

Table 48. Number of patients receiving each regimen, each year given NICE approval of trastuzumab combination therapy

Treatment Regimen	Value 2010	Value 2011	Value 2012	Value 2013	Value 2014
ECX	237	159	80	40	41
ECF	30	20	10	5	5
EOX	30	20	10	5	5
HCF	158	239	321	363	366
HCX	40	60	80	91	91

8.5 What unit costs were assumed? How were these calculated?

The costs of each regimen were taken directly from the economic model described in section 7. All unit costs used in these budget impact calculations are the same as those described previously.

Table 49. Total cost of each treatment regimen (from economic model)

Treatment Regimen	Administration Cost	Drug Cost	Total cost of regimen
ECF	£2,879	£1,416	£13,430
ECX	£1,471	£1,688	£12,353
EOX	£1,471	£4,367	£15,048
HCX	£2,285	£12,031	£25,066
HCF	£3,090	£11,536	£25,053

The above regimen costs were applied to the patient figures derived previously in order to determine the budget impact of NICE approval of trastuzumab for gastric cancer.

8.6 In addition to drug costs, consider other significant costs associated with treatment. What is the recommended treatment regime – for example, what is the typical number of visits, and does treatment involve daycase or outpatient attendance? Is there a difference between recommended and observed doses? Are there likely to be any adverse events or a need for other treatments in combination with the technology?

Details of all treatment regimens and resource requirements are detailed comprehensively in section 7.

8.7 Were there any estimates of resource savings? If so, what were they?

There were no estimates of resource savings.

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

No resource savings are anticipated given NICE approval of trastuzumab in gastric cancer.

9 References

Agrawal S et al. Assessing the total costs of blood delivery to hospital oncology and haematology patients. Curr Med Res Opin 2006; 22:1903-1909

AIOM 2009: Associazione Italiana di Oncologia Medica. Neoplasie Dello Stomaco. Available at: http://www.aiom.it/C_Common/Download.asp?file=/doc/upload/9_Neoplasie_stomaco_18_09_09_OK21_09.pdf. Accessed 18.02.2010

Ajani JA et al. Multicenter phase III comparison of cisplatin/S-1 (CS) with cisplatin/5-FU (CF) as first-line therapy in patients with advanced gastric cancer (FLAGS). ASCO Gastrointestinal Cancers Symposium 2009; Abstract 8

Ajani JA. Standard of Care for Gastric Cancer Based on Meta-Analysis? Treading On Thin Ice or It Is Very Nice! J Clin Oncol 2006; 24:5473-4

Al-Batran SE et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol 2008; 26:1435-1442.

Albanell J et al. Guidelines for HER2 testing in breast cancer:a national consensus of the Spanish Society of Pathology (SEAP) and the Spanish Society of Medical Oncology (SEOM). Clin Transl Oncol 2009; 11:363-375

Allgayer H et al. c-erbB-2 is of independent prognostic relevance in gastric cancer and is associated with the expression of tumor-associated protease systems. J Clin Oncol 2000; 18:2201-2209

Allum W et al. Guidelines for the management of oesophageal and gastric cancer. Gut 2002;50(Suppl V):v1-v23

Bachmann MO et al. Cohort study in South and West England of the influence of specialzation on the management and outcome of patients with oesophageal and gastric cancers. Br J Surg. 2002; 89: 914-922

Bang 2009a: Bang Y et al. Pathological features of advanced gastric cancer (GC): Relationship to human epidermal growth factor receptor 2 (HER2) positivity in the global screening programme of the ToGA trial. J Clin Oncol 2009; 27(15S): Abstr 4556 and Poster.

Bang 2009b: Bang Y et al. Trastuzumab with chemotherapy in untreated HER2-positive advanced or metastatic gastric cancer: Efficacy results from the ToGA trial. Annals of Oncology 2009; 20 (June Suppl): 7s, Abstract O-0015 and Oral Presentation.

Barone C et al. Treatment of patients with advanced gastric carcinoma with a 5-fluorouracil-based or a cisplatin-based regimen: two parallel randomized phase II studies. Cancer 1998; 82:1460–7

BNF58: British National Formulary. 58th ed. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2009

Bouche O et al. Randomized multicenter phase II trial of a biweekly regimen of fluorouracil and leucovorin (LV5FU2), LV5FU2 plus cisplatin, or LV5FU2 plus irinotecan in patients with previously untreated metastatic, gastric cancer: A Federation Francophone de Cancerologie Digestive Group Study - FFCD 9803. J Clin Onc 2004; 22:4319-4328.

Chia S et al. Human epidermal growth factor receptor 2 overexpression as a prognostic factor in a large tissue microarray series of node-negative breast cancers. J Clin Oncol 2008; 10:5697-704

Chung H et al. Human epidermal growth factor receptor 2 (HER2) in gastric cancer (GC): results of the ToGA trial screening programme and recommendations for HER2 testing. ECCO 15 - 34th ESMO Multidisciplinary Congress; 2009 September 20-24th; Berlin, Germany. Abstract PD-6511 and Poster.

Colucci G et al. Efficacy of the association of folinic acid and 5-fluorouracil alone versus folinic acid and 5-fluorouracil plus 4-epidoxorubicin in the treatment of advanced gastric carcinoma. American J Clin Oncol 1995; 18:519–24

Coyle D et al. Cost of palliative care in the community, in hospitals and in hospices in the UK. Critical reviews in oncology: Hematology 1999; 32:71-85

CRD 2008: Systematic Reviews. CRD's guidance for undertaking reviews in health care. Centre for Reviews and Dissemination, University of York, 2008. (Published January 2009). Available at: http://www.york.ac.uk/inst/crd/pdf/Systematic_Reviews.pdf. Accessed 18.02.2010

CRUK 2009a: Cancer Research UK. Stomach cancer - UK incidence statistics. Updated 11th August 2009. Available at: http://info.cancerresearchuk.org/cancerstats/types/stomach/incidence/index.htm. Accessed 18.02.2010

CRUK 2009b: Cancer Research UK. Stomach cancer - UK mortality statistics. Updated 13th May 2009. Available at: http://info.cancerresearchuk.org/cancerstats/types/stomach/mortality/index.htm. Accessed 18.02.2010

CRUK 2009c: Cancer Research UK. Statistics and outlook for stomach cancer. Updated 27th February 2009. Available at: http://www.cancerhelp.org.uk/type/stomach-cancer/treatment/statistics-and-outlook-for-stomach-cancer. Accessed 18.02.2010

CRUK 2007a: Cancer Research UK. Stomach cancer - survival statistics for England and Wales. Updated 8th October 2007. Available at: http://info.cancerresearchuk.org/cancerstats/types/stomach/survival/index.htm. Accessed 18.02.2010

CRUK 2007b: Cancer Research UK. Symptoms and Treatment of Stomach Cancer. Updated 16th October 2007. Available at: http://info.cancerresearchuk.org/cancerstats/types/stomach/symptomsandtreatment/index.htm . Accessed 18.02.2010

Cullinan SA et al.Controlled evaluation of three drug combination regimens versus fluorouracil alone for the therapy of advanced gastric cancer. North Central Cancer Treatment Group. J Clin Oncol 1994; 12:412–6.

Cullinan SA et al. A comparison of three chemotherapeutic regimens in the treatment of advanced pancreatic and gastric carcinoma. Fluorouracil vs fluorouracil and doxorubicin vs fluorouracil, doxorubicin, and mitomycin. JAMA 1985; 253:2061-7.

Cunningham D et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 2008; 358:36-46

Dank M et al. Randomized phase III study comparing irinotecan combined with 5-fluorouracil and folinic acid to cisplatin combined with 5-fluorouracil in chemotherapy naive patients with advanced adenocarcinoma of the stomach or esophagogastric junction. Ann Oncol 2008; 19:1450–1457

De Lisi V et al. Randomized comparison of 5-FU alone or combined with carmustine, doxorubicin, and mitomycin (BAFMi) in the treatment of advanced gastric cancer: A phase III trial of the Italian Clinical Research Oncology Group (GOIRC). Cancer Treat Rep 1986; 70:481–485

De Vivo R et al. The role of chemotherapy in the management of gastric cancer. J Clin Gastroenterol. 2000; 30(4): 364-71

Dolan P. Modelling valuations for EuroQol Health states. Medical Care 1997; 35:1095-1108

Dowsett M et al. Standardization of HER2 testing: results of an international proficiency-testing ring study. Modern Pathology 2007; 20:584-591

Ewer M, Lippman S. Type II chemotherapy-related cardiac dysfunction: time to recognize a new entity. J Clin Oncol 2005; 23:2900– 2902

Fujimoto-Ouchi K et al. Antitumor activity of trastuzumab in combination with chemotherapy in human gastric cancer xenograft models. Cancer Chemother Pharmacol. 2007; 59:795-805

Gravalos C et al. Correlation between Her2/neu overexpression/amplification and clinicopathological parameters in advanced gastric cancer patients: a prospective study. ASCO Gastrointestinal Cancers Symposium 2007; Abstr 89

Guarneri V et al. Long-term cardiac tolerability of trastuzumab in metastatic breast cancer: the M. D. Anderson Cancer Center experience. J Clin Oncol 2006; 24:4107–4115

Hanna W et al. Updated recommendations from the Canadian National Consensus Meeting on HER2/neu testing in breast cancer. Curr Oncol 2007; 14:149-153

Hofmann M et al. Assessment of a HER2 scoring system for gastric cancer: results from a validation study. Histopathology 2008; 52:979-805

Im SA et al: The prognostic significance of the overexpression of HER-2/neu in Korean gastric carcinomas and the in vitro effects of anti-HER-2/neu antibody on cell growth in the gastric carcinoma cell lines. Cancer Res Treat 2003; 35:109-116

Joensuu H et al. Amplification of erbB2 and erbB2 expression are superior to estrogen receptor status as risk factors for distant recurrence in pT1N0M0 breast cancer: a nationwide population-based study. Clin Cancer Res 2003; 9:923–930

Kang YK et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. Ann Oncol 2009; 20:666–673

Kim TW et al. A prospective randomized phase III trial of 5-fluorouracil and cisplatin (FP) versus epirubicin, cisplatin, and 5-fu (ECF) in the treatment of patients with previously untreated advanced gastric cancer (AGC). E J Cancer 2001; 37 (Suppl 6):314

Kim SY et al. Trastuzumab inhibits the growth of human gastric cancer cell lines with HER2 amplification synergistically with cisplatin. International Journal Of Oncology 2008; 32:89-95

Kono K et al. Impaired antibody-dependent cellular cytotoxicity mediated by Herceptin in patients with gastric cancer. Cancer Res 2002; 62:5813-5817

Leichman L, Berry BT. Cisplatin therapy for adenocarcinoma of the stomach. Semin Oncol 1991; 18(S3):25-33

Levi JA et al. Analysis of a prospectively randomized comparison of doxorubicin versus 5-fluorouracil, doxorubicin, and BCNU in advanced gastric cancer: implications for future studies. J Clin Oncol 1986; 4:1348–55

Loehrer PJ et al. 5-fluorouracil vs. epirubicin vs. 5-fluorouracil plus epirubicin in advanced gastric carcinoma. Investigational New Drugs 1994; 12:57–63

Marty M et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 Study Group. J Clin Oncol 2005; 23:4265-74

Matsui Y et al. Suppression of tumor growth in human gastric cancer with HER2 overexpression by an anti-HER2 antibody in a murine model. Int J Oncol 2005; 27:681-685

Millar DR et al. A service evaluation to compare secondary care resource use between XELOX and FOLFOX-6 regimens in the treatment of metastatic colorectal cancer from a UK National Health Service (NHS) perspective. ISPOR 11th Annual European Congress; Athens, Greece; 2008 November 9th-11th. Poster EE8.

