# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Health Technology Appraisal

## Trastuzumab for the treatment of HER2-positive metastatic gastric cancer

## Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

**Definitions:**

**Consultees –** Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

**Clinical specialists and patient experts** – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

**Commentators –** Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

**Public –** Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

## Comments received from consultees

| Consultee | Comment | Response |
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| Roche Products | 1.1 Revised economic analysis of the licensed population<br>The ERG presented to the committee the results of a revised base-case model correcting for some minor calculation errors and inconsistencies identified during the critique of the Excel model provided by Roche. In addition the ERG presented an alternative base-case as part of scenario analyses to explore the potential impact of altering a range of separate assumptions simultaneously.<br>The alternative base-case resulted in an ICER of £66,982, whilst the ERG indicated they considered it to be only equally as plausible as the ICER submitted by Roche, the ACD states the committee considered "that the estimate was at least £67,000" (ACD, Section 4.21).<br>Roche does not agree £67,000 represents the lowest plausible estimate of the ICER:<br>1. In this scenario the OS and PFS HR for ECX vs CX is assumed to be 0.96 based on the PFS HR from Yun et al (OS not reported). Based upon the available trial evidence we agree with the ERG than Yun et al best represents the comparison of interest. However it is also reasonable to consider the possibility that the CX regimen in ToGA could be equivalent to the epirubicin containing regimens used in the UK due to the higher cisplatin dose intensity resulting in a reduced ICER. | Comment noted.<br>The Committee concluded, on the basis of the evidence and the views of clinical specialists, that epirubicin provided some additional benefit when added to a cisplatin and fluoropyrimidine combination (see FAD section 4.5).<br>It further concluded that the survival benefit of a triple regimen including epirubicin compared with that of a double regimen without epirubicin was unlikely to be represented by a hazard ratio of 0.77, and that the estimate would be closer to 0.96. However, this was associated with considerable uncertainty (see FAD section 4.8). |
| Roche Products | 1.1 Revised economic analysis of the licensed population<br>2. The ICER of £67,000 is calculated not only assuming that ECX offers superior efficacy to CX but also that EOX is superior to ECX (HR = 0.87 taken from the REAL2 study) thus assuming a 16% reduction in the risk of death compared with CX. We consider this a favourable assumption towards the comparator and thus £67,000 certainly does not represent a "lower bound" of a plausible range as suggested by the committee. | The Committee recognised that the revised analysis included a hazard ratio of EX vs ECX of 0.96 and a hazard ratio of 0.87 for ECX vs EOX (FAD section 3.36). However, the dominant comparator in the range of ICERs accepted by the Committee for the IHC3+ subgroup was ECX (see FAD section 4.21). |
| Roche Products | 1.1 Revised economic analysis of the licensed population<br>3. This scenario assumes that patients quality of life (QoL) decreases over time during PFS. This is inconsistent with the opinion of the clinical expert and the actual trial data which indicates the reverse and appears to have been supported by the committee due to a misunderstanding of the way utilities are applied in the economic model. | The Committee considered that continuing, improvement in quality of life during progression free survival above that of the general population was not plausible. However, it was persuaded that because of the disease symptoms associated with gastric cancer it was plausible that quality of life could increase during progression free survival (see FAD sections 4.10 and 4.16). |

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| Roche Products | 1.2 IHC3+ Subgroup Analysis<br>As shown in the original submission (p.69) the IHC3+ patients had a higher reported survival gain compared to the licensed population. As the committee currently consider the use of trastuzumab not o to be cost effective, it may be informative for the committee to consider the cost-effectiveness of this specific population prior to issuing final guidance.<br>Presented below are summary results and conclusions of the cost effectiveness analysis of trastuzumab in this subpopulation, a more detailed presentation is provided in the appendix.<br>As expected based on the pharmacology of the antibody and clinical experience in breast cancer, the IHC 3+ subgroup of gastric cancer represents a group of patients who derive even greater benefit from the addition of trastuzumab to standard chemotherapy than those with lower levels of over-expression. The benefits to the IHC3+ group are quite remarkable with the risk of death reduced by 49% (stratified HR 0.51; 95% CI 0.36, 0.72; p=0.0001). This improvement far eclipses any other development in the treatment of this condition since the move from best supportive care alone to the use of chemotherapy almost two decades ago (Wagner et al. 2006).<br>Applying the clinical results from the IHC3+ subgroup in ToGA to the revised economic model, which assumes a benefit for the triplet regimens typically used in the UK vs the comparator in ToGA (see appendix), resulted in an ICER of £42,969 and a mean increase in life of 7.4 months when replacing the most used regimen in the UK (ECX) with HCX. As discussed at length in section 2.1 we believe that it is equally plausible that there is no difference in efficacy between the high dose doublet regimen used in ToGA and the triplet regimens typically used in the UK. Hence we consider this ICER estimate not to be the lowest plausible as they assume an efficacy advantage for triple therapy compared to the double therapy TOGA regimens.<br>The areas of uncertainty that were highlighted in the ACD as sbeing of concern to the Committee were explored in sensitivity analysis. Due to the greater incremental benefit in the IHC3+ subgroup compared to the licensed population, the ICER was found to be less sensitive to changes in the key assumptions than for the licensed population. Out of the scenarios explored, the greatest increase in the ICER (to £49,655) came from applying the un-stratified analysis of survival. The lowest ICER (£41,696) was recorded when assuming a benefit for the ToGA CX vs ECX and EOX (HR= 1.1)<br>In conclusion, optimising guidance to the IHC3+ subgroup significantly reduces the | The Committee noted the efficacy in the trial was greater for the subgroup than for the whole population and discussed the biological plausibility of greater benefit in the IHC3 positive subgroup. It considered that greater effect may be experienced with higher levels of HER2. The Committee concluded that the IHC3 positive subgroup was an appropriate subgroup to consider in its decision making (see FAD section 4.9).<br><br>The Committee noted that the ICER calculated by the manufacturer for the IHC3 positive subgroup included an increase in utility during progression free survival which could rise above that of the general population. It considered that this was not plausible and therefore concluded that the estimate of the ICER provided by the manufacturer was probably an underestimate (see FAD section 4.20).<br><br>The Committee noted that the ERG's exploratory ICERs for both of the deterministic (stratified and unstratified) analyses and the probabilistic (stratified and unstratified) analyses were in the range of £43,200 per QALY gained to £52,000 per QALY gained. The Committee agreed that the most plausible estimate of cost effectiveness of trastuzumab plus cisplatin and capecitabine lay in a range of £45,000 to £50,000 per QALY gained (see FAD section 4.21). |

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| | ICER compared to the entire licensed population. In addition the ICER is less sensitive to changes to key assumptions. Therefore suggesting one can place greater certainty over the robustness of this estimate. | |
| Roche Products | 1.3 Probabilistic Sensitivity Analysis (PSA)<br>Section 4.9 of the ACD states the committee "further noted that probabilistic sensitivity analysis did not incorporate uncertainty in the clinical-effectiveness estimates, and that these appeared to be a key driver of cost effectiveness from the ERG's exploratory analysis. The Committee concluded that the manufacturer's base-case ICER was likely to be an underestimate."<br>As part of the amendments to the base-case analysis uncertainty around the clinical-effectiveness estimates calculated by the indirect treatment comparison have now been included in the models, with the results summarised below.<br>For the analysis of the licensed population the mean PSA ICER was approximately £5,000 (HCX vs EOX = £67,786) higher than the deterministic value (HCX vs EOX = £62,829) when assuming both a benefit for ECX vs ToGA CX and in addition EOX vs ECX. However when assuming that EOX is equally effective as ECX this difference between the determinist and PSA means reduced to within 4% of the deterministic value. When limiting the analysis to the IHC3+ population the PSA results were similar to those of the deterministic values (<3% difference) in results between the PSA mean values and the deterministic values (the mean results are present for the IHC3+ along with scatter plots for this analysis in appendix 2) | This has been amended in the FAD to reflect the analyses provided.<br>For the total population covered by the marketing authorisation, the Committee noted the results of probabilistic sensitivity analysis around the alternative base case and concluded that there was a large degree of uncertainty around the alternative base case ICER of £62,800 per QALY gained (see FAD section 4.18).<br>For the IHC3 positive subgroup, the Committee noted that the ERG's exploratory ICERs for both of the deterministic (stratified and unstratified) analyses and the probabilistic (stratified and unstratified) analyses were in the range of £43,200 per QALY gained to £52,000 per QALY gained. The Committee agreed that the most plausible estimate of cost effectiveness of trastuzumab plus cisplatin and capecitabine lay in a range of £45,000 to £50,000 per QALY gained (see FAD section 4.21). |
| Roche Products | 2.1 How does the control arm of ToGA compare in efficacy with the ECF/X regimen that forms the basis of clinical care in the UK?<br>It seems that a lack of clarity in Roche's original submission may have diverted the Appraisal Committee from the crucial question of "Is the CF/X regimen used as the control in ToGA as active as ECF/X?" towards the question "Can epirubicin contribute anything to cisplatin-based chemotherapy in gastric cancer?" which is the question asked by the meta-analysis by Wagner et al (2006). Consequently they have put considerable weight on the conclusion from the meta-analysis which showed a 23% overall survival benefit from the addition of epirubicin to cisplatin based chemotherapy regimens different from those used in ToGA (Wagner et al 2006) and much less on a newer study (Yun et al, 2010) designed to answer the specific question of what, if anything, epirubicin can add to a higher dose cisplatin-fluropyrimidine regimen such as that used in ToGA. This concluded that any survival benefit from such an addition was minimal.<br>Roche's contention has always been that although epirubicin may add to the | The Committee noted comments from consultees that the quality of the studies in the meta analysis was poor. The evidence from the largest study (Ross) was from an unplanned subgroup which provided a greater estimate of the effect of epirubicin than the full population. The Committee further noted comments from consultees that the low doses of cisplatin in the studies did not reflect the higher dose used in the ToGA trial. The Committee concluded that the survival benefit of a triple regimen including epirubicin compared with that of a double regimen without epirubicin was unlikely to be represented by a hazard ratio of 0.77, and that the estimate would be closer to 0.96. However, this was associated with considerable |

