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BY E-MAIL

SINGLE TECHNOLOGY APPRAISAL –
Trastuzumab for the treatment of HER2-positive metastatic gastric cancer

Dear Lori,

Thank you for providing us with this opportunity to comment on the Appraisal Consultation Document (ACD) for the above technology appraisal. Please find below our response to the provisional guidance presented under the four standard headings.

In summary, the key points that Roche would like to make in response to the ACD are as follows:

1. Presentation of new cost-effectiveness evidence based upon the IHC3+ population.
2. Clarification of key clinical and economic assumptions affecting the estimated ICER.
3. Application of the End of Life Criteria

As illustrated in the original submission the clinical benefit seen in the IHC3+ patients in ToGA showed the greatest incremental benefit with an overall survival improvement of 45.2%, increasing from 12.4 months to 18.0 months..

When accounting for the committee and ERG feedback on key model assumptions and evaluating the IHC3+ patients only, the ICER for trastuzumab is approximately £43,000. Trastuzumab clearly represents the biggest survival improvement in two decades in the management of gastric cancer. Furthermore when considering the small number of estimated patients (311 IHC3+ patients) that would be eligible for treatment under such optimised guidance in conjunction with the magnitude of benefit derived by the use of trastuzumab in this patient population, it is reasonable to consider trastuzumab a cost-effective treatment option for the NHS.

Yours sincerely,

Gavin Lewis

1 WHETHER YOU CONSIDER THAT ALL OF THE RELEVANT EVIDENCE HAS BEEN TAKEN INTO ACCOUNT

1.1 Revised economic analysis of the licensed population

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.

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).

Roche does not agree £67,000 represents the lowest plausible estimate of the ICER for the following key reasons (discussed in detail in section 2):

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.

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.

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

Our original model was amended to reflect the assumptions made by the ERG in their alternative base-case, except with regards to PFS utility. These changes alone resulted in an ICER of £62,829. We consider this a more robust estimate of the ICER compared the £67,000 reported in the ACD. However rather than representing the lowest plausible ICER estimate there are a number of further credible changes to key assumptions that suggest the base-case ICER could be lower.

Taking £62,829 as the revised base-case we present below a series of scenario analysis illustrating the effect of applying reasonable changes to the key assumptions:

Parameter changed	**ICER**	**Cumulative Effect on ICER**
PFS and OS: EOX = ECX	£58,620	£58,620
PFS and OS: ECX = ToGA CX	£57,005	£54,492
PFS and OS based on European subgroup analysis	£52,147	£49,343

In conclusion taking into consideration the feedback from the ERG and the committee we consider the ICER for the licensed population lies between £49,000 and £63,000.

1.2 IHC3+ Subgroup Analysis

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.

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.

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).

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.

The areas of uncertainty that were highlighted in the ACD as being 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)

In conclusion, optimising guidance to the IHC3+ subgroup significantly reduces the 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.

1.3 Probabilistic Sensitivity Analysis (PSA)

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."*

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.

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)

2 Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate

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?

Central to the evaluation of the clinical and cost-effectiveness of the trastuzumab, cisplatin, capecitabine (HCX) combination in HER2 positive gastric cancer is its efficacy relative to the ECX regimen that dominates clinical practice in the UK. This has not been tested in a clinical study, the control arm in the pivotal ToGA study being the internationally accepted CX/F regimen.

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.

Roche's contention has always been that although epirubicin may add to the efficacy of low intensity regimens of cisplatin (15-20 mg/m^2/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/m^2/week cisplatin) which can therefore be deemed equivalent to the ECF/X standard of care in the UK.

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)"

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/m^2/week) relative to those used in ToGA (27 mg/m^2/week) and by Yun *et al* (25 mg/m^2/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.

These issues raised above will now be discussed in more detail under the following headings:

i) Quality of the Wagner meta-analysis and plausibility of outcomes
ii) Impact of cisplatin and fluoropyrimidine dose on contribution of epirubicin to chemotherapy for gastric cancer
iii) Does treatment duration in the UK compensate for lower cisplatin doses?

i) Quality of the Wagner meta-analysis and plausibility of outcomes

Since the Wagner meta-analysis appears to have featured strongly in the discussions by the Appraisal Committee, it is important to understand its deficiencies even as a tool for answering the question it asks (Can epirubicin add to the efficacy of cisplatin and 5-FU?) which, as has been explained above, will not, in itself, answer the question of the relative efficacy of the ECF/X regimen routinely used in the UK and the high intensity CF/X regimen used as the control arm of ToGA. The part of the Wagner meta-analysis that describes the contribution of epirubicin is weak in several areas:-

Quality of data inputs

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.