Mizutani T et al. Relationship of C-erbB-2 protein expression and gene amplification to invasion and metastasis in human gastric cancer. Cancer 1993; 72:2083-2088

Murad AM et al. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. Cancer 1993; 72:37–41

NCCN 2010a: National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Esophageal Cancer. V.1.2010. Available at: http://www.nccn.org/professionals/physician_gls/PDF/esophageal.pdf. Accessed 18.02.2010

NCCN 2010b: National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Gastric Cancer. V.1.2010. Available at: http://www.nccn.org/professionals/physician_gls/PDF/gastric.pdf. Accessed 18.02.2010

Nakajima M et al. The prognostic significance of amplification and overexpression of c-met and c-erb B-2 in human gastric carcinomas. Cancer 1999; 85:1894-902

NHS reference costs 2008/9. Department of Health, January 2010. Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_111591. Accessed 25.02.2010

National Institute for Health and Clinical Excellence (2009) CG80: Early and locally advanced breast cancer: NICE guideline; costing template. Available at: http://guidance.nice.org.uk/CG80/CostTemplate/xls/English. Accessed 19.02.2010

National Institute for Health and Clinical Excellence (2009) CG81: Advanced breast cancer: diagnosis and treatment: NICE guideline. Available at: http://guidance.nice.org.uk/CG81/Guidance/pdf/English. Accessed 19.02.2010

National Institute for Health and Clinical Excellence (2009) TA176: Cetuximab for the first-line treatment of metastatic colorectal cancer. Available at: www.nice.org.uk/nicemedia/pdf/TA176Guidance.pdf. Accessed 19.02.2010

National Institute for Health and Clinical Excellence (2009) TA179: Sunitinib for the treatment of gastrointestinal stromal tumours. Available at: http://guidance.nice.org.uk/TA179. Accessed 19.02.2010

National Institute for Health and Clinical Excellence (2007) TA107: Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer. Available at: http://www.nice.org.uk/nicemedia/pdf/TA107guidance.pdf. Accessed 19.02.2010

National Institute for Health and Clinical Excellence (2005) TA91: Ovarian cancer (advanced) - paclitaxel, pegylated liposomal doxorubicin hydrochloride and topotecan (review). Available at: http://guidance.nice.org.uk/TA91. Accessed 25.02.2010

National Institute for Health and Clinical Excellence (2002) TA34: The clinical effectiveness and cost effectiveness of trastuzumab for breast cancer. Available at: http://www.nice.org.uk/nicemedia/pdf/advancedbreastcancerno34PDF.pdf. Accessed 19.02.2010

Okines AF et al. Meta-analysis of the REAL-2 and ML17032 trials: evaluating capecitabine-based combination chemotherapy and infused 5-fluorouracil-based combination chemotherapy for the treatment of advanced oesophago-gastric cancer. Annals of Oncology 2009; 20: 1529–1534

Ouchi KF et al. Antitumor activity of trastuzumab (Herceptin) in human gastric cancer models. EJC Supplements 2003; 1(S294): Abstract 98

Parkin DM et al. Global cancer statistics, 2002. CA Cancer J Clin 2005; 55: 74–108

Perez E et al. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. J Clin Oncol 2008; 26:1231-8

Preusser P et al. Chemotherapy of gastric cancer. Cancer Treat Rev 1988; 15: 257-277

PSSRU 2009: Curtis L. Unit Costs of Health & Social Care 2009. Personal Social Services Research Unit. Available at: http://www.pssru.ac.uk/pdf/uc/uc2009/uc2009.pdf. Accessed 18.02.2010

Roche 2010: Roche data on file.

Ross JS, McKenns BJ. The HER-2/neu oncogene in tumors of the gastrointestinal tract. Cancer Investigation 2001; 19:554-568

Ross P et al. Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) with epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. J Clin Oncol. 2002; 20: 1996-2004

Sakai K et al. Expression of epidermal growth factor receptors on normal human gastric epithelia and gastric carcinomas. J Natl Cancer Inst 1986; 77:1047-52

Satoh T et al. Quality of life results from a phase III trial of trastuzumab plus chemotherapy in first-line HER2-positive advanced gastric and GE junction cancer.

2010 Gastrointestinal Cancers Symposium; 2010 January 22-24th; Orlando, Florida. Abstract 7 and Poster.

Schnall S, Macdonald JS. Mitomycin therapy in gastric cancer. Oncology 1993; 50(S1): 70-77

Slamon D et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 1987; 235:177-182

Smith IE. Efficacy and safety of Herceptin in women with metastatic breast cancer: results from pivotal clinical studies. Anti-Cancer Drugs 2001; 12(Suppl 4):S3-S10

Suter TM et al. Trastuzumab-associated cardiac adverse effects in the Herceptin adjuvant trial. J Clin Onc 2007; 25:3859-3865

Synovate Healthcare. Gastric Cancer patient record based market research (Roche data on file); September 2009

Synovate Healthcare. Gastric Cancer perception based market research (Roche data on file); June 2009

Tanner M et al. Amplification of HER-2 in gastric carcinoma: association with Topoisomerase IIa gene amplification, intestinal type, poor prognosis and sensitivity to trastuzumab. Annals Oncol 2005; 16:273-278
Tappenden P. The cost-effectiveness of bevacizumab in the first-line treatment of metastatic colorectal cancer in England and Wales. Eur J Cancer 2007; 43:2487-2494

Tobe T et al. A randomized, comparative-study of combination chemotherapies in advanced gastric-cancer - 5-fluorouracil and cisplatin (fp) versus 5- fluorouracil, cisplatin, and 4'-epirubicin (fpepir). Anticancer Research 1992;12:1983-1988

Tovey S et al. Poor survival outcomes in HER2 positive breast cancer patients with low grade, node negative tumours. EJSO 2008; 34:1159

Uchino S et al. Overexpression of c-erbB-2 protein in gastric cancer. Its correlation with long-term survival of patients. Cancer 1993; 72:3179-84

Van Custsem 2009a: Van Cutsem E et al. Efficacy results from the ToGA trial: A phase III study of trastuzumab added to standard chemotherapy (CT) in first-line human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer (GC). J Clin Oncol 2009; 27(15S): Abstr LBA4509 and Oral Presentation.

Van Cutsem 2009b: Van Cutsem E et al. Trastuzumab added to standard chemotherapy (CT) as first-line treatment in human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer (GC): efficacy and safety results from the Phase III ToGA trial. ECCO 15 - 34th ESMO Multidisciplinary Congress; 2009 September 20-24th; Berlin, Germany. Abstract 7BA and Oral Presentation.

Van Cutsem E et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol 2006; 24:4991–4997.

Vanhoefer U et al. Final results of a randomized phase III trial of sequential high-dose methotrexate, fluorouracil, and doxorubicin versus etoposide, leucovorin, and fluorouracil versus infusional fluorouracil and cisplatin in advanced gastric cancer: a trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group. J Clin Oncol 2000; 18:2648–2657.

Wagner AD et al. Combination chemotherapies in advanced gastric cancer: An updated systematic review and meta-analysis. Journal of Clinical Oncology 2007; 25(18S): Abstr 4555

Wagner AD et al. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. J Clin Oncol. 2006; 18:2903-2909.

Wagner AD et al. Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev 2005, Issue 2. Art. No: CD004064. (Reprint published in The Cochrane Library 2009, Issue 1)

Walker RA et al. HER2 testing in the UK: further update to recommendations. J Clin Pathol 2008; 61:818-824

Ward S et al. Trastuzumab for the treatment of primary breast cancer in HER2 positive women: a single technology appraisal. University of Sheffield, School of Health and Related Research. Available at: http://www.nice.org.uk/nicemedia/pdf/Breastcancer_trastuzumab_erg.pdf. Accessed 20.02.2010

Waters JS et al. Long-term survival after epirubicin, cisplatin and fluorouracil for gastric cancer: results of a randomized trial. Br J Cancer 1999; 80:269-272

Wolff AC et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol 2007; 25: 118-145

Weisgerber-Kriegl U et al. Estimation of the epidemiological effect of trastuzumab over 10 years in 5 European countries. J Clin Oncol 2008; 26 (May 20 suppl; abstr 6589).

Yano T et al. Expression of HER2 in gastric cancer: comparison between protein expression and gene amplification using a new commercial kit. J Clin Oncol 2004; 22 (14S): Abstr 4053

Yun et al. A randomised phase II study of combination chemotherapy with epirubicin, cisplatin and capecitabine (ECX) or cisplatin and capecitabine (CX) in advanced gastric cancer. Eur J Cancer 2010. [Epub Jan 6]

Other literature

Jadad A.R., *et al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled Clinical Trials* 1996;**17**:1-12.

Please use the Vancouver style (that is, consecutive numbering throughout the main text). In the reference list, the names of up to six authors should be given, followed by et al.; for example:

Coyle D, Small N, Ashworth A, Hennnessy S, Jenkins-Clarke S, Mannion R et al. Cost of palliative care in the community, in hospitals and in hospices in the UK, *Critical reviews in oncology: Hematology* 1999. 32:71-85

10 Appendices

10.1 Appendix 1

Summary of Product Characteristics or Technical Manual or drafts

10.2 Appendix 2: search strategy for section 5

The following information should be provided.

10.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Medline (MEYY), Medline In-Process (MEIP), EMBASE (EMYY), EMBASE Alert (EMBA), BIOSIS Previews (BIYY), and BIOL – Last Updated (BIOX) were searched using Dialog DataStar.

The Cochrane Library was interrogated via Wiley Interscience online at http://www.mrw.interscience.wiley.com/cochrane/cochrane_search_fs.html.

The American Society of Clinical Oncology (ASCO) Annual Meeting, the ASCO Gastrointestinal Cancers Symposium, the European Society for Medical Oncology (ESMO) World Congress on Gastrointestinal Cancer, the ESMO Congresses, and the European CanCer Organisation (ECCO) Congresses were also search as described in section 6.1.

10.2.2 The date on which the search was conducted.

24th January 2010:

- Medline, Medline In-Process, EMBASE, EMBASE Alert, BIOSIS Previews, and BIOL – Last Updated
- The American Society of Clinical Oncology (ASCO) Annual Meeting
- The European Society for Medical Oncology (ESMO) World Congress on Gastrointestinal Cancer
- The ESMO Congresses
- The European CanCer Organisation (ECCO) Congress
- The joint ECCO 15 – 34th ESMO Multidisciplinary Congress

2nd February 2010:

- The Cochrane Library
- The ASCO Gastrointestinal Cancers Symposium

10.2.3 The date span of the search.

- Dialog DataStar, Medline 1993 to 24th January 2010
- Dialog DataStar, Medline-In process-Latest eight weeks prior to 24th January 2010
- Dialog DataStar, Embase 1993 to 24th January 2010
- Dialog DataStar, Embase latest eight weeks prior to 24th January 2010
- Dialog DataStar, Biosis Previews 1993 to 24th January 2010
- Dialog DataStar, BIOL – Last Updated latest eight weeks prior to 24th January 2010
- The Cochrane Library, http://www.mrw.interscience.wiley.com/cochrane/cochrane_search_fs.html, searched with unrestricted dates to 2nd February 2010

Please see section 6.1 for the date span of congress materials searched.

10.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Medline (MEYY), Medline In-Process (MEIP), EMBASE (EMYY), EMBASE Alert (EMBA), BIOSIS Previews (BIYY), and BIOL – Last Updated (BIOX) were interrogated individually, and results combined with duplicate records dropped using Dialog Datastar.

Search Strategy

No.	Database	Search term	Info added since	Results
1	MEYY	Stomach−Neoplasms#.MJ.	unrestricted	25999
2	MEYY	Esophagogastric−Junction#.MJ.	unrestricted	1770
3	MEYY	1 OR 2	unrestricted	27487
4	MEYY	herceptin	unrestricted	1103
5	MEYY	trastuzumab	unrestricted	3181
6	MEYY	4 OR 5	unrestricted	3442
7	MEYY	3 AND 6	unrestricted	26
8	MEYY	7 AND PT=CLINICAL−TRIAL# AND HUMAN=YES	unrestricted	0
9	MEIP	gastric ADJ cancer	unrestricted	1087
10	MEIP	stomach ADJ cancer	unrestricted	75
11	MEIP	gastroesophageal ADJ junction	unrestricted	33
12	MEIP	9 OR 10 OR 11	unrestricted	1173
13	MEIP	herceptin	unrestricted	43
14	MEIP	trastuzumab	unrestricted	216
15	MEIP	13 OR 14	unrestricted	235
16	MEIP	12 AND 15	unrestricted	7
17	MEIP	16 AND PT=CLINICAL−TRIAL#	unrestricted	0
18	EMYY	Stomach−Cancer#.MJ.	unrestricted	20668
19	EMYY	Lower−Esophagus−Sphincter#.MJ.	unrestricted	832
20	EMYY	18 OR 19	unrestricted	21432
21	EMYY	Trastuzumab#.W..MJ.	unrestricted	1833
22	EMYY	20 AND 21	unrestricted	12
23	EMYY	22 AND CLINICAL−TRIAL# AND HUMAN=YES	unrestricted	5
24	EMBA	gastric ADJ cancer	unrestricted	290
25	EMBA	stomach ADJ cancer	unrestricted	17
26	EMBA	gastroesophageal ADJ junction	unrestricted	6
27	EMBA	24 OR 25 OR 26	unrestricted	309

No.	Database	Search term	Info added since	Results
28	EMBA	herceptin	unrestricted	15
29	EMBA	trastuzumab	unrestricted	77
30	EMBA	28 OR 29	unrestricted	84
31	EMBA	27 AND 30	unrestricted	2
32	BIYY	gastric ADJ cancer	unrestricted	17938
33	BIYY	stomach ADJ cancer	unrestricted	2965
34	BIYY	gastroesophageal ADJ junction	unrestricted	857
35	BIYY	32 OR 33 OR 34	unrestricted	21244
36	BIYY	herceptin	unrestricted	1624
37	BIYY	trastuzumab	unrestricted	2589
38	BIYY	36 OR 37	unrestricted	3548
39	BIYY	35 AND 38	unrestricted	44
40	BIYY	39 AND HUMANS#	unrestricted	41
41	BIOX	gastric ADJ cancer	unrestricted	35
42	BIOX	stomach ADJ cancer	unrestricted	3
43	BIOX	gastroesophageal ADJ junction	unrestricted	1
44	BIOX	41 OR 42 OR 43	unrestricted	39
45	BIOX	herceptin	unrestricted	3
46	BIOX	trastuzumab	unrestricted	12
47	BIOX	45 OR 46	unrestricted	13
48	BIOX	44 AND 47	unrestricted	1
49	BIOX	48 AND HUMANS#	unrestricted	1
50	BIOX BIYY EMBA EMYY MEIP MEYY	combined sets 8, 17, 23, 31, 40, 49	unrestricted	49
51	BIOX BIYY EMBA EMYY MEIP MEYY	dropped duplicates from 50	unrestricted	4
52	BIOX BIYY EMBA EMYY MEIP MEYY	unique records from 50	unrestricted	45

Please see section 6.1 for a description of search strategies employed for the Cochrane Library and congress materials.