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| | efficacy of low intensity regimens of cisplatin (15-20 mg/m2/week cisplatin) and fluoropyrimidine such as those included in the Wagner meta-analysis (including ECF/X as used in the UK), it adds little or nothing to (except toxicity) to higher intensity regimens such as those used in the ToGA study (27 mg/m2/week cisplatin) which can therefore be deemed equivalent to the ECF/X standard of care in the UK.<br><br>Roche feels that this contention has been misunderstood by the AC who state in Section 3.16 of the ACD states that Roche "made an assumption of no difference in effectiveness from the addition of epiribicin to cisplatin and 5-fluorouracil based on studies by Tobe (hazard ratio for overall survival for epirubicin, cisplatin and 5-fluorouracil compared with cisplatin and 5-fluorouracil 0.57 , 95% CI 0.27-1.2) and the study by Kim (hazard ratio for overall survival for epirubicin, cisplatin and 5-fluorouracil compared with cisplatin and 5-fluorouracil 0.83 , 95% CI 0.42-1.2) (hazard ratio for overall survival 0.83, 95% CI 0.42-1.2)"<br><br>Whilst it is true that these small studies do not provide statistically robust evidence of benefit for the addition of epirubicin, and suffer from various deficiencies, the point estimates of Hazard Ratio (HR) do suggest a benefit from epirubicin in the context of these studies. However this is not the primary reason for assuming that CX and ECF/X can be considered comparable. The primary reason is that the cisplatin/fluoropyrimidine regimens in these studies is very different from that used in ToGA and by Yun et al (2010) who could see minimal if any benefit from adding epirubicin. The lower cisplatin dose in the studies meta-analysed by Wagner et al (15-20 mg/m2/week) relative to those used in ToGA (27 mg/m2/week) and by Yun et al (25 mg/m2/week) is critical in this regard and is not compensated for, as suggested in Section 4.5 of the ACD, by longer treatment durations in the UK. | uncertainty (see FAD section 4.8).<br><br>On the basis of their discussion of clinical effectiveness the Committee concluded that it was appropriate to consider the ICERs that had used a hazard ratio of 0.96 (see FAD section 4.13). |
| Roche Products | <u>Quality of data inputs</u><br>Any meta-analysis is only as good as the quality of data of the contributing studies and study quality is particularly important when the number of studies included is small (just three in this case) or when an individual study, by virtue of its size, has a disproportionate impact on the final result. In this case none of the three data sets comes from a Phase III study designed and powered to detect an impact of epirubicin on survival when added to cisplatin and 5-FU.<br><br>The study showing the biggest treatment effect for epirubicin (Tobe et al 1992, referred to as KRGCGC by Wagner et al) is very small with only 47 patients enrolled and with statistically significant differences in baseline characteristics between the two study arms. There is also unacceptable loss of patients between randomisation | The Committee noted comments from consultees that the quality of the studies in the meta analysis was poor. The evidence from the largest study (Ross) was from an unplanned subgroup which provided a greater estimate of the effect of epirubicin than the full population. The Committee further noted comments from consultees that the low doses of cisplatin in the studies did not reflect the higher dose used in the ToGA trial. The Committee concluded that the survival benefit of a triple regimen including epirubicin compared with that of a double regimen without epirubicin was |

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| | and analysis with only 72% evaluable.<br><br>Equally the data set which contributes 67% of patients and therefore has the greatest impact (82% weighting) on the result is also extremely problematic. It derives from a subset of patients with gastric or oesophago-gastric junction adenocarcinomas tumours taken from a larger study which also included patients with oesophageal tumours. This subgroup analysis was not pre-planned and carries the risks inherent in all subgroup analyses of losing the benefits of randomisation and the creation of treatment subgroups with inherently different baseline risks which can diminish or exaggerate treatment effects. This objection is not simply a theoretical one. The epirubicin treatment effect on OS reported by Wagner for the subpopulation of the Ross et al study included in the meta-analysis was far greater (hazard ratio 0.79, 95% CI 0.62-1.04) than that reported for the trial population as a whole (0.91, 95% CI 0.76-1.04). No plausible explanation has been given for this difference which would not appear to be due to any fundamental difference in responsiveness between gastric and oesophageal cancers. The group of investigators who carried out the ECF versus MCF study included in the meta-analysis by Wagner et al, have meta-analysed individual patient data from 1775 patients from this study along with 3 others and found no differences in responsiveness to chemotherapy, overall survival, or toxicity according to primary tumour origins and they conclude that future studies should include oesophageal as well as gastric tumours (Chau et al 2009). Had the whole population from the Ross study been included in the Wagner meta-analysis, one could be much more confident that any difference in outcomes between the study arms was due to a treatment effect, rather than an artefact of sub-group analysis, and the benefit from epirubicin in the meta-analysis as a whole would diminish considerably. It should be noted that even in its entirety, the study by Ross et al was not designed to test the value of adding epirubicin to a high dose cisplatin and 5-FU regimen<br><br>It is hard to assess the methodological quality of the third study included in the meta-analysis (Kim et al 1991), since, almost 10 years after being presented at a conference the results have not been published in a peer-reviewed journal. | unlikely to be represented by a hazard ratio of 0.77, and that the estimate would be closer to 0.96. However, this was associated with considerable uncertainty (see FAD section 4.8).<br><br>On the basis of their discussion of clinical effectiveness the Committee concluded that it was appropriate to consider the ICERs that had used a hazard ratio of 0.96 (see FAD section 4.13). |
| Roche Products | <u>Control regimens in included studies</u><br><br>To answer the question of whether epirubicin adds to the benefit achieved with cisplatin and 5-FU the correct approach is to take an adequate cisplatin 5-FU regimen and add epirubicin to it. In none of the three studies included in the Wagner meta-analysis is the cisplatin-5-FU regimen one that is routinely used by those | On the basis of their discussion of clinical effectiveness the Committee concluded that it was appropriate to consider the ICERs that had used a hazard ratio of 0.96 (see FAD sections 4.8 and 4.13). |

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| | clinicians and research groups that use a fluoropyrimidine and cisplatin as their treatment standard. In each case a less intensive two-drug regimen is used as the control. In effect the Wagner can be seen as asking "Does the addition of epirubicin compensate for the use of a suboptimal cisplatin/fluoropyrimidine regimen?" Notably, the meta-analysis was carried out before the publication of, and hence does not include, the one study (Yun 2010) that adds epirubicin to the sort of cisplatin/fluoropyrimidine regimen that is used by those whose standard treatment is dual therapy with fluoropyrimidine plus cisplatin. The impact of cisplatin dose is discussed in more detail below. | |
| Roche Products | <u>Plausibility of the conclusions from the Wagner meta-analysis</u><br>If the conclusion drawn by Wagner that the addition of epirubicin to any cisplatin and fluoropyrimidine therapy reduces the risk of death by 29%, the obvious conclusion is that survival in trial cohorts receiving cisplatin and a fluoropyrimidine alone should be inferior to those receiving three drugs. This is simply not reflected in recent trials, as shown in Figure 1.<br><br>Indeed what can be seen from Figure 1 is that there is a modest improvement in outcomes with both two drug and three drug regimens in the most recent trials, seemingly due to a move from 5-FU to capecitabine as the fluoropyrimidine element, otherwise survival has been remarkably similar with adequately dosed two drug regimens and ECF/X over the last decade, with only one regimen clearly offering advantages over both – the trastuzumab containing arm of ToGA. It should be noted that even control arm of the ToGA study also outperforms the EOX/F regimen which has limited use in the UK (despite oxaliplatin being unlicensed in gastric cancer) based on the study by Cunningham et al depicted in Figure 1 [Figure 1 not reproduced here but available as part of the full response from the manufacturer on the website]. | The Committee noted comments from consultees that the quality of the studies in the meta analysis was poor. The evidence from the largest study (Ross) was from an unplanned subgroup which provided a greater estimate of the effect of epirubicin than the full population. The Committee further noted comments from consultees that the low doses of cisplatin in the studies did not reflect the higher dose used in the ToGA trial. The Committee concluded that the survival benefit of a triple regimen including epirubicin compared with that of a double regimen without epirubicin was unlikely to be represented by a hazard ratio of 0.77, and that the estimate would be closer to 0.96. However, this was associated with considerable uncertainty (see FAD section 4.8). |
| Roche Products | <u>Impact of cisplatin and fluoropyrimidine dose on contribution of epirubicin to chemotherapy for gastric cancer</u><br>The ERG seem to have accepted that any impact of epirubicin added to higher cisplatin-dose doublets is very small, and identify the Yun et al study as the best source for estimating the survival benefit from epirubicin (see Section 3.28 of the ACD), presumably recognising that this study was designed to answer the relevant question which those studies included in Wagner's meta-analysis were not. This conclusion that epirubicin plus low dose cisplatin is equivalent to a higher dose of cisplatin is supported by the data in Figure 1, which shows the results achieved in the active and control arms of recent large randomised controlled trials in gastric | The Committee noted comments from consultees that the quality of the studies in the meta analysis was poor. The evidence from the largest study (Ross) was from an unplanned subgroup which provided a greater estimate of the effect of epirubicin than the full population. The Committee further noted comments from consultees that the low doses of cisplatin in the studies did not reflect the higher dose used in the ToGA trial. The Committee concluded that the survival benefit of a |

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| | cancer. In the studies by Kang et al, Ajani et al and Dank et al and the ToGA studies, the doses of cisplatin were 25-27 mg/m2/week. In each case, the results were as good or better than the 3 drug ECF regimen with its lower dose of cisplatin and, as has already been stated, the control arm of ToGA represents probably the best chemotherapy result ever obtained in this condition.<br>In the light of the above, the ERG's exploratory analysis using a 23% reduction in the risk of death accruing from the addition of epirubicin to cisplatin and a fluoropyrimidine as used in ToGA (see Section 3.34) is implausible. The most reasonable assumption is that that the advantage seen in moving from cisplatin plus a fluoropyrimidine to the same regimen plus trastuzumab in ToGA is the minimum that would be seen in moving from ECF/X as used in the UK to combination of trastuzumab, cisplatin and capecitabine/5-FU used in ToGA. | triple regimen including epirubicin compared with that of a double regimen without epirubicin was unlikely to be represented by a hazard ratio of 0.77, and that the estimate would be closer to 0.96. However, this was associated with considerable uncertainty (see FAD section 4.8).<br><br>On the basis of their discussion of clinical effectiveness the Committee concluded that it was appropriate to consider the ICERs that had used a hazard ratio of 0.96 (see FAD section 4.13). |
| Roche Products | <u>Does treatment duration in the UK compensate for lower cisplatin doses?</u><br>Section 4.5 of the ACD explains that the Appraisal Committee was not persuaded that the lower dose of cisplatin in ECF versus the ToGA regimens of CX and CF was important because "it heard from clinical specialists that people in the UK receive up to eight cycles of treatment, whereas only 6 cycles had been provided in the ToGA trial"<br>This thinking is flawed for two reasons:<br>Whatever the treatment intent, it is doubtful that many patients receive 8 cycles of ECF/X. In the large (n=1002) UK, investigator led randomised, controlled trial of ECF versus ECX versus EOX, versus EOF the mean number of treatment cycles ranged from 5.24-5.76 across the 4 treatment arms, despite a treatment target of 8 cycles for patients not experiencing disease progression or unacceptable toxicity. Treatment duration in the probably less fit patients treated outside of a clinical trial is likely to be even shorter<br>Even if treatment durations were longer and they did receive the same dose of cisplatin, this cannot be assumed to be equally as effective as the same dose delivered over a shorter period i.e. delivered at greater dose-intensity (dose per unit time). The concept of dose-intensity is recognised as being crucial to the effectiveness of cytotoxic chemotherapy. DeVita's "Cancer. Principles and Practice of Oncology" probably the best known text on its subject, states that "because anticancer drugs are associated with toxicity, it is often appealing for clinicians to avoid acute toxicity by simply reducing the dose or by increasing the time interval between each cycle of treatment. Such empiric modifications in dose represent a major reason for treatment failure in patients with drug sensitive tumours who are receiving chemotherapy in either the adjuvant or advanced disease settings". As | The Committee noted that the ToGA trial had used a higher dose of cisplatin than would be used as part of a triple regimen in UK clinical practice, and recognised the manufacturer's view that the addition of epirubicin to high-dose cisplatin would offer less benefit than to lower-dose cisplatin. It also noted comments from consultation that dose intensity was an important factor in chemotherapy and that reduced doses over a longer number of cycles could not be considered equivalent to higher doses over a shorter number of cycles. However the Committee was not persuaded that the outcomes for the chemotherapy comparator group in the ToGA trial were representative of the outcomes of triple regimens in the UK on the basis of clinical specialist testimony (see FAD section 4.6). |

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| | already explained, ToGA by virtue of using a dose of cisplatin higher than that used in the UK clinical practice and the studies used in the Wagner meta-analysis, also achieves a substantially higher dose-intensity which cannot be compensated by prolonged treatment at lower doses. | |
| Roche Products | 2.1 How does the control arm of ToGA compare in efficacy with the ECF/X regimen that forms the basis of clinical care in the UK?<br>Overall, and in the acknowledged absence of a head-to-head trial of ECF/X (as used in the UK) versus HCF/X in patients with HER2 positive gastric cancer, which does not exist and, even if started today, would take half a decade or more to report, the most plausible assumption must be that patients with HER2 positive gastric cancer would not fare any better on ECF/X than on the control regimen used in the ToGA study and, as such, the treatment benefit seen in the ToGA study would accrue to UK patients too. Indeed, in view of the survival duration seen in the control arm of ToGA relative to the survival achieved with ECF/X in phase III trials (see Figure 1) there is an argument that switching patients with HER2 positive gastric cancer from ECF/X to HCF/X as used in ToGA would result in a bigger survival gain than was seen in ToGA. Although this type of cross-trial comparison would normally be considered naïve, it is probably at least as credible as relying on the meta-analysis by Wagner, which for the reasons already discussed is not fit for this purpose, especially as the ERG concede that the preferred approach to indirect treatment comparison – a network meta-analysis – is not possible in this case because of adequate relevant studies (see Section 3.26 of the ACD) | The Committee was not persuaded that the outcomes for the chemotherapy comparator in the ToGA trial were representative of the outcomes of triple therapies in the UK (see FAD section 4.6).<br><br>The Committee noted comments from consultees that the quality of the studies in the meta analysis was poor. The evidence from the largest study (Ross) was from an unplanned subgroup which provided a greater estimate of the effect of epirubicin than the full population. The Committee further noted comments from consultees that the low doses of cisplatin in the studies did not reflect the higher dose used in the ToGA trial. The Committee concluded that the survival benefit of a triple regimen including epirubicin compared with that of a double regimen without epirubicin was unlikely to be represented by a hazard ratio of 0.77, and that the estimate would be closer to 0.96. However, this was associated with considerable uncertainty (see FAD section 4.8).<br><br>On the basis of their discussion of clinical effectiveness the Committee concluded that it was appropriate to consider the ICERs that had used a hazard ratio of 0.96 (see FAD section 4.13). |
| Roche Products | 2.2 Quality of Life<br>It is well established that effective systemic drug therapy can improve both survival and QoL providing the two motivations for using such treatment a fact verified by the clinical expert present at the Appraisal Meeting. Therefore correct interpretation of the data in this area is paramount and seems to be somewhat flawed in this case. A comparable improvement in quality of life (QoL) in both arms of ToGA, as | The Committee considered that continuing, improvement in quality of life during progression free survival above that of the general population was not plausible. However, it was persuaded that because of the disease symptoms associated with gastric cancer it was plausible that quality of life could increase during progression free survival (see |