10.2.5 Details of any additional searches, for example searches of company databases (include a description of each database).

The Roche internal "Publication Planning" database for Herceptin (trastuzumab) was also interrogated for citations relating to gastric cancer (though this did not identify any publications not already found using the external sources described above).

10.2.6 The inclusion and exclusion criteria.

Inclusion criteria

Records which evaluated the following were included:

1. Trastuzumab had to be the major focus of the study, in order to eliminate references which merely mentioned trastuzumab as part of a discussion of treatments for advanced/metastatic adenocarcinoma of the stomach or gastro-oesophageal junction

2. Advanced/metastatic adenocarcinoma of the stomach or gastro-oesophageal junction had to be a major focus of the study, in order to eliminate papers addressing the use of trastuzumab in other types of cancers

3. Studies in which patients received trastuzumab therapy in combination with capecitabine or 5 fluorouracil and cisplatin, to be consistent with the trastuzumab licence.

4. Studies in which patients received study therapy for the first-line treatment of their disease, to be consistent with the trastuzumab licence.

5. Comparative efficacy and safety endpoints associated with the treatment of advanced/metastatic adenocarcinoma of the stomach or gastro-oesophageal junction were the focus for the data, i.e., progression-free survival, overall survival, response rates, quality of life, safety

6. Randomised controlled trials – rather than case reports, retrospective reviews, etc.

7. Documents relating to humans – since work in animal models is not relevant to this application

Exclusion criteria

Records which evaluated the following were excluded:

1. Any references providing a review or commentary on data published elsewhere were excluded, as only current clinical trial data are required

2. Any papers where duplicate records were already identified through other searches

3. Studies in which trastuzumab was administered in combination with chemotherapeutic agents other than capecitabine or 5 fluorouracil and cisplatin (as per licence) and/or in non-relevant populations, i.e. non first-line setting in advanced/metastatic disease

4. Animal studies or *in vitro* research – only human data are required

10.2.7 The data abstraction strategy.

Titles were reviewed for those records which did not have abstracts readily available. Records clearly unrelated to the appraisal were excluded, where necessary the full record was obtained and evaluated in more detail for RCT status and relevance.

Records with abstracts readily available were assessed for RCT status and relevance. Where necessary the full record was obtained and evaluated in more detail for relevance.

The data abstraction strategy is further detailed in the tables below.

Search output for MEYY, MEIP, EMYY, EMBA, BIYY, BIOX combined

Search Database	Result No.	Publication Author	Publication Year	Abstract viewed	Full publication viewed	RCT
COMBINED	1	Meza	2009	Y		N
COMBINED	2	Helwick	2009	n/a	Y	N
COMBINED	3	Gong	2010	Y		N
COMBINED	4	Bekaii	2009	Y		N
COMBINED	5	Van Cutsem	2009	Y	Oral presentation	Y
COMBINED	6	Junker	2009	n/a	Y	N
COMBINED	7	Wagner	2009	Y		N
COMBINED	8	Gravalos	2008	Y		N
COMBINED	9	Mahindroo	2009	Y		N
COMBINED	10	Anon	2001	N – reviews EGFR inhibitors		
COMBINED	11	Wagner	2009	Y		N
COMBINED	12	Marx	2009	Y		N
COMBINED	13	Yokoyama	2006	Y		N

Search Database	Result No.	Publication Author	Publication Year	Abstract viewed	Full publication viewed	RCT
COMBINED	14	Ford	2009	Y		N
COMBINED	15	Marx	2008	Y		N
COMBINED	16	Ohtsu	2008	Y		N
COMBINED	17	Hofmann	2008	Y		N
COMBINED	18	Kim	2008	Y		N
COMBINED	19	Fazekas	2008	Y		N
COMBINED	20	Rueschoff	2008	Y		N
COMBINED	21	Lordick	2007	Y		N
COMBINED	22	Press	2007	Y		N
COMBINED	23	Kim	2007	Y		N
COMBINED	24	Hori	2007	Y		N
COMBINED	25	Nakamura	2007	N – study at cellular level		
COMBINED	26	Fujimoto	2007	Y		N
COMBINED	27	Hanada	2007	Y		N
COMBINED	28	Abbadessa	2006	n/a	Y	N
COMBINED	29	Park	2006	Y		N
COMBINED	30	Katoh	2006	Y		N
COMBINED	31	Tuma	2006	Y		N
COMBINED	32	Ramaswamy	2006	Y		N
COMBINED	33	Roda	2005	Y		N
COMBINED	34	Szolosi	2005	Y		N

Search Database	Result No.	Publication Author	Publication Year	Abstract viewed	Full publication viewed	RCT
COMBINED	35	Matsui	2005	Y		N
COMBINED	36	Vizoso	2004	Y		N
COMBINED	37	Gong	2004	Y		N
COMBINED	38	Hinoda	2004	Y		N
COMBINED	39	Tufeanu	2004	N - study at cellular level		
COMBINED	40	Ouchi	2003	Y		N
COMBINED	41	Subongkot	2003	Y		N
COMBINED	42	Kono	2002	Y		N
COMBINED	43	Takenhana	2002	Y		N
COMBINED	44	Akishi	2001	Y		N

Search output for the Cochrane Library

Search Database	Result No.	Publication Author	Publication Year	Abstract viewed	Full publication viewed	RCT Y/N
Cochrane	1	National Horizon Scanning Centre	2009	Y		N

Search output for ASCO

Search Database	Result No.	Publication Author	Publication Year	Abstract viewed	Full publication viewed	RCT Y/N
ASCO	1	Bang	2009	Y	Poster	Y
ASCO	2	Boers	2009	Y		N

Search Database	Result No.	Publication Author	Publication Year	Abstract viewed	Full publication viewed	RCT Y/N
ASCO	3	Cinieri	2009	Y		N
ASCO	4	Van Cutsem	2009	Duplicate of COMBINED 5		
ASCO	5	Bang	2008	Y		N
ASCO	6	Tokuda	2008	N – animal study		
ASCO	7	Wang	2008	N – pertains to breast cancer		
ASCO	8	Sarti	2008	N – case report		
ASCO	9	León-Chong	2007	Y		N
ASCO	10	Cortés-Funes	2007	Y		N
ASCO	11	Gravalos	2006	Y		N
ASCO	12	Chacon	2006	Y		N
ASCO	13	Carson	2005	N – phase I study		
ASCO	14	Yano	2004	Y		N

Search output for ASCO Gastrointestinal Cancers Symposium

Search Database	Result No.	Publication Author	Publication Year	Abstract viewed	Full publication viewed	RCT Y/N
ASCO GI	1	Geissler	2010	N – pertains to pancreatic cancer		N
ASCO GI	2	Satoh	2010	Y	Poster	Y

Search output for the ESMO World Congress on Gastrointestinal Cancer

Search Database	Result No.	Publication Author	Publication Year	Abstract viewed	Full publication viewed	RCT Y/N
WCGIC	1	Rubin	2009	N – pertains to GISTs		
WCGIC	2	Bang	2009	Y	Oral presentation	Y
WCGIC	3	Negri	2008	N – pertains to colorectal cancer		
WCGIC	4	Lordick	2007	Y		N

Search output for ECCO and ESMO

Search Database	Result No.	Publication Author	Publication Year	Abstract viewed	Full publication viewed	RCT Y/N
ECCO ESMO	1	Van Cutsem	2009	Y	Oral presentation	Y
ECCO ESMO	2	Van Custsem	2009	Y		N
ECCO / ESMO	3	Tabernero	2009	Y		N
ECCO ESMO	4	Chung	2009	Y	Poster	Y
ECCO	5	Lordick	2007	n/a	Y	N
ESMO	6	Rech	2006	Y		N
ESMO	7	Nicholas	2006	Y		N

10.3 Appendix 3: search strategy for section 7

The following information should be provided.

10.4 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

Medline (MEYY), Embase (EMYY) and Medline in process (MEIP) were searched using Dialogue Datastar. NHS EED was searched via the University of York's Center for Reviews and Dissemination (CRD) website. HEED was searched using the Wiley InterScience HEED portal.

10.5 The date on which the search was conducted.

The search was conducted on 22/12/09.

10.6 The date span of the search.

MEYY and EMYY were searched from 1993 to the present day. No limits were placed on alternate searches.

10.7 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Dialogue datastar search strategy (MEYY, EMYY, MEIP)

No.	Database	Search term	Info added since	Results
1	MEYY	STOMACH-NEOPLASMS.DE.	unrestricted	30575

2	MEYY	(gastr$5 OR stomach) NEAR (cancer OR carcinom$5 ADJ tumor$5 OR tumour$5 OR carcinoma$5 OR neoplasm$5 OR polyp$5 OR metastasis)	unrestricted	41466
3	MEYY	trastuzumab OR Herceptin	unrestricted	3370
4	MEYY	COST-BENEFIT-ANALYSIS.DE. OR MODELS-ECONOMIC.DE. OR ECONOMICS-PHARMACEUTICAL.DE.	unrestricted	40626
5	MEYY	Economic ADJ Evaluation	unrestricted	4029
6	MEYY	cost ADJ effectiv$5	unrestricted	45103
7	MEYY	cost ADJ utility ADJ analysis	unrestricted	913
8	MEYY	Health ADJ technology AND (assessment OR appraisal)	unrestricted	2563
9	MEYY	1 OR 2	unrestricted	41466
10	MEYY	4 OR 5 OR 6 OR 7 OR 8	unrestricted	71815
11	MEYY	9 AND 3	unrestricted	50
12	MEYY	11 AND 10	unrestricted	0
13	EMYY	STOMACH-CANCER.DE. OR STOMACH-CARCINOMA.DE.	unrestricted	26471
14	EMYY	(gastr$5 OR stomach) NEAR (cancer OR carcinom$5 ADJ tumor$5 OR tumour$5 OR carcinoma$5 OR neoplasm$5 OR polyp$5 OR metastasis)	unrestricted	36509
15	EMYY	trastuzumab OR Herceptin	unrestricted	9843
16	EMYY	ECONOMIC-EVALUATION.DE. OR HEALTH-ECONOMICS.DE. OR COST-EFFECTIVENESS-ANALYSIS.DE. OR QUALITY-ADJUSTED-LIFE-YEAR.DE.	unrestricted	70005
17	EMYY	Economic ADJ Evaluation OR cost ADJ effectiv$5 OR cost ADJ utility ADJ analysis	unrestricted	75260
18	EMYY	Health ADJ technology AND (assessment OR appraisal)	unrestricted	1547
19	EMYY	13 OR 14	unrestricted	36509
20	EMYY	19 AND 15	unrestricted	261
21	EMYY	16 OR 17 OR 18	unrestricted	84165
22	EMYY	20 AND 21	unrestricted	1
23	MEIP	(gastr$5 OR stomach) NEAR (cancer OR carcinom$5 ADJ tumor$5 OR tumour$5 OR carcinoma$5 OR neoplasm$5 OR polyp$5 OR metastasis)	unrestricted	916
24	MEIP	trastuzumab OR Herceptin	unrestricted	161
25	MEIP	Economic ADJ Evaluation OR cost ADJ effectiv$5 OR cost ADJ utility ADJ analysis	unrestricted	1637
26	MEIP	Health ADJ technology AND (assessment OR appraisal)	unrestricted	110
27	MEIP	23 AND 24	unrestricted	6

28	**MEIP**	**25 OR 26**	**unrestricted**	**1708**
29	**MEIP**	**27 AND 28**	**unrestricted**	**0**
30	**MEYY EMYY MEIP** [all]	**combined sets 12, 22, 29**	**unrestricted**	**1**
31	**MEYY EMYY MEIP** [all]	**dropped duplicates from 30**	**unrestricted**	**0**
32	**MEYY EMYY MEIP** [all]	**unique records from 30**	**unrestricted**	**1**

The singular study identified through the MEYY/EMYY/MEIP search was not an economic evaluation and was therefore deemed irrelevant in this decision context. In the interest of complete transparency this search result is referenced below.

Romano M, Ricci V, Zarrilli R. 'Mechanisms of disease: Helicobacter pylori-related gastric carcinogenesis - Implications for chemoprevention.' Nature Clinical Practice Gastroenterology and Hepatology, November 2006, vol. 3, no. 11, p. 622-632

NHS EED search strategy:

(trastuzumab OR Herceptin) AND gastric

No results identified

HEED search strategy:

(trastuzumab OR Herceptin) AND gastric

No results identified

10.8 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No other searches were conducted for economic studis. As only one paper was retrieved (found to be irrelevant after assessment) it was deemed unnecessary to present a QUORUM diagram detailing the search.

However additional a separate search was conducted for utility values appropriate for use within the economic analysis, the details of which are shown below.

Gastric Cancer Utilities Search

Objective:

To obtain UK relevant utility values for patients with advanced gastric cancer for use in de novo economic modelling.

Strategy:

MEDLINE (MEYY), EMBASE (EMYY), MEDLINE in process (MEIP), the NICE and SMC websites and a well known repository of utility values (Tengs et al. 2000) were searched for utility values/studies in patients with advanced gastric cancer.

Search strategies did not include search terms or filters that would limit results to specific publication types. Each search result's title and abstract were assessed for relevance according to the pre-defined inclusion criteria. Studies identified as being potentially relevant were retrieved for full assessment. Utilities not conforming to the NICE reference case are reported in the interest of transparency. Dialogue Datastar was utilised to access the databases of interest. The search was conducted on 05/02/2010.

Table 50: Utility search inclusion criteria

Population:	Any aGC patients
Intervention:	Any
Comparators:	Any
Outcomes:	Utility values conforming to NICE reference case
Study Design:	Any

The search strategies were constructed using 2 components; an 'advanced gastric cancer' component (containing terms such as advanced, gastric cancer, stomach cancer, gastric carcinoma,

stomach neoplasm etc) and a 'utility/HRQL' component (containing terms relating to the valuation of health states such as 'EQ-5D, health utility, time trade off, standard gamble etc). This search strategy was designed to capture all potential utility sources for use in the de novo economic modeling .

The NICE and SMC websites were searched for the term 'gastric' and scanned for gastric cancer technology appraisals that may have contained utility values whilst Tengs et al was reviewed for gastric cancer utilities.

EMYY / MEYY / MEIP Search Strategy:

No.	Database	Search term	Info added since	Results
1	EMYY	STOMACH-CANCER.DE. OR STOMACH-CARCINOMA.DE. OR (STOMACH OR GASTRIC) ADJ (CANCER OR CARCINOMA)	unrestricted	30602
2	EMYY	ADVANCED OR METASTATIC	unrestricted	209628
3	EMYY	HEALTH ADJ UTILITY OR HEALTH ADJ UTILITIES OR UTILITY ADJ VALUE OR UTILITY ADJ SCORE OR HRQL OR HRQoL OR Health ADJ related ADJ quality ADJ of ADJ life	unrestricted	5810
4	EMYY	STANDARD ADJ GAMBLE OR TIME ADJ TRADE ADJ OFF	unrestricted	793
5	EMYY	QUALITY-OF-LIFE.DE. AND ECONOMICS.DE. OR QUALITY-ADJUSTED-LIFE-YEARS.DE.	unrestricted	7658
6	EMYY	1 AND 2	unrestricted	5868
7	EMYY	3 OR 4 OR 5	unrestricted	13425
8	EMYY	6 AND 7	unrestricted	3
9	MEYY	STOMACH-NEOPLASMS.DE. OR (STOMACH OR GASTRIC) ADJ (CANCER OR CARCINOMA)	unrestricted	35849
10	MEYY	ADVANCED OR METASTATIC	unrestricted	243054
11	MEYY	HEALTH ADJ UTILITY OR HEALTH ADJ UTILITIES OR UTILITY ADJ VALUE OR UTILITY ADJ SCORE OR HRQL OR HRQoL OR Health ADJ related ADJ quality ADJ of ADJ life	unrestricted	6544
12	MEYY	STANDARD ADJ GAMBLE OR TIME ADJ TRADE ADJ OFF	unrestricted	870
13	MEYY	QUALITY-OF-LIFE.DE. AND ECONOMICS.DE. OR QUALITY-ADJUSTED-LIFE-YEARS.DE.	unrestricted	8513
14	MEYY	9 AND 10	unrestricted	6793
15	MEYY	11 OR 12 OR 13	unrestricted	14888

16	MEYY	14 AND 15	unrestricted	4
17	MEIP	(STOMACH OR GASTRIC) ADJ (CANCER OR CARCINOMA OR NEOPLASM$3)	unrestricted	1246
18	MEIP	ADVANCED OR METASTATIC	unrestricted	12870
19	MEIP	HEALTH ADJ UTILITY OR HEALTH ADJ UTILITIES OR UTILITY ADJ VALUE OR UTILITY ADJ SCORE OR HRQL OR HRQoL OR Health ADJ related ADJ quality ADJ of ADJ life	unrestricted	520
20	MEIP	STANDARD ADJ GAMBLE OR TIME ADJ TRADE ADJ OFF	unrestricted	40
21	MEIP	QUALITY ADJ ADJUSTED ADJ LIFE ADJ YEAR$2 OR QALY	unrestricted	301
22	MEIP	17 AND 18	unrestricted	317
23	MEIP	19 OR 20 OR 21	unrestricted	803
24	MEIP	22 AND 23	unrestricted	0
25	EMYY MEYY MEIP [all]	combined sets 8, 16, 24	unrestricted	7
26	EMYY MEYY MEIP [all]	dropped duplicates from 25	unrestricted	2
27	EMYY MEYY MEIP [all]	unique records from 25	unrestricted	5

Results:

In total 7 potentially relevant results were identified through searching. The review of the Tengs et al. utility repository uncovered two utility values for patients with Gastric cancer (0.75 for primary chemotherapy and 0.58 for best supportive care). Upon reviewing the source of these values it was found that they were from a paper retrieved in the EMYY/MEYY/MEIP search (Gliemlius et al. 1995 – discussed below). This duplication between databases/repositories searched is reassuring and validates the quality of the search undertaken.

5 of the 7 studies identified were retrieved for further evaluation. The two not retrieved were the NICE and SMC appraisals of capecitabine in advanced gastric cancer. As capecitabine is a Roche product that is currently undergoing NICE appraisal the individual screening the search results for relevance was aware that no utility values for gastric cancer were utilized, or quoted, in either the SMC or NICE appraisals as a cost-minimisation, and not a cost-utility model, formed the core of the analysis undertaken. As the objective of the search was to obtain utility values the two results were not investigated further.

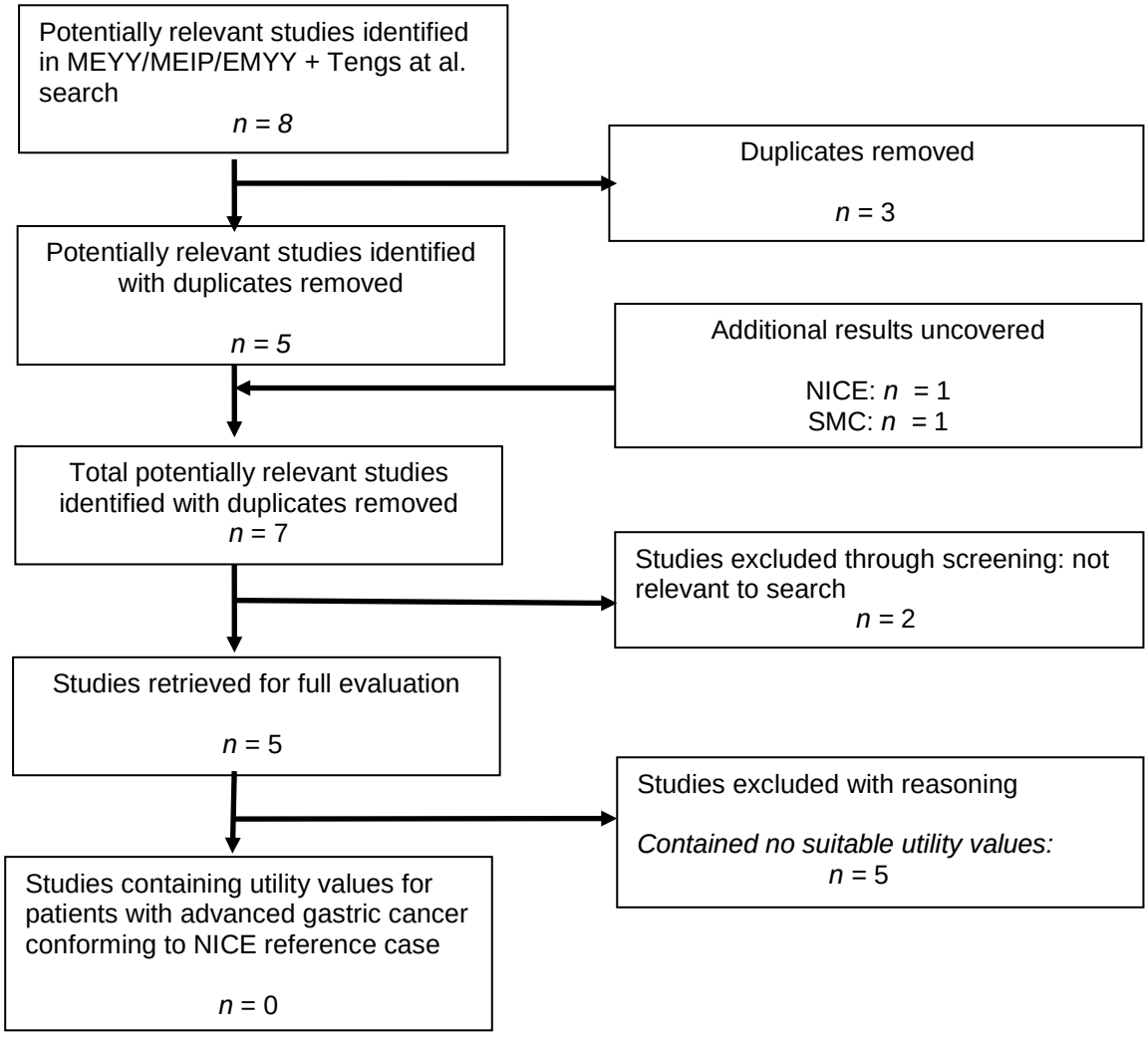
The remaining 5 search results (Sadighi et al. (2006), Dan et al. (2006), Redaelli et al. (2002), Web et al. (1997) and Glimelius et al. (1995)) were retrieved and assessed for utility values relevant to this decision context.

The Sadighi et al. paper detailed the results of the collection of EORCT QLQ-C30 data during an RCT comparing docetaxel, cisplatin and 5-FU with epirubicin, cisplatin and 5-FU in 71 patients with advanced gastric in Iran. As the EORCT QLQ-C30 is not preference based it is incapable of directly informing utility scores for use in health economic modeling. Therefore it's use in this analysis was dismissed.

Upon retrieval the Redaelli et al. paper was searched for any reference to utility values. Whilst providing a review of the management of gastric cancer and two paragraphs on the assessment of the quality of life of patients with gastric cancer no utility values were provided in the text.

The paper by Glimelius et al (as found in the EMYY/MEYY/MEIP and Tengs et al. searches) was a cost effectiveness analysis of palliative chemotherapy in advanced gastrointestinal cancer in Sweden published in 1995. 18 gastric cancer patients were non-randomly assigned to treatment with etoposide, leucovorin and 5-FU or leucovorin and 5-FU and assessed for quality of life by two observers. Where a patient was deemed to have an 'unchanged high quality of life and no symptoms of systematically progressive disease, or improvements in quality of life estimates without being hospitalized' their survival time was weighted with a value of 1 and where the above criteria was not the case their survival time was weighted with a value of 0. This methodology produced utility values of 0.75 for patients receiving 'primary chemotherapy' and 0.58 for patients receiving 'best supportive care'. As the above technique of quality of life adjustment does not conform to the NICE reference case the Glimelius paper was deemed inadequate as a source of utility values for use in this evaluation.