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| | measured by the EORTC-QLQ-C30 and QLQ-ST022 instruments, was recorded (Satoh 2010). In addition the patients compliance was high (around 90% in both arms) (Satoh 2010). However section 4.6 states that the progressive rise in QoL with time beyond the trial period [presumably chemotherapy administration period] is implausible and that the appearance was likely to be explained by "survivor bias (that is, including only data for people who had survived and not taking into account the people who had not survived)".<br>For patients who are progression-free a steady rise in QoL with time is not only plausible but seems likely. Indeed Section 4.6 states the committee "considered that the reduced symptoms outweighed the side effects of chemotherapy" suggesting there is agreement that for the period patients are treated the average QoL of patients would be expected to increase. However, the side-effects of platinum-based chemotherapy are significant and act as a counterweight to the upward pressure on QoL. Once the 6 cycles of chemotherapy are finished (and in patients still progression-free) chemotherapy-related toxicity will resolve resulting in a steady upward trend in quality of life, reinforced by a generalised steady increase in physical wellbeing (strongly associated with sustained ability to obtain adequate nutrition and a reduction in other symptoms) mental adjustment to diagnosis and an appreciation that treatment is achieving something.<br>It is also true that because the addition of trastuzumab to chemotherapy keeps more patients free of progression for longer i.e. in a state associated with a higher QoL, the addition of trastuzumab can be expected to increase the average QoL/utility of a group of patients compared with a similar group receiving chemotherapy alone. This is not to say that for patients who have progressed QoL does not decline; Roche agree this would be an unreasonable assumption, and was not what was being suggesting. | FAD sections 4.10 and 4.16). |
| Roche Products | <u>2.3 PFS Utility</u><br>It is noted in section 4.15 of the ACD that "the Committee concluded that a rise in utility for people in progression-free survival had not been robustly demonstrated and a more likely estimate was that utility would decrease, as modelled by the ERG."<br>The rationale provided for this conclusion by the Committee is that "It was aware that this assumption was based on data only for people in the clinical trial surviving without progression and was not adjusted for those who had died or had otherwise left the trial during treatment. It therefore considered that assuming a rise in utility was not plausible."<br>The ERG originally raised the assumed PFS utility values as an issue for discussion | The Committee considered that continuing, improvement in quality of life during progression free survival above that of the general population was not plausible. However, it was persuaded that because of the disease symptoms associated with gastric cancer it was plausible that quality of life could increase during progression free survival (see FAD sections 4.10 and 4.16). |

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| | as they questioned the plausibility of QoL increasing whilst patients were on cytotoxic treatment not that they considered that the model didn't account for the decrement in utility due to patients progressing or dying. However as discussed under the Quality of Life subheading (above) the QoL of patients remaining in PFS is expect to increase over time, as supported by the clinical expert at the Committee meeting and indeed the committee appear to have accepted this in part (that QoL increases during treatment). It should be noted that it has long been accepted that QoL is increased by chemotherapy for advanced gastric cancer providing one of the main reasons for giving the treatment and the trial results confirm this as verified by the clinical expert at the Appraisal Committee Meeting<br><br>It appears though that the Committee has misunderstood how utility values are applied in the economic model. The model is split in to three health states: progression free survival (PFS), progressive disease (PD) and death. All patients start in PFS and the number of patients in PFS declines (and therefore the number of patients filling in the questionnaires reduce) as patients progress or die. It is correct that the PFS utility values used in the model were elicited only from patients that were surviving without progression, however this is entirely appropriate as these values are applied in the model only to the patients that are surviving without progression. In the model once a patient progresses a lower utility value is assigned to them and a utility of zero is assigned to patients that die. In fact in Roche's original base case model the average utility for patients remaining alive does decrease over time due to patients progressing.<br><br>It is worth noting that even if the increase in QoL were due to purely survivor bias, where patients that have a higher QoL are less likely to progress or die and thus the ones left in PFS have a higher QoL, it would still be appropriate to apply a higher average utility to the patients that remaining in PFS as this is merely reflecting the average utility for this specific subgroup. | |
| Roche Products | 2.4 Cardiac Monitoring<br><br>We accept that cardiac monitoring may occur less frequently in clinical practice than recommended in by the SPC for epirubicin and that indeed the ERG change to the base case may therefore better reflect the true ICER . However we don't consider it underestimates the ICER as suggested in the ACD (section 4.13) as there is likely to be variation in the cardiac monitoring frequency for both product in clinical practice. However even when one assumes only a base line test for epirubicin rather than the 3 monthly monitoring used in the ERG's alternative base-case the ICER increases by less than £250 (<1% of the base case ICER) | The Committee concluded that assuming equal monitoring may still slightly overestimate the cost of the comparator strategies. However, it noted that the ICER was not very sensitive to this parameter. It therefore agreed to consider the ICERs that assumed equal frequency of cardiac monitoring for trastuzumab and epirubicin (see FAD section 4.14). |
| Roche Products | 2.5 Degree of Health Gain | This paragraph has been removed from the FAD. |

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| | Section 4.8 of the ACD is somewhat confusing and appears to deal with two issues: degree of innovation and extent of clinical benefit. It seems to suggest that because trastuzumab has been used in HER2 positive breast cancer for 8 years it cannot be considered innovative whilst the degree of benefit offered is small – "there were no additional potential significant health-related benefits to take into consideration". Both of these seem to be rather perverse interpretations of the evidence.<br>It is true that trastuzumab has, over the last 8 years, transformed the lives of the 20% or so of women with breast cancer whose tumours overexpress HER2 and, as such, HER2 directed therapy is not in itself innovative. But to suggest that evidence of similar benefit to patients with gastric cancer resulting in the availability of the first targeted agent for gastric cancerthis terminal disease and the first significant addition to cisplatin and fluoropyrimidine-based chemotherapy in two decades does not represent therapeutic innovation is wrong.<br>Furthermore not only is it a therapeutic innovation in this area, it is also one that has the potential to deliver substantial health-related benefits. Whether NICE ultimately considers that trastuzumab represents a cost-effective treatment from an NHS perspective, it is disingenuous to suggest that an intervention that produces an increase in median survival from 11.8 to 16 months i.e. an increase of 4.2 months or 35.6% (EMA licensed population), while not adding additional toxicity and without deteriorating patients quality of life as compared to chemotherapy alone, does not deliver very substantial health-related benefit. | The Committee was aware that there are currently no treatment options for metastatic gastric cancer which target HER2 overexpression, and that trastuzumab offers a new option for the licensed patient group (see FAD section 4.2 ).<br>The Committee concluded that the results of the ToGA trial demonstrated that trastuzumab plus cisplatin and capecitabine or 5-fluorouracil offers clinical benefit above cisplatin and capecitabine or 5-fluorouracil alone (see FAD section 4.4).<br>The Committee noted that the median overall survival gain for the licensed population from the ToGA trial was 4.2 months for trastuzumab plus cisplatin and capecitabine or 5-fluorouracil compared with cisplatin and capecitabine or 5-fluorouracil alone. It further noted that the median overall survival gain for the subgroup of people whose tumours were IHC3 positive in the ToGA trial was 5.6 months for trastuzumab plus cisplatin and capecitabine or 5-fluorouracil compared with cisplatin and capecitabine or 5-fluorouracil alone (see FAD section 4.24). |
| Roche Products | 2.6 Interpretation of the End of Life Criteria<br>There is no clear definition of "small patient population" in the current NICE guidance on EoL considerations, but earlier documents suggested an approximate cut-off of 7,000 p.a. On this basis Roche's estimate of patient numbers is a very close approximation to what some of those involved in formulating the EoL criteria considered "a small population". Given the uncertainty around such estimates, Roche's estimate of patient numbers is probably not significantly different from 7,000 .<br>However, it is now proposed that NICE considers providing positive guidance for the IHC 3+ patients to be treated with trastuzumab under the NHS in order to improve the cost effectiveness – these represent 62% of the licensed population and so reduce eligible gastric cancer patient numbers from the 492 estimated in the original Roche submission to 311 and the total number of patients eligible to receive | The advice on appraising treatments that extend life at the end of life indicates that the Committee must consider the cumulative population (that is, the entire population for which a technology is indicated). The Committee considered that 7000 was at the upper end of the population size for which it understood the supplementary advice to apply. However, the Committee concluded overall that applying the supplementary advice on end-of-life was appropriate. (see FAD section 4.25). |

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| | trastuzumab each year in England and Wales to 6,963 – below the 7,000 patients originally considered to represent the upper limit of a "small" population.<br>In addition Roche's original calculation of gastric cancer incidence was based on 2006 registry figures. It is well established that the incidence of gastric cancer has fallen dramatically and steadily over the last 30 years by about 0.5 cases/100,000 population pa. Therefore, any estimate of current incidence based on 2006 figures will almost certainly represent an overestimate. | |
| Roche Products | 2.6 Interpretation of the End of Life Criteria<br>The EoL supplementary advice states (section 3.3): "Second and subsequent licences for the same product will be considered on their individual merits". Regardless of the total number of patients eligible for treatment with trastuzumab within its licensed indications, it is clear that the HER2 overexpressing gastric cancer population is very small at around 492 (entire licensed population) or 311 (IHC 3+ group). As such, trastuzumab in gastric cancer would easily qualify for EoL considerations were it not for the fact that trastuzumab was first developed for the more common condition of breast cancer. It seems perverse that gastric cancer patients should not benefit from a treatment that offers them great benefit simply because it was approved in this condition after rather than before approval for breast cancer. | The advice on appraising treatments that extend life at the end of life indicates that the Committee must consider the cumulative population (that is, the entire population for which a technology is indicated). The Committee considered that 7000 was at the upper end of the population size for which it understood the supplementary advice to apply. However, the Committee concluded overall that applying the supplementary advice on end-of-life was appropriate. (see FAD section 4.25). |
| Roche Products | 2.6 Interpretation of the End of Life Criteria<br>Equally, if one of the purposes behind the EoL considerations is to provide an incentive for the pharmaceutical industry to develop treatments in rarer cancers, the approach of denying this incentive when a drug already has a Marketing Authorisation in a more common condition will largely negate it. | The advice on appraising treatments that extend life at the end of life indicates that the Committee must consider the cumulative population (that is, the entire population for which a technology is indicated). The Committee considered that 7000 was at the upper end of the population size for which it understood the supplementary advice to apply. However, the Committee concluded overall that applying the supplementary advice on end-of-life was appropriate. (see FAD section 4.25). |
| Roche Products | 2.6 Interpretation of the End of Life Criteria<br>Beyond these points Roche consider that the original premise behind the End of Life criteria (as the name implies) was to reflect the increased value attached to life extension when one has a short life expectancy. This was necessary as the relationship between proximity to death and the value placed on the extension of life is not adequately captured by NICE's reference case and is a well established concept in the available health economic literature. | Comment noted. The Committee concluded overall that it was appropriate to apply the supplementary advice on end of life (see FAD section 4.25). |

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| Roche Products | 2.6 Interpretation of the End of Life Criteria<br>We therefore do not consider the size of the population of relevance to calculating the cost effectiveness of medicines as the cost benefit ratio is not effected by the number of patients receiving or eligible for the medicine unless one considers the extension of life more valuable in patients with a rare disease than those with a common one . | The advice on appraising treatments that extend life at the end of life indicates that the Committee must consider the cumulative population (that is, the entire population for which a technology is indicated). The Committee considered that 7000 was at the upper end of the population size for which it understood the supplementary advice to apply. However, the Committee concluded overall that applying the supplementary advice on end-of-life was appropriate. (see FAD section 4.25). |
| Roche Products | 3 Are there any equality related issues that need special consideration that are not covered in the ACD?<br>The incidence and mortality from gastric cancer are strongly related to social class and measures of deprivation, with higher rates in socially and economically deprived groups (Quinn M, W.H., Cooper N, Rowan S, Cancer Atlas of the United Kingdom and Ireland 1991-2000. 2005, National Statistics).<br>Whilst this point was raised by the clinical expert in the meeting it appears to have been omitted from the ACD.<br>In addition trastuzumab produces a similar health gain in mGC which is a predominantly male disease, but has been given provisional negative guidance, whilst it has been funded in a predominantly female disease – mBC. | See table summarising the Committee's considerations:<br>The Committee heard that incidence of gastric cancer arises in certain social classes but did not consider that the recommendations would lead to differential access to the technology according to social class. |
| Royal College of Nursing | *Has the relevant evidence has been taken into account?*<br>We would ask that the evidence should include all relevant current evidence. | Comment noted. The Committee has considered all the evidence submitted by consultees for this appraisal. |
| Royal College of Nursing | *Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence, and are the preliminary views on the resource impact and implications for the NHS appropriate?*<br>The summaries of the clinical and cost effectiveness of this appraisal should be aligned to the clinical pathway followed by these patients. The preliminary views on resource impact and implications should be in line with established standard clinical practice. | Comment noted. The Committee considered the evidence available in the context of current care (see FAD section 4.2). Clinical specialists attended the Committee meeting to advise on aspects of clinical practice. |
| Royal College of Nursing | *Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS?*<br>Nurses working in this area of health have reviewed the recommendations of the | Comment noted. No actions required. |

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| | Appraisal Committee and do not have any further comments to make at this stage. | |
| Royal College of Nursing | *Are there any equality related issues that need special consideration that are not covered in the ACD?*<br><br>None that we are aware of at this stage. We would however, ask that any guidance issued should show that equality issues have been considered and that the guidance demonstrates an understanding of issues concerning patients' age, faith, race, gender, disability, cultural and sexuality where appropriate. | Comment noted. The Committee considered equality and diversity issues. The Committee heard that incidence of gastric cancer arises in certain social classes but did not consider that the recommendations would lead to differential access to the technology according to social class. |
| Cancer Research UK | At Cancer Research UK we are very disappointed that trastuzumab will not be available to patients with metastatic gastric cancer in England and Wales. This treatment offers a significant and meaningful improvement for patients and is a real step forward in the systemic treatment of stomach cancer.<br>Results from the ToGA study, included in NICE's deliberations, clearly demonstrated a clinically significant survival advantage for the addition of trastuzumab to chemotherapy in HER2 positive gastric cancer. Trastuzumab is now globally accepted as standard care for this disease.<br><br>Every year around 7,900 people are diagnosed with stomach cancer in the UK. Stomach cancer has an incidence rate of 8.9 per 100,000 and a mortality rate of 5.5 per 100,000 population in the UK. Currently prognosis is poor.<br><br>Trastuzumab is indicated for use in patients with metastatic gastric cancer who have not previously received treatment for metastatic disease and whose tumours have HER-2 overexpression. It is administered intravenously three weekly until disease progression providing it is well tolerated. It is the first biological drug for use in gastric cancer. | The Committee considered that the most plausible estimate of the ICER for the total population covered by the marketing authorisation (between £63,100 per QALY gained and £71,500 per QALY gained) exceeds what can be considered a reasonable use of NHS resources even with the application of the supplementary advice on appraising treatments that extend life at the end of life (see FAD section 4.26).<br>The Committee considered the ICERs for a subgroup proposed by the manufacturer of patients whose disease was IHC3 positive. It agreed that the most plausible estimate lay within a range of between £45,000 and £50,000 per QALY gained. The Committee considered this estimate within the context of the supplementary advice on appraising treatments that extend life at the end of life. It considered that the magnitude of weight required for the ICER to be within a range normally considered cost-effective within the NHS was acceptable. The Committee therefore concluded that trastuzumab plus cisplatin and capecitabine or 5-fluorouracil is recommended as an option for the treatment of people with HER 2-positive, metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior treatment for their metastatic disease and whose tumours express high levels of HER-2 as defined by a positive immunohistochemistry score of 3 (see |

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| | | FAD section 4.27). |
| Cancer Research UK | Firstly, NICE has accepted the efficacy of the treatment. The quality of the evidence submitted was accepted by the committee. This showed that trastuzumab in addition to chemotherapy offered a 4.2 month improvement in survival (16 months in trastuzumab plus chemotherapy compared to 11.8 months in chemotherapy alone group). Trastuzumab also improved secondary outcome measures. Progression-free survival increased from 5.2 months to 6.7 months and overall response rate increased from 34.5% to 47%. These are both clinically and statistically significant. | The Committee have made a positive recommendation for a subgroup of the full population (see FAD section 4.27). |
| Cancer Research UK | Secondly we do not believe that Epirubicin can be used as an alternative to trastuzumab. Epirubicin is greatly more toxic than the antibody, especially in terms of mucositis and myelosuppression. Even if the trial results had not shown additional benefit from trastuzumab treatment the antibody would still be greatly preferable. | Comment noted. The comparators in an appraisal are the treatments that will be displaced by the introduction of the technology being appraised. The Committee heard from clinical specialists, that current care for patients with gastric cancer was triple therapy with epirubicin, cisplatin or oxaliplatin and capecitabine or 5-FU (See FAD section 4.2). |
| Cancer Research UK | Finally we believe it is inappropriate of NICE not to apply the end of life criteria to this treatment. The small number of patients with gastric cancer brings this clearly inside the limit for the end of life criteria. The short life expectancy of these patients coupled with the extension of life offered by trastuzumab over other treatments should make this drug a good candidate for inclusion. | The advice on appraising treatments that extend life at the end of life indicates that the Committee must consider the cumulative population (that is, the entire population for which a technology is indicated). The Committee considered that 7000 was at the upper end of the population size for which it understood the supplementary advice to apply. However, the Committee concluded overall that applying the supplementary advice on end-of-life was appropriate. (see FAD section 4.25). |
| Cancer Research UK | We are deeply disappointed with this decision in the face of the first real step forward in the systemic treatment of stomach cancer for more than a decade. We hope that NICE will now work with the manufacturer to reach an agreement that will make this drug available to patients on the NHS, so that the UK isn't left behind while the rest of the world benefits from this advance in treatment for gastric cancer. | The Committee considered all the clinical and cost effectiveness evidence submitted and discussed the application of the supplementary advice on appraising treatments that extend life at the end of life. The Committee concluded that it was appropriate to recommend the use of trastuzumab for a subgroup of the population, those with IHC 3+ disease (see FAD section 4.27). |
| Royal College of Physicians | <u>Clinical Effectiveness – The significance of trastuzumab to this patient population</u><br><br>The ToGA study represents a truly significant advance in the management of this | The Committee was aware that there are currently no treatment options for metastatic gastric cancer which target HER2 overexpression, and that |