A QUORUM diagram detailing the utility search:



The Dan et al. paper was a 2006 cost-effectiveness analysis on the use of endoscopic screening for gastric cancer in Singapore. In the economic model used in their analysis Dan et al. used a utility value of 0.5 for patients with stage 4 (metastatic) gastric cancer. This value was referenced to the Glimelius et al. paper discussed above and a validation exercise of the EORTC QLQ-STO 22 quality of life questionnaire (Blazeby et al. (2004)). Given the extremely primitive methodology Glimelius et al utilised to develop their utilities it is clear that any utility sources founded on this work will be equally as flawed as the original values. Therefore the metastatic gastric cancer utility value listed in Dan et al. cannot be be relied upon for use in this analysis.

The Webb et al. paper detailed an RCT comparing epirubicin, cisplatin and 5-FU to doxorubicin, methotrexate and 5-FU in patients with advanced esophogastric cancer. Similarly to the Sadighi et al. paper EORTC QLQ-C30 data was collected from patients taking part in the trial. As EORTC QLQ-C30 is not a preference based instrument it is incapable of directly informing utilities for use in an economic model. Therefore the Sadighi et al paper is of no assistance in this evaluation.

Results:

No utilities conforming to the NICE guide to methods are available in the literature. Those values that have been used in economic evaluations in, or related to, gastric cancer (Glimelius et al. and Dan et al.) stem from the 1995 Glimelius paper in which an extremely primitive method of utility elicitation was utilised in a very small number of patients. The two values produced by Glimelius are listed below:

Primary Chemotherapy = 0.75

Best Supportive Care = 0.58

Whilst these values were not obtained using methods recommended in the NICE guide to methods it is encouraging that they are roughly equivalent to the values obtained through EQ-5D collection in ToGA and those utilised in the economic evaluation. However as the methods utilised by Glimelius were so primitive the strength of validation that can be drawn from this similarity is relatively weak.

As advanced gastric cancer is a relatively rare disease with few treatments having been assessed by NICE and the SMC this lack of reliable utility values that conform to the NICE reference case is unsurprising. Given that EQ-5D data from the trial of interest is the gold standard of quality adjustment and is recommended in the NICE guide to methods it is clear that the EQ-5D data from ToGA should be utilised in de novo modelling.

Appendix C1

Primary endpoint: Superiority of OS

The study met its primary endpoint of demonstrating a significant improvement in OS in patients receiving HCX/F compared with CX/F chemotherapy alone using Kaplan-Meier estimates and Cox regression analyses.

In the FAS population, the hazard ratio for HCX/F versus CX/F was 0.74 (95% CI 0.60-0.91). This indicates a 26% reduction in the risk of death for patients treated with HCX/F compared with CX/F based on the non-stratified analysis (two-sided Log-Rank test) of OS. The results demonstrated that the addition of trastuzumab to CX/F provided a clinically relevant and statistically significant 2.7 month improvement (P=0.0046) in the primary endpoint of OS (median 11.1 months vs 13.8 months) compared to CX/F alone (Figure 38).

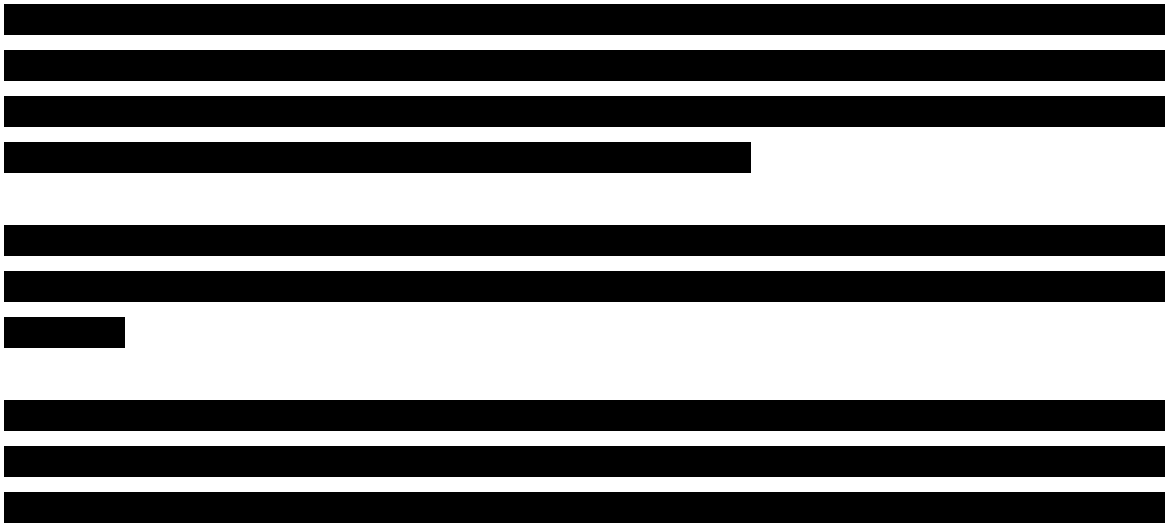
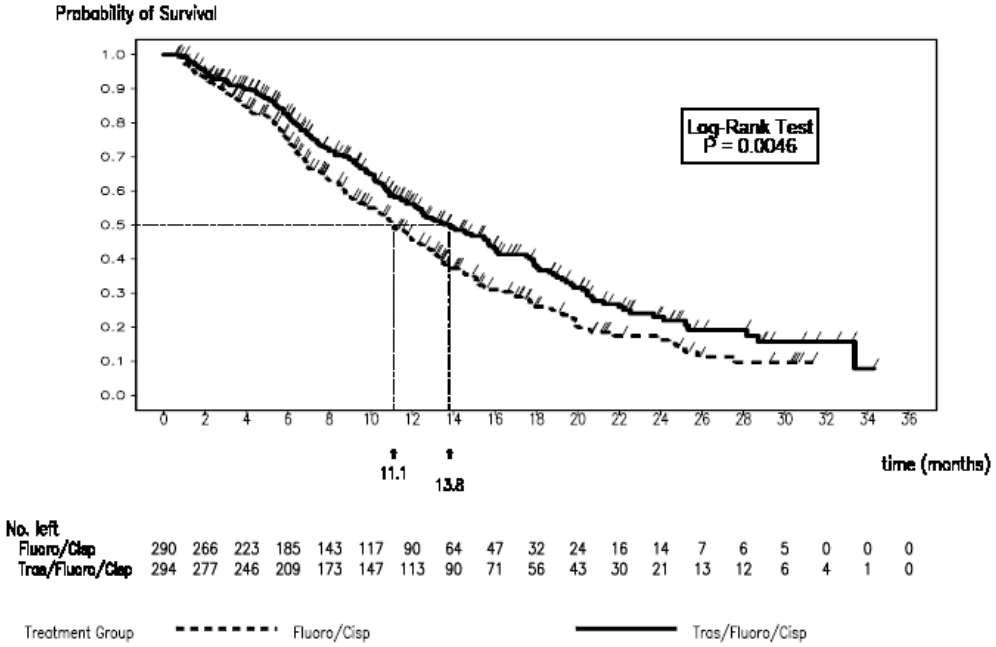


Figure 38: Kaplan-Meier Curve of Overall Survival (FAS) of patients treated with HCX/F versus CX/F in the ToGA study



	Events	Median OS	HR	95% CI	p value
HCX/F	167	13.8	0.74	0.60, 0.91	0.0046
CX/F	182	11.1			

[redacted]

Table 51: Stratified and Non-Stratified Log-Rank Test and Risk Ratios of Overall Survival (FAS)

		Cox regression		
HCX/F VS CX/F	**Log-rank test (p-value)**	**Hazard Ratio**	**95% CI**	**p-value**
No stratification	0.0046	0.74	0.60-0.91	0.0046
[redacted]				

Table 52: OS results for superiority of HCX/F vs CX/F

FAS (non-stratified)	**Median OS (Months)**	**HR (95% CI)**	**P value**
HCX/F	16.0	Reference regimen	
CX/F	11.8	0.74 (0.60-0.91)	0.0046
[redacted]			

6.4.5 Secondary endpoints

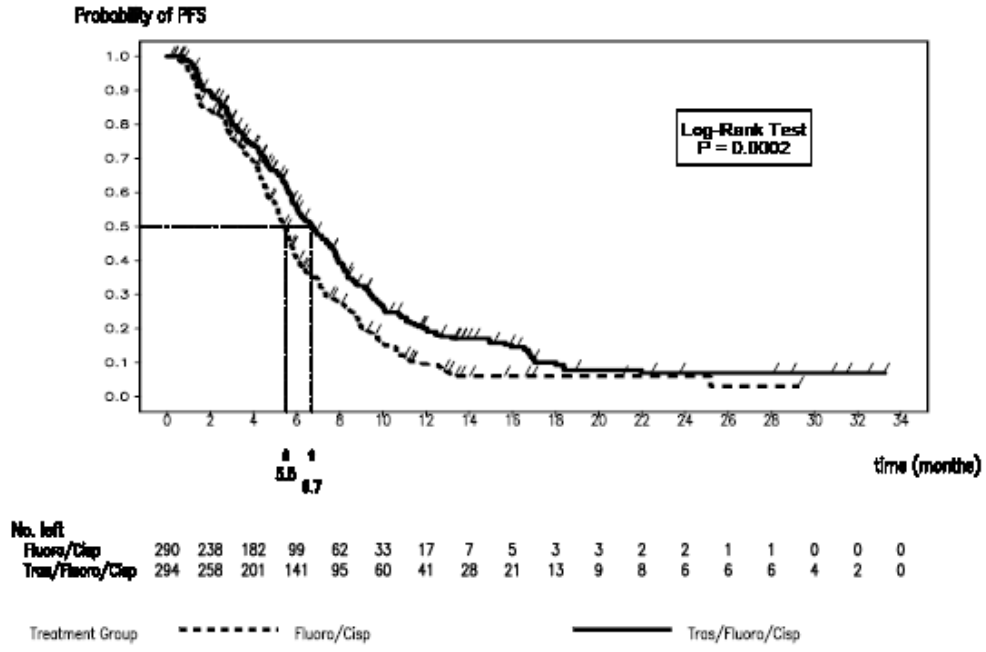
As shown in Table 53, as well as reaching its primary goal of demonstrating that HCX/F improves OS by three months compared with CX/F, the secondary efficacy end-points (PFS, ORR, CBR [clinical benefit rate], TTP, DoR [duration of response]) in this study all demonstrated clinical significance for

the addition of trastuzumab to CX/F chemotherapy in the FAS population with similar hazard ratios. The Kaplain Meier for PFS is shown in Figure 39.

Table 53: Summary of Overall Efficacy Results (Clinical Cut-Off January 7, 2009; FAS)

Parameter	FP N = 290	FP+H N = 294
Overall Survival		
Median (months)	11.1	13.8
p-value (Log-Rank test)	0.0046	
HR (95% CI) p-value		
Unstratified	0.74 (0.60-0.91) p = 0.0046	
Stratified	0.71 (0.57-0.88) p = 0.0020	
Progression-Free Survival		
Median (months)	5.5	6.7
p-value (Log-Rank test)	0.0002	
HR (95% CI) p-value		
Unstratified	0.71 (0.59-0.85) p = 0.0002	
Stratified	0.71 (0.59-0.86) p = 0.0004	
Time to Disease Progression		
Median (months)	5.6	7.1
p-value (Log-Rank test)	0.0003	
HR (95% CI) p-value		
Unstratified	0.70 (0.58-0.85) p = 0.0003	
Stratified	0.69 (0.57-0.84) p = 0.0003	
Overall Response Rate		
No. of patients with:		
Complete Response	7 (2.4%)	16 (5.4%)
p-value (Chi-squared test)	p = 0.0599	
Partial Response	93 (32.1%)	123 (41.8%)
p-value (Chi-squared test)	p = 0.0145	
Stable Disease	101 (34.8%)	93 (31.6%)
Progressive Disease	53 (18.3%)	35 (11.9%)
Missing assessment	36 (12.4%)	27 (9.2%)
Responders (CR + PR)	100 (34.5%)	139 (47.3%)
Non-Responders	190 (65.5%)	155 (52.7%)
Difference in Response Rate	12.80	
p-value (Chi-squared test)	0.0017	
Odds Ratio (95% CI)	1.70 (1.22-2.38)	
Clinical Benefit Rate		
Patients with Clinical Benefit (CR + PR + SD)	201 (69.3%)	232 (78.9%)
Patients with no Clinical Benefit	89 (30.7%)	62 (21.1%)
Difference in Clinical Benefit	9.60	
p-value (Chi-squared test)	p = 0.0081	
Odds Ratio (95% CI)	1.66 (1.14-2.41)	
Duration of Response		
Patients included in analysis	100	139
Median (months)	4.8	6.9
p-value (Log-Rank test)	p < 0.0001	
HR (95% CI) p-value		
Unstratified	0.54 (0.40-0.73) p < 0.0001	
Stratified	0.53 (0.39-0.73) p < 0.0001	

Figure 39: Kaplan-Meier Curve of PFS (FAS) of patients treated with HCX/F versus CX/F in ToGA study



[redacted]

Preplanned subgroup efficacy analysis by HER2 status

The results of the pre-planned HER2 subgroup analysis indicated that there is little contribution to the overall increase in efficacy from the subgroups with low expression of HER2 protein (IHC 0/FISH+: HR 0.92; IHC 1+/FISH+: HR 1.24) and instead, the results indicate that the main effect is derived in the subgroups of patients expressing high levels of HER2 protein (IHC 2+/FISH+: HR 0.75; IHC 3+/FISH+: HR 0.58) (Figure 40).