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| | patient group. The survival benefit in the licensed patient population was greater than 4 months, for a disease with a median survival of less than 12 months, and with a Hazard Ratio of 0.65. This is the largest survival benefit recorded in a high quality randomized clinical trial for any single agent or combination in advanced gastric cancer and represents a major advance in this disease. Oesophagogastric cancer is considered among the tumour types with the highest level of medical need. The survival outcomes in this disease are amongst the poorest of all the common cancers with little progress made over recent decades (figure 1). Modern cytotoxic agents have failed to result in significant gains and overall survival in this disease setting has stagnated at 9-11 months over the previous 15 years (figure 2). As such, it is vital that where there are clear opportunities for progress, as is the case for trastuzumab, that investment in to improving patient outcomes is made. | trastuzumab offers a new option for the licensed patient group (see FAD section 4.2 ).<br>The Committee concluded that the results from the ToGA trial demonstrated that trastuzumab plus cisplatin and capecitabine or 5-fluorouracil offers clinical benefit above cisplatin and capecitabine or 5-fluorouracil alone (see FAD section 4.4).<br>The Committee noted that the median overall survival gain for the licensed population from the ToGA trial was 4.2 months for trastuzumab plus cisplatin and capecitabine or 5-fluorouracil compared with cisplatin and capecitabine or 5-fluorouracil alone. It further noted that the median overall survival gain for the subgroup of people whose tumours were IHC3 positive in the ToGA trial was 5.6 months for trastuzumab plus cisplatin and capecitabine or 5-fluorouracil compared with cisplatin and capecitabine or 5-fluorouracil alone (see FAD section 4.24). |
| Royal College of Physicians | <u>Cost Effectiveness – The evaluation of ECX/EOX as a comparator</u><br><br>The use of a triplet chemotherapy regimen comprising epirubicin, platinum and capecitabine (ECX/EOX) has evolved in the UK over two decades of sequential randomized controlled clinical trials. ECF was initially developed as a triplet regimen based on evidence of single agent activity for each individual agent, and in comparison with the previous triplet regimen in use, rather than as a step-wise addition of epirubicin to existing doublet regimens. The specific benefit of epirubicin to the CX/OX doublet has never been robustly studied and hence can not be reliably estimated. In the cost-effectiveness model the benefit of epirubicin has been overstated with a Hazard Ratio as significant as 0.77 based on the Wagner meta-analysis1. As indicated at the initial appraisal meeting this meta-analysis was felt to significantly over state the benefit of epirubicin and its use in cost effectiveness model is inappropriate. A Hazard Ratio of 0.77 is far in excess of the observed benefit demonstrated in successive randomized clinical trials for any single chemotherapy intervention in this disease. The value of the meta-analysis is further debated given that the included studies used regimens with lower doses and lower dose-intensity of cisplatin &/or fluoropyrimidine than used in the ToGA comparator regimens. In addition, none of the studies utilised capecitabine containing regimens | The Committee noted comments from consultees that the quality of the studies in the meta analysis was poor. The evidence from the largest study (Ross) was from an unplanned subgroup which provided a greater estimate of the effect of epirubicin than the full population. The Committee further noted comments from consultees that the low doses of cisplatin in the studies did not reflect the higher dose used in the ToGA trial. The Committee concluded that the survival benefit of a triple regimen including epirubicin compared with that of a double regimen without epirubicin was unlikely to be represented by a hazard ratio of 0.77, and that the estimate would be closer to 0.96. However, this was associated with considerable uncertainty (see FAD section 4.8).<br><br>On the basis of their discussion of clinical |

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| | which may influence the relative benefit of epirubicin. Epirubicin is considered to provide some additional benefit to CF/CX and in the absence of any more active alternative therapies epirubicin containing triplet regimens should remain the standard of care in HER2 negative gastric cancer. However for HER2 positive gastric cancer the addition of trastuzumab to a CF/CX backbone has demonstrated a clear survival benefit with a favourable toxicity profile and should be the standard of care in this disease setting. | effectiveness the Committee concluded that it was appropriate to consider the ICERs that had used a hazard ratio of 0.96 (see FAD section 4.13). |
| Royal College of Physicians | End-of-life Criteria – Rational for inclusion of the breast cancer population<br><br>This submission fails to meet the end–of–life criteria solely because trastuzumab is already licensed for breast cancer. Herceptin is licensed for both early and advanced breast cancer, and the median survival of patients with early breast cancer treated with adjuvant herceptin is of the order of several years. It is surprising and inappropriate that this patient group should influence the end–of–life treatment decisions of patients with gastric cancer, a clearly distinct patient population. The end-of-life rules as applied have the consequence of disadvantaging patients with rarer tumours, often with more limited therapeutic options and poorer overall survival, as is the case in gastric cancer. In addition, we believe that, the application of end-of-life criteria in this way results in the nonsensical position where if trastuzumab had been licensed in gastric cancer prior to breast cancer the outcome of a NICE appraisal would likely be more favourable. During the committee meeting it was implied that this situation was acceptable and that the manufacturer would be expected to in some way support the adoption in rarer indications. We are uncertain as to how NICE envisage this being facilitated and further consideration and clarification with regard to the application of the end-of-life criteria appears necessary. The number of patients the current appraisal will apply to is small and comfortably within the end-of-life criteria thresholds. Additionally, the availability of generic formulations of trastuzumab in the medium term will reduce the cost of this therapy and as such the overall impact on NHS budgets will be modest. | The advice on appraising treatments that extend life at the end of life indicates that the Committee must consider the cumulative population (that is, the entire population for which a technology is indicated). The Committee considered that 7000 was at the upper end of the population size for which it understood the supplementary advice to apply. However, the Committee concluded overall that applying the supplementary advice on end-of-life was appropriate. (see FAD section 4.25). |
| Royal College of Physicians | Impact on UK Research Practice<br><br>Through undertaking pivotal studies such as OEO22, MAGIC3 and REAL-II4, the UK has played a central role in shaping international standards of care in oesophagogastric cancer. Trastuzumab represents a further significant advance in the treatment of gastric cancer and is a globally accepted standard of care in the management of HER2 positive disease. As such, we believe that, the rejection of funding for trastuzumab across England and Wales amounts to a retrograde step for gastric cancer care in the UK. Furthermore, ongoing academic and commercial | The Committee considered that the most plausible estimate of the ICER for the total population covered by the marketing authorisation (between £63,100 per QALY gained and £71,500 per QALY gained) exceeds what can be considered a reasonable use of NHS resources even with the application of the supplementary advice on appraising treatments that extend life at the end of life (see FAD section 4.26). |

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| | clinical research would be hindered without access to the accepted standard of care in this patient group. Current research practice is focused on identifying patient/tumour characteristics associated with response &/or resistance to targeted therapies, with the aim of improving the cost/benefit ratio of treatment. The strategy of defining a response enhanced biological sub-group is at the core of all NCRI research strategy and indeed Pharma research strategy going forward. A NICE position not supporting this approach may be difficult to maintain in the long term.<br><br>To summarise the outcome of the first Appraisal Committee meeting. The Appraisal Committee felt that the use of trastuzumab in combination with cisplatin and fluoropyrimidine chemotherapy was likely to offer a survival benefit over the current UK standard of care in HER2 over-expressing gastric cancer. It was noted that the survival gain was likely to be achieved without compromising quality of life. In addition, no resource or infrastructure related barriers to the adoption of HER2 testing or the introduction of trastuzumab therapy were identified. Trastuzumab was not recommended based on the committee's conclusion that the estimated cost to the NHS exceeded what could be considered a reasonable use of NHS resources. In view of the concerns highlighted above it is felt that further evaluation of trastuzumab is required in this indication where the benefits have been clearly defined. | The Committee considered the ICERs for a subgroup proposed by the manufacturer of patients whose disease was IHC3 positive. It agreed that the most plausible estimate lay within a range of between £45,000 and £50,000 per QALY gained. The Committee considered this estimate within the context of the supplementary advice on appraising treatments that extend life at the end of life. It considered that the magnitude of weight required for the ICER to be within a range normally considered cost-effective within the NHS was acceptable. The Committee therefore concluded that trastuzumab plus cisplatin and capecitabine or 5-fluorouracil is recommended as an option for the treatment of people with HER 2-positive, metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior treatment for their metastatic disease and whose tumours express high levels of HER-2 as defined by a positive immunohistochemistry score of 3 (see FAD section 4.27). |
| Welsh Assembly Government | Ever since chemotherapy has been shown to offer advantages to patients with advanced oesophago-gastric cancer, in terms of overall survival and quality of life, the subsequent improvements in treatment regimen, can at best be described as modest.<br>In recent years there has been a move towards personalised oncology where treatments are not based on population risks and crude parameters such as stage and organ based tumour origin, but on individual molecular characteristics that predict for response to targeted treatments in that individual.<br>In patients with breast cancer, probably the most exciting development in the last 10 years has been the benefit of trastuzumab in those patients that over express the epidermal growth factor receptor (Her-2). Initially this led to an improvement in median survival of patients with advanced disease, when combined with non-anthracycline based chemotherapy, by approximately 5 months. These results were considered so persuasive that the then Health Minister Patricia Hewitt decided ahead of NICE to make this treatment to patients with breast cancer. The | The Committee was aware that there are currently no treatment options for metastatic gastric cancer which target HER2 overexpression, and that trastuzumab offers a new option for the licensed patient group (see FAD section 4.2 ).<br>The Committee concluded that the results from the ToGA trial demonstrated that trastuzumab plus cisplatin and capecitabine or 5-fluorouracil offers clinical benefit above cisplatin and capecitabine or 5-fluorouracil alone (see FAD section 4.4).<br>The Committee noted that the median overall survival gain for the licensed population from the ToGA trial was 4.2 months for trastuzumab plus cisplatin and capecitabine or 5-fluorouracil compared with cisplatin and capecitabine or 5- |

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| | subsequent benefits for appropriate patients receiving this treatment after surgery were quite remarkable with a reduction in rates of recurrence of disease of approximately 50%.<br>It was of little surprise therefore that when it is known that Her-2 is over expressed in gastric cancer at similar rates to that seen in breast cancer (~20%), that a trial was designed to assess it's benefit in this setting. The standard of care worldwide was based on cisplatin and fluoropyrimidine chemotherapy. In the UK, the addition of anthracyclines has become standard, although no trial has specifically shown the benefit of this triplet over doublet therapy. Based on previous experience on breast cancer it was certainly felt unacceptably hazardous from a cardiotoxic point of view to combine trastuzumab with an anthracycline. This trial showed that median survival was prolonged by approximately 5 months in Her-2 positive patients (as has been defined for use in breast cancer and in the patient population which would be considered for treatment under it's current license). Of note also was that the comparator arm in this trial appeared to perform as well as any previous combination therapy seen in contemporary published world wide trials. | fluorouracil alone. It further noted that the median overall survival gain for the subgroup of people whose tumours were IHC3 positive in the ToGA trial was 5.6 months for trastuzumab plus cisplatin and capecitabine or 5-fluorouracil compared with cisplatin and capecitabine or 5-fluorouracil alone (see FAD section 4.24). |
| Welsh Assembly Government | This negative initial appraisal appears to be partly based on the interpretation that this does not fall under 'end of life' rules because the numbers of patients suitable for this treatment is greater than the threshold (of 7000) because of the inclusion of breast cancer patients. This is intrinsically unfair for patients with gastric cancer and I believe goes in the face of the reason this initiative was initially brought in, and will always unfairly discriminate against appraisals for license extensions smaller cancer populations as trials will always be first performed in more common diagnoses. | The advice on appraising treatments that extend life at the end of life indicates that the Committee must consider the cumulative population (that is, the entire population for which a technology is indicated). The Committee considered that 7000 was at the upper end of the population size for which it understood the supplementary advice to apply. However, the Committee concluded overall that applying the supplementary advice on end-of-life was appropriate. (see FAD section 4.25). |
| Welsh Assembly Government | Most improvements in cancer care are of course incremental. However the use of trastuzumab in gastric cancer, is, as it was in breast cancer, a step improvement rarely seen and it would be a massive blow for patients with this disease if this decision was not reversed. | The Committee was aware that there are currently no treatment options for metastatic gastric cancer which target HER2 overexpression, and that trastuzumab offers a new option for the licensed patient group (see FAD section 4.2 ).<br>The Committee considered all the clinical and cost effectiveness evidence submitted and discussed the application of the supplementary advice on appraising treatments that extend life at the end of life. The Committee concluded that it was appropriate to recommend the use of trastuzumab |

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| | | for a subgroup of the population, those with IHC 3 positive disease (see FAD section 4.27). |
| Department of Health | Thank you for the opportunity to comment on the Appraisal Consultation Document and evaluation report for the above single health technology appraisal.<br>I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation. | Comment noted. |
| Royal College of Pathologists | Please note that the Royal College of Pathologist has not comments to make on the ACD and evaluation report. | Comment noted. |

## Comments received from clinical specialists and patient experts

| Nominating organisation | Comment | Response |
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| | No comments received. | |

## Comments received from commentators

| Commentator | Comment | Response |
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| | No comments received. | |

## Comments received from members of the public

| Role* | Section | Comment | Response |
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| NHS Professional | 1 (Appraisal Committee's preliminary recommendations) | ToGA is a pivotal study in this rare cancer. This is the first time a molecularly targeted drug has been shown to benefit patients with a disease that has an otherwise dismal prognosis. Given that this is a relatively uncommon cancer (with even fewer patients fit enough to receive this technology), the guidance is disappointing. The hazard ratios for OS and PFS are substantial. It seems these patients are being treated differently to those with breast cancer. | The Committee considered all the clinical and cost effectiveness evidence submitted and discussed the application of the supplementary advice on appraising treatments that extend life at the end of life. The Committee concluded that it was appropriate to recommend the use of trastuzumab for a subgroup of the population, those with IHC 3 positive disease (see FAD section 4.27). |
| NHS | 2 (the | No comment. | Comment noted. |

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

| Role* | Section | Comment | Response |
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| Professional | technology) | | |
| NHS Professional | 3 (manufacturer's submission) | I agree with the ERG comments on comparator arm. For this group of patients either ECX or EOX would be UK standard of care. The relative contribution of epirubicin is a difficult one to get clarity on but many clinicians would see this as a moot point. | The Committee concluded, on the basis of the evidence and clinical specialist testimony, that epirubicin provided some additional benefit when added to a cisplatin and fluoropyrimidine combination (see FAD section 4.5). |
| NHS Professional | 4 (consideration of the evidence) | Probably a little too much emphasis on the Wagner metanalysis. 3 trials were used to look at the anthracycline issue. 2 showed no benefit while a third showed some. The third study (Ross et al) was a large RCT comparing MCF vs ECF. While it suggested benefit for ECF, there was no OS benefit. Also MCF is a toxic treatment. Mitomycin may have been detrimental! In my practice I have found MCF to be a particularly tough treatment with many patients unable to complete a full course of treatment. The first two trials in the Wagner metanalysis are more relevant (KRGCGC and Kim et al) as these studies compare platinum + fluropyrimidine versus the same + anthracycline. Neither showed a significant benefit for anthracycline. Also, I don?t think the Wagner data is from individual patient data. | The Committee noted comments from consultees that the quality of the studies in the meta analysis was poor. The evidence from the largest study (Ross) was from an unplanned subgroup which provided a greater estimate of the effect of epirubicin than the full population. The Committee further noted comments from consultees that the low doses of cisplatin in the studies did not reflect the higher dose used in the ToGA trial. The Committee concluded that the survival benefit of a triple regimen including epirubicin compared with that of a double regimen without epirubicin was unlikely to be represented by a hazard ratio of 0.77, and that the estimate would be closer to 0.96. However, this was associated with considerable uncertainty (see FAD section 4.8). |
| NHS Professional | 5 (implementation) | No comment. | Comment noted. No actions requested. |
| NHS Professional | 6 (related NICE guidance) | Waste of money. Many networks have done time in motion audits and looked at the toxicity implications of central lines/PICCs. In Kent our data clearly showed that oral 5FU was a cost neutral treatment. We have been using oral 5FU for many years. Going back to central lines/PICCs would be a retrograde step. Many other networks have seen sense and moved in this way. I think this piece of work is not needed. The world has moved on. | Comment noted. The NICE technology appraisal of capecitabine for advanced gastric cancer has now been published as technology appraisal guidance TA191. |
| NHS Professional | 7 (review date) | Far too late. The whole model may change if there are price changes in herceptin and also Â if there are cost reductions in the testing methodology. | Comment noted. Consultees may request an early review where they feel that evidence has become available that may change the recommendations. No changes made to the FAD. |