[redacted]

Based on these findings, a post-hoc exploratory analysis was conducted to analyse the HER2 subgroups in more detail as HER2 protein expression is the target for trastuzumab therapy. Patients who had a HER2 status of IHC2+/FISH+ or IHC3+ were defined as high HER2 expressors and this subgroup represents the EMEA approved license population for trastuzumab in mGC.

Figure 40: Hazard ratios and 95% confidence interval for overall survival by HER2 subgroups for (FAS)

		Fluoropyrimidine/ Cisplatin			Trastuzumab/Fluoro-pyrimidine/Cisplatin				
Subgroup		Patients per group	N Events	Median time	Patients per group	N Events	Median time	Hazard Ratio	95% CI for Hazard Ratio
HER2 Result	FISH+/IHC0	38	24	7.2	23	15	10.6	0.92	[0.48;1.76]
	FISH+/IHC1+	32	21	10.2	38	28	8.7	1.24	[0.70;2.20]
	FISH+/IHC2+	79	53	10.8	80	51	12.3	0.75	[0.51;1.11]
	FISH+/IHC3+	125	76	12.3	131	61	17.9	0.58	[0.41;0.81]
	FISH-/IHC3+	6	4	17.7	9	5	17.5	0.83	[0.20;3.38]

Appendix C2: Indirect treatment comparison literature review results and summary of trial characteristics

Table A1. Overview of the design of included studies (n=7)

Study	Treatment arms	Study design	Patient population	Inclusion criteria	Exclusion criteria	Survival	Trial duration	Length of follow-up	Dose, frequency and duration of treatment
Van Cutsem (2006)	DCF	Multinational, multicenter, randomised, phase III study	gastric or esophagogastric junction adenocarcinoma	metastatic or locally recurrent disease with one or more measurable lymph nodes; KPS > 70; no prior palliative chemotherapy; adequate hepatic, renal, and hematologic function.	concurrent cancer, neuropathy, brain, or leptomeningeal involvement	OS, PFS	November 1999 and January 2003	Median duration of therapy was 19 weeks with DCF and 16 with FP	Docetacel: e3w docetaxel 75 mg/m2 (day 1) plus cisplatin 75 mg/m2 (day 1) and fluorouracil 750 mg/m2/d continuous infusion (days 1 to 5; DCF)
	FP								once every 4 weeks cisplatin 100 mg/m2 (day 1) and fluorouracil 1,000 mg/m2/d continuous infusion (days 1 to 5; CF).
Al-Batran (2008)	FLO	Randomised, multicenter study	adenocarcinoma of the stomach or EGJ	locally advanced or metastatic, no prior palliative chemotherapy, ECOG<= 2	peripheral neuropathy of National Cancer Institute grade >= 2 at baseline; brain metastases; coronary heart disease	OS, PFS	June 2003 and January 2006	Median : 14 months	oxaliplatin 85 mg/m2 and leucovorin 200 mg/m2, each intravenous infusion, followed by FU 2,600 mg/m2 continuous infusion every 2 weeks
	FLP								cisplatin 50 mg/m2 infusion every 2 weeks combined with leucovorin 200mg/m2 infusion and FU 2,000mg/m2 every week for 6 weeks followed by a 2-week rest
Cunningham (2008, REAL-2)	ECF	Randomised, multicenter study	adenocarcinoma, squamous-cell carcinoma, or undifferentiated carcinoma of the oesophagus, gastroesophageal junction, or stomach	locally advanced (inoperable) or metastatic; ECOG of 0 to 2; and adequate renal, hepatic, and hematologic function.	previous chemotherapy or radiotherapy, uncontrolled cardiac disease	OS, PFS	June 2000 and May 2005	Median: 17.1 months	on day 1 of every 3-week cycle, epirubicin (50 mg/m2); cisplatin (60 mg/m2) given with hydration in the ECF and ECX groups, and oxaliplatin (130 mg/m2) intravenously in the EOF and EOX groups. Fluorouracil (at a daily dose of 200 mg /m2) and capecitabine (at a twice daily dose of 625 mg /m2) were given throughout treatment in the appropriate groups
	ECX								
	EOF								
	EOX								

Study	Treatment arms	Study design	Patient population	Inclusion criteria	Exclusion criteria	Survival	Trial duration	Length of follow-up	Dose, frequency and duration of treatment
Dank (2008)	ILF	Randomised	adenocarcinoma (including diffuse type, intestinal type and linitis) of the stomach or esophagogastric junction	measurable or evaluable metastatic disease or locally recurrent disease with one or more measurable lymph node; KPS >70%	resectable disease; prior palliative chemotherapy or treatment with camptothecin; cumulative dose of prior cisplatin >300 mg/m2	OS, PFS	June 2000 to March 2002	Median treatment duration was 21 weeks in the ILF arm and 17 weeks in the FP arm.	irinotecan 80 mg/m2 infusion, followed by FA 500 mg/m2 infusion, immediately followed by 5-FU 2000 mg/m2 infusion, day 1 every week for 6 weeks followed by a 1-week rest.
	FP								cisplatin 100 mg/m2 i.v. infusion, day 1, followed by 5-FU 1000 mg/m2/day infusion, days 1–5, every 4 weeks.
Bouche (2004)	5-FU, Leucovorin	Randomised multicenter phase II trial	gastric or cardial adenocarcinoma without linitis	Metastatic, ECOG <= 2 Adjuvant chemotherapy without cisplatin or irinotecan allowed if completed at least 6 months before randomization. adequate haematologic, hepatic, renal, and cardiac function.	chronic diarrhoea, prior enteropathy, or extensive intestinal resection.	OS, PFS	January 1999 and October 2001	Median : 26 months	LV 200 mg/m2 intravenous (IV) followed by FU 400 mg/m2 IV bolus then FU 600 mg/m2 continuous infusion on days 1 and 2, repeated every 14 days (one cycle 15 days)
	FLP								cisplatin 50 mg/m2 IV on day 1 or 2 with LV5FU2 (one cycle 15 days).
	ILF								irinotecan 180 mg/m2 IV on day 1 with LV5FU2 (one cycle 15 days).
Kim (2001)	FP	Randomised phase III trial	gastric cancer	nr	nr	OS, PFS	Mar 1997 to Apr 2000	nr	5FU 1,000 mg/m2 IV on days 1 to 5, and cisplatin 60 mg/m2 IV on day 1 every 4 weeks
	ECF								epirubicin 50 mgIm2 on day 1, cisplatin 60 mg/m2 on day 1, and 5-FU 1,000 mg/rn2 IV on days 1 to 5 every 4 weeks
Yun (2010)	XP	randomised phase II study	gastric cancer	Confirmed, measurable AGC. ECOG <=2, adequate bone marrow, hepatic, cardiac and renal functions. Only adjuvant	Severe comorbid illness, including cardiac dysfunction, or a history of	PFS	During 2008	Median treatment duration: 4.4 months in the	cisplatin 75 mg/m2 on day 1, and oral capecitabine 1000 mg/m2 twice daily as an intermittent regimen of 2 weeks of treatment followed by a 1-week rest, every 3 weeks

ECX	chemotherapy that had been completed more than 6 months before registration and no radiotherapy within 4 weeks before registration.	anaphylaxis.	XP arm, 4.2 months in the ECX arm	epirubicin 50 mg/m2 was administered on day 1 in addition to regular XP regimen every 3 weeks

Table A2. Overview of the patient characteristics of included studies (n=9)

Study	Treatment arm	Male	Median age (years, range)	Intestinal GC	Diffuse GC	Prior surgery	Metastatic disease	Primary site: stomach	Primary site: GE junction	Primary site: esophagus	ECOG PS 0	ECOG PS 1	ECOG PS 2	KPS 90	KPS 80	KPS 70	1 organ involved	2 organs involved	>2 organs involved	HER-2 positive	population (N)	population (N)	Per protocol population
Van Cutsem (2006)	DCF	72	55 (26-79)	18	42	31	96	81	19	nr	Nr	nr	nr	35	51	13	15	39	45	nr	227	221	nr
	FP	71	55 (25-76)	20	34	32	97	74	25					35	51	13	21	34	45		230	224	
Al-Batran (2008)	FLO	57.1	64 (33-86)	nr	nr	45.6	97.3	82	18	nr	92 (0-1)		8	nr	nr	nr	23.2	29.5	47.4	nr	112	112	nr
	FLP	75	64 (27-85)			41.8	98	84	22		89.8		11				22.2	36.1	41.7		108	106	
Cunningham (2008, REAL-2)	ECF	81	65 (22-83)	nr	nr	7.6	79.5	36.1	28.9	34.9	88.4 (0-1)		11.6	nr	nr	nr	nr	nr	Nr	nr	263	263	249
	ECX	81	64 (25-82)			7.5	76.8	42.3	28.2	29.5	87.6		12.4								250	250	241
	EOF	81	61 (33-78)			7.7	77	37	23.4	39.6	91.5		8.5								245	245	235
	EOX	83	62 (25-80)			8.8	75.7	43.5	22.2	34.3	90		10								244	244	239
Dank (2008)	ILF	73.5	58 (29-76)	28.8	35.3	41.2	95.9	80	20.0	nr	nr	nr	nr	38.8	34.1	0.6	41.8	37.6	14.7	nr	172	170	144

Study	Treatment arm	Male	[illegible] (years, range)	Intestinal GC	Diffuse GC	Prior surgery	Metastatic disease	Primary site: stomach	Primary site: GE junction	Primary site: esophagus	ECOG PS 0	ECOG PS 1	ECOG PS 2	KPS 90	KPS 80	KPS 70	1 organ involved	2 organs involved	>2 organs involved	HER-2 positive	population (N)	population (N) Per protocol population
	FP	66.3	59 (28-77)	25.8	28.2	40.5	95.1	81	19.0					41.7	40.5	1.2	38.7	40.5	16		165	163	127
Bouche (2004)	5-FU, Leucovorin	82	64 (45-75)	nr	nr	51	nr	nr	nr	nr	73 (0-1)	27		nr	nr	nr	33	47	20	nr	nr	45	nr
	FLP	80	64 (43-76)	nr	nr	50					75	25					46	39	16	nr		44	
	ILF	84	65 (37-76)	nr	nr	51					78	22					36	47	18	nr		45	
Kim (2001)	FP	70	56.5	nr	nr	nr	95.0	nr	nr	nr	88.3 (0-1)	nr		nr	nr	nr	nr	nr	nr	nr	60	60	nr
	ECF	75	55				95.0				90										61	60	
Yun (2010)	XP	72	58 (33-75)	nr	nr	34	nr	nr	nr	nr	87	8		nr	nr	nr	nr	nr	nr	nr	47	45	nr
	ECX	64	55 (35-71)			36					91	2									44	44	

Data reported is the percentage of the total patient population in each trial arm, unless otherwise stated.

Table A3. Overview of the outcomes reported in the included studies (n=7)

Study	Treatment arms	Hazard Ratio for OS	95% CIs	OS at one year (%)	OS at 1 year (n/N)	Hazard Ratio for PFS	95% CIs	PFS at six months (%)	PFS at six months (n/N)
Van Cutsem (2006)	DCF	1.29	1.0-1.6	40	88/221	1.47	1.19-1.82	43.9	97/221
	FP	(FP vs DCF)		32	72/224	(FP vs DCF)		29.5	66/224
Al-Batran (2008)	FLO	nr	nr	45	50/112	nr	nr	45.9	51/112
	FLP			40	42/106			31.2	33/106
Cunningham (2008, REAL-2)	ECF			37.7	99/263			nr	nr
	ECX	0.92 (ECX vs ECF)	0.76-111	40.8	102/250	0.98 (ECX vs ECF)	0.82- 1.17	nr	nr
	EOF	0.96 (EOF vs ECF)	0.79-1.15	40.4	99/245	0.97 (EOF vs ECF)	0.81- 1.17		
	EOX	0.80 (EOX vs ECF)	0.66-0.97	46.8	114/244	0.85 (EOX vs ECF)	0.70- 1.02		
Dank (2008)	ILF	1.08	0.86-1.35	36.5	62/170	1.23	0.97- 1.57	30	51/170
	FP	(FP vs ILF)		30.1	49/163	(FP vs ILF)		25.2	41/163
Bouche (2004)	5-FU, Leucovorin	nr	0.54-1.32	31	14/45	nr	nr	29.4	13/45
	FLP			43	19/44			41.3	18/44
	ILF			43	19/45			59.7	27/45
Kim (2001)	FP	0.83	0.42-1.61	nr	nr	nr	nr	nr	nr
	ECF	(ECF vs FP taken from Wagner 2005)							
Yun (2010)	XP	nr	nr	nr	nr	0.96	0.58-1.57	56	25/45

ECX	(ECX vs XP)	59	26/44

Table A4. Quality Assessment of trials according to Jadad scale

Study Ref	*JADAD TOTAL SCORE*	*Study described as randomized 0/1*	*Method sequence of randomization described 0/1*	*Study described as double Blind 0/1*	*Method described of double blind 0/1*	*Description withdrawals/ dropouts 0/1*	*Method randomization described but not appropriate 0/-1*	*Method double blind described but not appropriate 0/-1*
Van Cutsem et al 2006	**3**	1	1	0	0	1	0	0
Al-Batran et al 2008	**3**	1	1	0	0	1	0	0
Cunningham et al 2008	**3**	1	1	0	0	1	0	0
Dank et al 2008	**3**	1	1	0	0	1	0	0
Bouche et al 2004	**3**	1	1	0	0	1	0	0
Kim et al 2001	**1**	1	0	0	0	0	0	0
Yun et al 2010	**3**	1	1	0	0	1	0	0

search strategy

The search strategy displayed below is defined for Medline searches, but was adapted accordingly for other databases. The search strategy combines the following terms:

No	Search terms
1	text words: ((stomach adj5 neoplas$).OR (stomach adj5 cancer$).OR(stomach adj5 carcin$).OR (stomach adj5 tumo$).OR(stomach adj5 metasta$).OR(stomach adj5 malig$).OR(gastric adj5 neoplas$).OR(gastric adj5 cancer$).OR(gastric adj5 carcin$).OR(gastric adj5 tumo$).OR(gastric adj5 metasta$).OR(gastric adj5 malig$)).OR(gastro adj5 neoplas$).OR(gastro adj5 cancer$).OR(gastro adj5 carcin$).OR(gastro adj5 tumo$).OR(gastro adj5 metasta$).OR(gastro adj5 malig$))
2	MESH terms: exp stomach neoplasms/
3	Text words: chemothera$.
4	MESH terms exp drug therapy/ OR exp chemotherapy adjuvant/ OR exp drug therapy combination/ OR exp antineoplastic agents combined/ OR exp chemotherapy/
5	text words: palliat$.ORunresect$. OR inopera$. OR advanc$. OR (best adj5 support$ adj5 care).OR unoperable OR (non adj5 resect$).
6	MESH exp palliative care/
7	1 OR 2

8	3 OR 4
9	5 OR 6
10	7 AND 8
11	9 AND 10
12	Capecitabine OR Xeloda OR Cisplatin OR Flurouracil OR 5-FU OR 5FU OR Epirubicin OR Ellence OR Pharmorubicin OR Epirubicin Ebewe OR Docetaxel OR Taxotere OR Oxaliplatin OR Eloxatin OR Oxaliplatin Medac OR Leucovorin OR Levoleucovorin OR Levoleucovorin 1 OR Irinotecan OR Camptosar OR Campto OR S-1 OR TS-1 *in Title or Abstract*
13	(randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR randomised [tiab] placebo [tiab] clinical trials as topic [mesh: noexp] randomly [tiab] trial [ti]) NOT (animals [mh] not (humans [mh] and animals [mh]))
14	11 AND 12 AND 13 Limits: Human, English, Adult, from January 2005
15	Combined sets from databases
16	Dropped duplicates from 6
17	Unique records from 7

Economic Evaluation Appendices

Appendix E1: Resource use

Unit cost (£'s)		ECX	EOX	ECF	HCX	HCF	H mono	HX	X Mono	HF	F Mono
	Cycles per month	1.29	1.29	1.29	1.29	1.29	1.29	1.29	1.29	1.29	1.29
	Per cycle pharmacy preparation and dispensing										
9	Pharmacy Infution	2	2	3	2	3	1	1		2	1
9	Pharmacy oral	1	1		1			1	1		
	Pharmacy cost per cycle (£'s)	**28**	**28**	**28**	**28**	**28**	**9**	**19**	**9**	**19**	**9**
	Per cycle administration:										
30	patient transport	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
38.5	Ambulatory pump			3		1				1	1
125.5	Monitoring additional to admin visit										
39	District Nurse Visit			2		1				1	1
268	Day case	1	1	1	1	1					
159	5-FU + Trastuzumab									1	
133	Administration Trastuzumab / 5-FU Monotherapy						1	1			1
1,989	Administration overnight visits										
	Administration cost per cycle (£'s)	**277**	**277**	**472**	**277**	**355**	**142**	**142**	**9**	**246**	**220**
	Total: admin and pharmacy cost / month	**393**	**393**	**644**	**393**	**494**	**197**	**209**	**24**	**344**	**297**
	Monthly Monitoring during treatment										
125	Consultation OP appointment in PFS	1.44	1.44	1.44	1.44	1.44	0.72	0.72	0.72	0.72	0.72
133	cardiac monitoring	1.29	1.29	1.29	0.33	0.33	0.33	1.33		0.33	
	Monthly monitoring cost (£'s)	**352**	**352**	**352**	**225**	**225**	**134**	**267**	**91**	**134**	**91**
	Total admin, pharmacy and monitoring cost / month	**655**	**655**	**905**	**528**	**628**	**329**	**474**	**114**	**476**	**385**

Table 54: Drug Costs

Product	mg/unit	Unit Price	£/mg
Oxaliplatin non proprietary			
50mg vial	50	149.75	2.9950
100mg vial	100	299.5	2.9950
Average per mg			**2.9950**
5FU non proprietary			
25mg/ml * 10	250	3.2	0.0128
25mg/ml * 20	500	6.4	0.0128
25mg/ml * 100	2500	32	0.0128
50mg/ml * 10	500	6.4	0.0128
50mg/ml * 20	1000	12.8	0.0128
50mg/ml * 50	2500	32	0.0128
50mg/ml * 100	5000	64	0.0128
Average per mg			**0.0128**
Capecitabine			
150mg * 60 tab	9000	40.02	0.0044
500mg * 120 tab	60000	265.55	0.0044
Average per mg			**0.004429**
Epirubicin non-proprietary			
5ml	10	16.99	1.6990
25ml	50	84.95	1.6990
50ml	100	169.92	1.6992
100ml	200	308.93	1.5447
Average per mg			**1.6133**
Cisplatin non-proprietary			
10ml	10	5.85	0.5850
50ml	50	24.50	0.4900
100ml	100	50.22	0.5022
Average per mg			**0.5036**
Trastuzumab			
150mg	150	407.40	2.7160
Average per mg			**2.7160**

Table 55: Adverse event costs taken from the 2008/9 reference costs

Currency Code	Currency Description	Activity	National Average Unit Cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost	Average Length of Stay - Days
PA45Z	Febrile Neutropenia with Malignancy long-stay	941	£3,570	£2,189	£4,829	5,078
PA45Z	Febrile Neutropenia with Malignancy short-stay	114	£817	£417	£792	114
Weighted Average Febrile Neutropenia Event			3,272	1,997	4,393	4,542
PA28A	Feeding Difficulties and Vomiting with CC Long Stay	2,055	£2,022	£1,302	£2,403	7,579
PA28B	Feeding Difficulties and Vomiting without CC Long Stay	3,606	£1,053	£717	£1,268	7,120
PA28A	Feeding Difficulties and Vomiting with CC	3,010	£484	£356	£563	3,010
PA28B	Feeding Difficulties and Vomiting without CC	11,364	£455	£338	£546	11,364
Weighted Vomiting Event			728	508	869	8,957

Appendix E2: Personal Communication and Roche advisory board

Attendees of Roche Advisory board meeting Thursday 25 Febuary 2009

Chair
Gavin Lewis (Head of Health Economics Roche UK)

Advisors
Tom Crosby - Velindre
Simon Gollins- N Wales
Anne Thomas Leicester
Jeff Evans - Beatson
Sherif Raouf - Queens Romford
Was Manoor - Christie
Mark Harrison - Mount Vernon
Ian CHau - Royal Marsden

Personal communication to elicit estimates for clinical practice assumptions were held with the following experts prior to meeting:

Tom Crosby, Velindre, Wales

Jeff Evans, beatson, Glasgow

Appendix E3: Probabilistic sensitivity analysis

For costs taken from the NHS reference costs the s.e. was calculated by assuming that the costs are normally distributed allowing the calculation of the s.e. by using the following formula in Excel. ((UQ - LQ) / (NORMSINV(0.75)*2); where UQ and LQ represent the upper and lower quartiles respectively.

Where costs were not obtained from the reference costs the s.e. was estimated apply the average ratio of s.e. to mean values estimated across the reference case estimates used in the model.

The sampling distribution used for the PSA for all costs parameters was the gamma function.

Table 56: Supportive care, adverse events, and pharmacy cost PSA parameters

	Most-Likely Estimate	Estimated Lower Quartile	Estimated Upper Quartile	s.e.	Sampling distribution
Monitoring Costs (PFS supportive care costs):					
Consultation OP appointment in PFS	£125.49	£72.46	£156.81	£62.53	
cardiac monitoring	£133	£81	£161	£59	
Pharmacy Costs					
Pharmacy Infusion	£9	£6	£12	£4	
Pharmacy oral	£9	£6	£12	£4	
Administration					
patient transport	£29.87	£20.72	£38.67	£13.31	
District Nurse Visit	£39.37	£33.53	£46.74	£9.80	
Day case	£268.44	£148.58	£362.40	£158.50	
5-FU + Trastuzumab	£161.23	£98.74	£195.49	£71.72	
Administration Trastuzumab / 5-FU Monotherapy	£134.36	£82.28	£162.91	£59.77	
ADVERSE EVENTS					
Anaemia	582	368	721	261	
Anorexia	250	158	310	112	
Diarrhoea	237	150	293	106	
Nausea and vomiting	728	461	901	326	
Neutropenia	140	89	173	63	
Hand-foot syndrome	156	99	193	70	
Febrile Neutropenia	3272	2071	4052	1,468	
Progressive Disease BSC costs	£542	£407	£650	£181	
End of life cost	£4,000	£2,600	£4,800	£1,631	

S.E. = (UQ-LQ)/(NORMINV(75%,0,1)*2)

Frequency of adverse events
Estimation of adverse event frequencies used in the PSA came from the beta distribution calculated as follows: BETAINV(RAND(),observed number of events, observed number of non-event).

Utilities

The sampling distribution used for the PSA for all costs parameters was the gamma function.