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| Rarer Cancers Foundation | 1 (Appraisal Committee's preliminary recommendations) | We are extremely disappointed that the recently issued Appraisal Consultation Document (ACD) on trastuzumab for the treatment of HER2-positive metastatic gastric cancer is negative. New treatments for metastatic gastric cancer are desperately needed and this treatment, which NICE is minded to reject, has been shown to be clinically effective and extend the lives of people with this subset of a rare form of cancer. | The Committee considered all the clinical and cost effectiveness evidence submitted and discussed the application of the supplementary advice on appraising treatments that extend life at the end of life. The Committee concluded that it was appropriate to recommend the use of trastuzumab for a subgroup of the population, those with IHC 3 positive disease (see FAD section 4.27). |
| Rarer Cancers Foundation | 4 (consideration of the evidence) | 1. Clinical trials<br><br>1.1 It is difficult to establish robust clinical trials in England and Wales for rare and very rare conditions, due to small patient populations. This is true in the case of gastric cancer and is perpetuated for this treatment as trastuzumab is only effective in HER2-positive patients. | Comment noted. No changes required to the FAD. |
| Rarer Cancers Foundation | 4 (consideration of the evidence) | 1.2 In point 4.3 of the ACD, the Appraisal Committee noted that the main pivotal trial (the ToGA trial) was an international trial and therefore the regimen and comparator were not standard clinical practice in England and Wales. Due to the small patient population (approximately 500 patients) it would be extremely difficult to recruit enough patients to a clinical trial exclusively in England and Wales in this instance, and end points in collection of trial data would take a long time to reach. Conducting an international trial is the only feasible way of making available a treatment for such a small patient population in a timely manner. | Comment noted. The Committee considered whether the population in the ToGA trial could be considered representative of the population of people with HER2-positive metastatic gastric cancer in England in Wales. The Committee discussed subgroup analyses which appeared to confirm a similar overall survival benefit for the group of European people in the trial. (see FAD section 4.3). |
| Rarer Cancers Foundation | 4 (consideration of the evidence) | 2. Innovation<br><br>2.1 In section 4.8 of the ACD, the Appraisal Committee considers the innovation provided by the product and the impact on health-related benefits. Given that trastuzumab has been used in breast cancer for a number of years the Committee does not consider this treatment to provide an innovation to the NHS. Despite this, targeting of therapy is innovative in the treatment of metastatic gastric cancer. We would therefore urge the Committee to weight their considerations to appropriately recognise the innovation that this product provides in gastric cancer. | This paragraph has been removed from the FAD.<br><br>The Committee noted that the median overall survival gain for the licensed population from the ToGA trial was 4.2 months for trastuzumab plus cisplatin and capecitabine or 5-fluorouracil compared with cisplatin and capecitabine or 5-fluorouracil alone. It further noted that the median overall survival gain for the subgroup of people whose tumours were IHC3 positive in the ToGA trial was 5.6 months for trastuzumab plus cisplatin and capecitabine or 5-fluorouracil compared with |

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| | | | cisplatin and capecitabine or 5-fluorouracil alone (see FAD section 4.24). |
| Rarer Cancers Foundation | 4 (consideration of the evidence) | 2.2 NICE has clarified that the small patient population criterion exists to encourage and reward innovation. However, innovation can occur in different forms. The use of an existing molecule in a rare group of patients can be every bit as significant in terms of the relative health benefits it brings as the development of an entirely new chemical entity. | Comment noted. The Committee was aware that there are currently no treatment options for metastatic gastric cancer which target HER2 overexpression, and that trastuzumab offers a new option for the licensed patient group (see FAD section 4.2 ). |
| Rarer Cancers Foundation | 4 (consideration of the evidence) | 3. Criteria for appraising life extending, end of life treatments<br><br>3.1 When the addition to the NICE Technology Appraisal methodology, 'Appraising life-extending, end of life treatments' was introduced in January 2009, it was seen as a great step forward in the appraisal of treatments for rarer cancers. The supplementary guidance gave patients renewed confidence that NICE recognises the specific problems experienced when appraising treatments at the end of life for small patient populations by allowing greater flexibility in appraising medicines, particularly for treatments for advanced cancers. In this appraisal however, we believe that the Committee has interpreted this guidance in a perverse way in relation to trastuzumab. | The advice on appraising treatments that extend life at the end of life indicates that the Committee must consider the cumulative population (that is, the entire population for which a technology is indicated). The Committee considered that 7000 was at the upper end of the population size for which it understood the supplementary advice to apply. However, the Committee concluded overall that applying the supplementary advice on end-of-life was appropriate. (see FAD section 4.25). |
| Rarer Cancers Foundation | 4 (consideration of the evidence) | 3.2 In point 4.20 of the ACD the Appraisal Committee has interpreted the 'patient population' to mean not only the appropriate patient population for HER2-positive metastatic gastric cancer, but also the other potential patients for which trastuzumab has licences (HER2-positive early and locally advanced breast cancer, and HER2-positive metastatic breast cancer). The total patient population who could benefit from trastuzumab across all of its licences is noted to be 7,144 people. This in itself could be considered on the margins of what is considered a small and therefore acceptable patient population for acceptance under the scheme. Of this figure, it is estimated that there are only 500 patients with HER2-positive metastatic gastric cancer. | The advice on appraising treatments that extend life at the end of life indicates that the Committee must consider the cumulative population (that is, the entire population for which a technology is indicated). The Committee considered that 7000 was at the upper end of the population size for which it understood the supplementary advice to apply. However, the Committee concluded overall that applying the supplementary advice on end-of-life was appropriate. (see FAD section 4.25). |
| Rarer Cancers Foundation | 4 (consideration of the evidence) | 3.3 By counting all of the patients for which trastuzumab has licences this significantly increases the patient population and as such the Appraisal Committee has not allowed trastuzumab to be considered under the supplementary guidance. We consider this to | The advice on appraising treatments that extend life at the end of life indicates that the Committee must consider the cumulative population (that is, the entire population for which a technology is |

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| | | be perverse and not in the spirit in which the guidance was developed. | indicated). The Committee considered that 7000 was at the upper end of the population size for which it understood the supplementary advice to apply. However, the Committee concluded overall that applying the supplementary advice on end-of-life was appropriate. (see FAD section 4.25). |
| Rarer Cancers Foundation | 4 (consideration of the evidence) | 3.4 In the guidance 'Appraising life-extending, end of life treatments', point 3.2 of the guidance states, 'second and subsequent licences for the same product will be considered on their individual merits.' We strongly believe that licences for other conditions should not be 'counted' in the size of the patient population because, as in this case, it is patients with rarer diseases that miss out on important new treatment options. We believe that in the case of trastuzumab for metastatic gastric cancer the individual licences should be considered separately. | The advice on appraising treatments that extend life at the end of life indicates that the Committee must consider the cumulative population (that is, the entire population for which a technology is indicated). The Committee considered that 7000 was at the upper end of the population size for which it understood the supplementary advice to apply. However, the Committee concluded overall that applying the supplementary advice on end-of-life was appropriate. (see FAD section 4.25). |
| Rarer Cancers Foundation | 4 (consideration of the evidence) | 3.5 Furthermore, trastuzumab was licenced for breast cancer approximately ten years ago and, to all extents and purposes, its clinical development for gastric cancer has been entirely separate. We therefore do not believe that the cumulative patient population for breast and gastric indications is relevant. | The advice on appraising treatments that extend life at the end of life indicates that the Committee must consider the cumulative population (that is, the entire population for which a technology is indicated). The Committee considered that 7000 was at the upper end of the population size for which it understood the supplementary advice to apply. However, the Committee concluded overall that applying the supplementary advice on end-of-life was appropriate. (see FAD section 4.25). |
| Rarer Cancers Foundation | 1 (Appraisal Committee's preliminary recommendations) | The Rarer Cancers Foundation urges the NICE Appraisal Committee to reconsider its interim decision, allowing HER2-positive patients with metastatic gastric cancer access to trastuzumab. By recommending this treatment NICE would give clinicians and patients a much needed alternative option in treating this disease. | The Committee considered all the clinical and cost effectiveness evidence submitted and discussed the application of the supplementary advice on appraising treatments that extend life at the end of life. The Committee concluded that it was appropriate to recommend the use of trastuzumab for a subgroup of the population, those with IHC 3 positive disease (see FAD section 4.27). |