Table 57: Utility PSA parameters

	Most-Likely Estimate	s.e.	Sampling distribution
Baseline PFS utility	0.7292	0.0109	
Increase in Utility per day from baseline	0.0001	0.0001	Beta
Utility in progressive disease (PD)	0.5770	0.04	

The parameters for the distributions used for the probabilistic sensitivity analysis were calculated based on a beta distribution using the following calculation taking the PD utility value (u_prog) as an example

=BETAINV(RAND(),u_prog*(((u_prog*(1-u_prog))/(F46*F46))-1), (1-u_prog)*(((u_prog*(1-u_prog))/(F46*F46))-1))

Kaplan-Meier PFS
The transition probability for the element of the PFS and OS curves that are based on the Kaplan-Meier curves were calculated as follows: BETAINV(Rand(),number of event, number of non-events)

Weibull OS parameter estimates

5-FU + Cisplatin		Trastuzumab + 5-FU/ Cisplatin	
Deterministic Estimates		**Deterministic Estimates**	
Lambda (λ)	0.019144391	Lambda (λ)	0.012383713
Gamma (γ)	1.457504857	Gamma (γ)	1.457504857
PSA Estimates		**PSA Estimates**	
Lambda (λ)	0.017951021	Lambda (λ)	0.012236329
Gamma (γ)	1.434942793	Gamma (γ)	1.434942793
Model Parameters (Deterministic or PSA)			
olcw	0.019144391	**olnw**	0.012383713
ogcw	1.457504857	**ognw**	1.457504857

Overall Survival - Full Data

	Estimate	StdErr
Intercept (μ)	3.01293892	0.06410613
FC	-0.29888588	0.08731142
Scale (σ)	0.68610406	0.03476235

Estimated Covariance Matrix ☐

	Intercept (μ)	Placebo	Scale (σ)	Scale (σ)
Intercept (μ)	0.00411	-0.004096	0.000323	
FC	-0.004096	0.007623	-0.00027	
Scale (σ)	0.000323	-0.00027	0.001208	

Lower Triangular (Decomposition) Matrix (T)

	Intercept (μ)	Placebo	Scale (σ)	Scale (σ)
Intercept (μ)	0.064109282	0	0	
FC	-0.063890905	0.059505901	0	
Scale (σ)	0.005038272	0.000872178	0.03437812	

Upper Triangular (Decomposition) Matrix (T)

	Intercept (μ)	Placebo	Scale (σ)	Scale (σ)
Scale (σ)	0.064109282	-0.063890905	0.005038272	
FC	0	0.059505901	0.000872178	
FCR	0	0	0.03437812	

Estimate Covariance Matrix (Σ=TT') - Validation step

	Intercept (μ)	Placebo	Scale (σ)	Scale (σ)
Intercept (μ)	0.004110000	-0.004096000	0.000323000	
FC	-0.004096000	0.007623000	-0.000270000	
Scale (σ)	0.000323000	-0.000270000	0.001208000	

Z-Matrix (Std Normal random generated number)

Intercept (μ)	0.869097248
FC	1.467720578
Scale (σ)	0.149192895

Parameter Estimates incorporating uncertainty (Mu + Tz)

Intercept (μ)	3.06865612
FC	-0.267075253
Scale (σ)	0.696891894

Weibull PFS PSA parameter estimates

5-FU + Cisplatin		Trastuzumab + 5-FU/ Cisplatin	
Deterministic Estimates		**Deterministic Estimates**	
Lambda (λ)	0.061428405	Lambda (λ)	0.036642015
Gamma (γ)	1.424785732	Gamma (γ)	1.424785732
PSA Estimates		**PSA Estimates**	
Lambda (λ)	0.082778703	Lambda (λ)	0.048737383
Gamma (γ)	1.289087468	Gamma (γ)	1.289087468

Model Parameters (Deterministic or PSA)			
plcw	0.061428405	**plnw**	0.036642015
pgcw	1.424785732	**pgnw**	1.424785732

Progression Free - Full Data

	Estimate	StdErr
Intercept (μ)	2.32074176	0.05472733
FC	-0.36263475	0.07669657
Scale (σ)	0.70185992	0.02911258

Estimated Covariance Matrix S

	Intercept (μ)	Placebo	Scale (σ)	Scale (σ)
Intercept (μ)	0.002995	-0.002967	-0.000153	
FC	-0.002967	0.005882	-0.000003628	
Scale (σ)	-0.000153	-0.000003628	0.000848	

Lower Triangular (Decomposition) Matrix (T)

	Intercept (μ)	Placebo	Scale (σ)	Scale (σ)
Intercept (μ)	0.054726593	0	0	
FC	-0.054214959	0.054247011	0	
Scale (σ)	-0.002795716	-0.002860943	0.028844392	

Upper Triangular (Decomposition) Matrix (T)

	Intercept (μ)	Placebo	Scale (σ)	Scale (σ)
Intercept (μ)	0.054726593	-0.054214959	-0.002795716	
FC	0	0.054247011	-0.002860943	
Scale (σ)	0	0	0.028844392	

Estimate Covariance Matrix (Σ=TT') - Validation step

	Intercept (μ)	Placebo	Scale (σ)	Scale (σ)
Intercept (μ)	0.002995000	-0.002967000	-0.000153000	
FC	-0.002967000	0.005882000	-0.000003628	
Scale (σ)	-0.000153000	-0.000003628	0.000848000	

Z-Matrix (Std Normal random generated number)

Intercept (μ)	0.42056574
FC	-0.469963276
Scale (σ)	2.555570367

Parameter Estimates incorporating uncertainty (Mu + Tz)

Intercept (μ)	2.34375789
FC	-0.410929807
Scale (σ)	0.775742551

Appendix E4: 2nd line Treatments ToGA

Table 21 Summary of Subsequent Chemotherapy (FAS)

Treatment	FP N = 290	FP+H N = 294
Cytotoxic therapy received by > 5% of patients		
Docetaxel	40 (14%)	38 (13%)
Paclitaxel	35 (12%)	38 (13%)
5-FU	52 (18%)	53 (18%)
Irinotecan	56 (19%)	47 (16%)
Cisplatin	21 (7%)	21 (7%)
Oxaliplatin	20 (7%)	14 (5%)
S-1	21 (7%)	22 (7%)
HER2 targeting therapy		
Lapatinib	3 (1%)	4 (1%)
Trastuzumab	2 (< 1%)	3 (1%)

Data source: page 811

Sourced from ToGA CSR p93

Appendix E5: Breast cancer patients elibible for trastuzumab

Figure 41: Mestastatic breast cancer patients elibible for trastuzumab

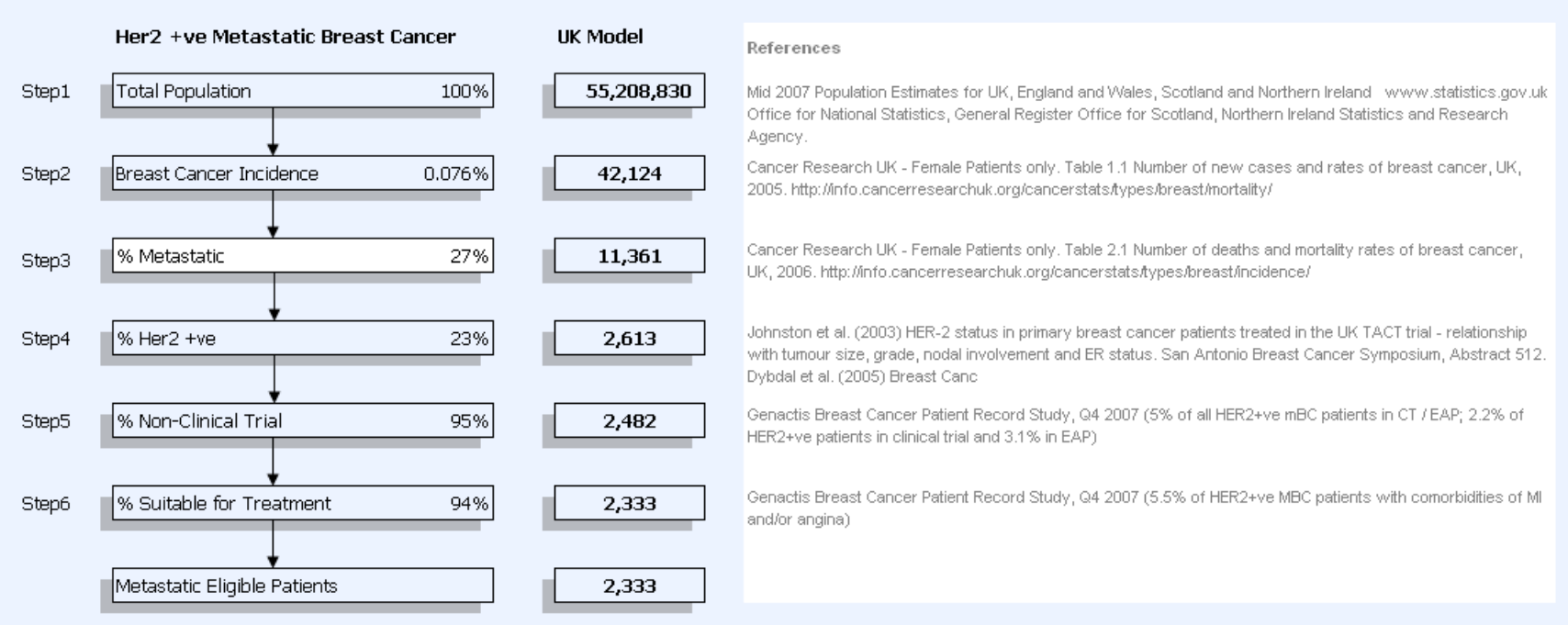
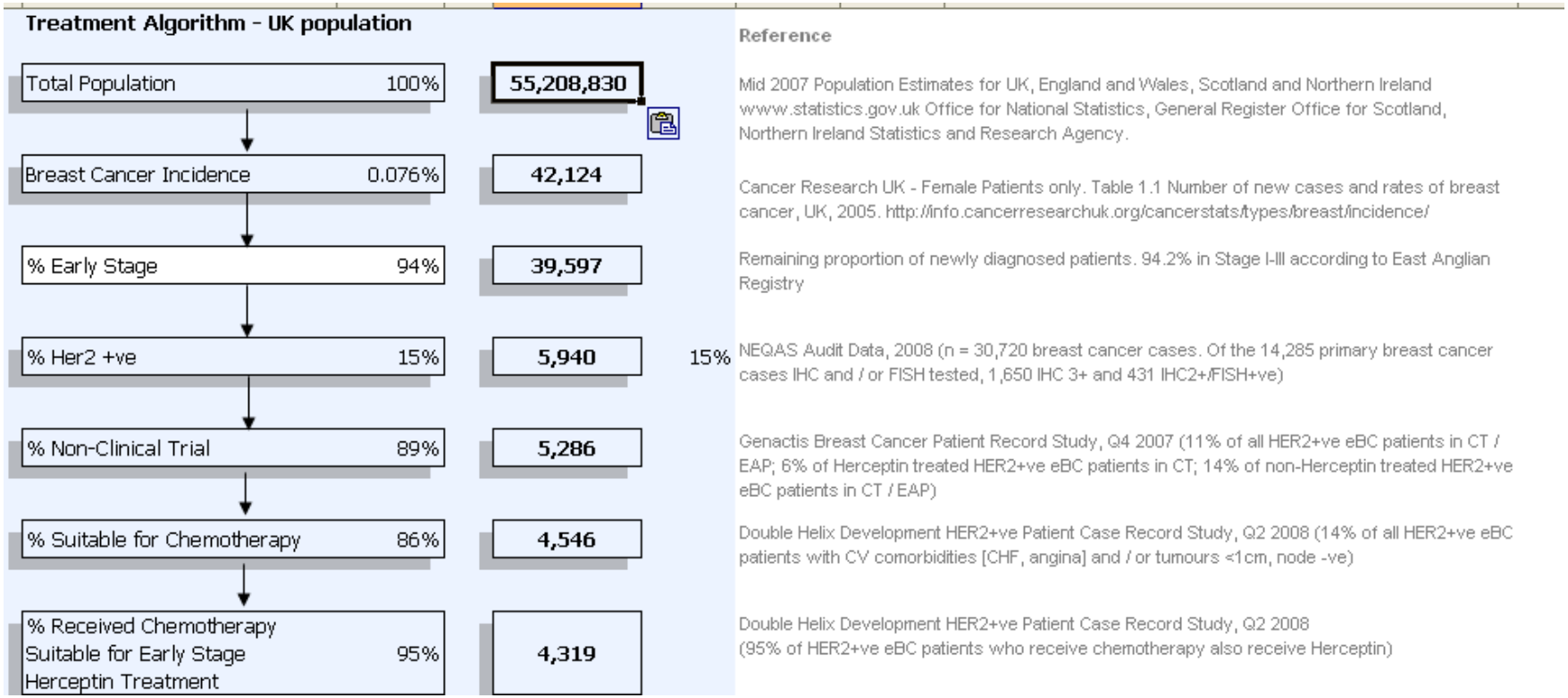


Figure 42: Early breast cancer elibible for trastuzumab



Appendix E6: Market Research

Chart Review (MAT September 2009)

The charts of patients with stage IV gastric data was sampled from 20 clinicians accorss 15 cancer networks. A further breakdown of the geographical spread of the sample is shown below:

	Total	**20**
		100%
Region	North East/ Yorkshire and Humber	3
		15%
	Northwest England	4
		20%
	Wales	4
		20%
	West Midlands	1
		5%
	South West England	1
		5%
	South East England	2
		10%
	London	1
		5%
	East Midlands	1
		5%
	East England	1
		5%
	Scotland	2
		10%

Roche commission perceptin based market research (June 2009)

50 oncologists were approached and asked if they treated gastric cancer. Those that confirmed that they did so were asked which chemotherapy regimens they used by self-completion using an on-line questionnaire. The number of clinicians answering the gastric questionnaire was 32. Of the 50 clinicians approached 28 were clinical oncologists, 22 medical oncologists, 40 were consultants and 10 specialist registrars.The results of this research are shown below:

Regimen	**Usage**
Capecitabine	5%
CX	5%
ECX	39%
EOX	20%
5FU	4%
CF	6%
ECF	20%
EOF	3%