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 and analysis with only 72% evaluable.

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 a*l 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

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.

Control regimens in included studies

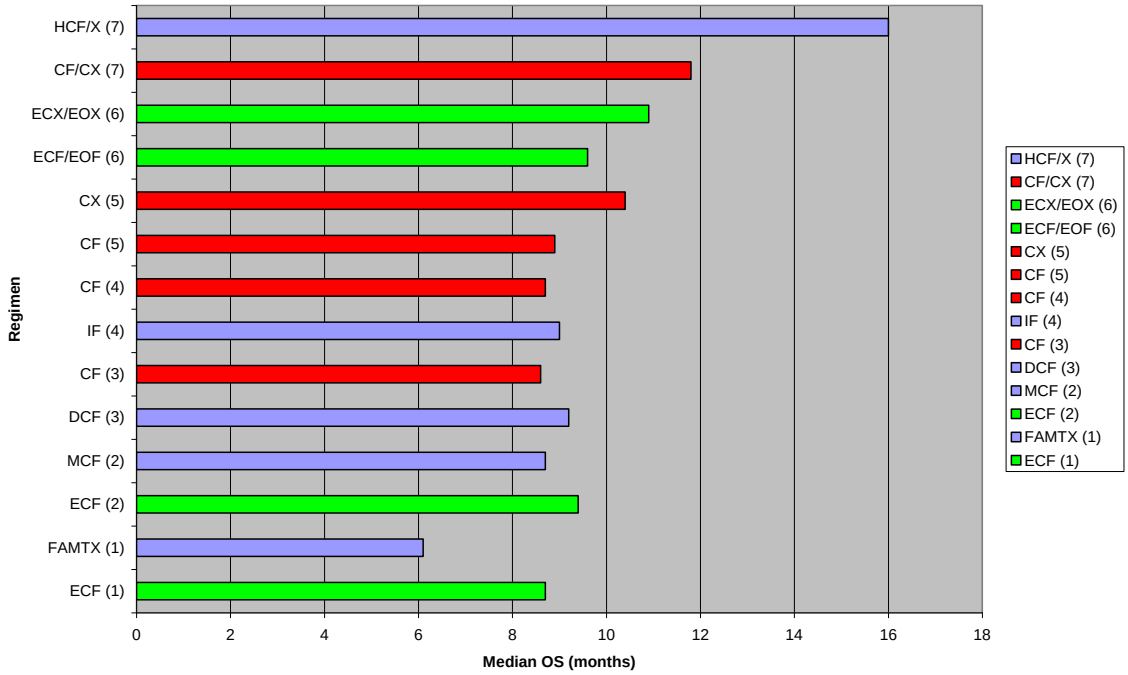
To answer the question of whether epirubicin adds to the benefit achieved with cisplatin and 5-FU the correct approach is to take an adequate cisplatin 5-FU regimen and add epirubicin to it. In none of the three studies included in the Wagner meta-analysis is the cisplatin-5-FU regimen one that is routinely used by those 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.

Plausibility of the conclusions from the Wagner meta-analysis

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.

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. Median overall survival results from recent randomised trials in gastric cancer utilising either ECF/X as used in the UK (green) or CF/X with a cisplatin dose of 25-27 mg/m^2/week as used in ToGA (red)



Abbreviations: A, doxorubicin (Adriamycin); C, cisplatin; D, docetaxel; F, 5-fluorouracil; H, trastuzumab (Herceptin); I, irinotecan; M, mitomycin; MTX, methotrexate; O, oxaliplatin; X, capecitabine (Xeloda)

References

1. Waters *et al* (1999)
2. Ross *et al* (2002)
3. Ajani *et al* (2007)
4. Dank *et al* (2008)
5. Kang *et al* (2009)
6. Cunningham *et al* (2008)
7. ToGA Clinical Study Report (2009)

ii) Impact of cisplatin and fluoropyrimidine dose on contribution of epirubicin to chemotherapy for gastric cancer

Since Roche is contending that the three drug regimen ECF/X is only minimally more active than the two drug regimens of cisplatin and a fluoropyrimidine used elsewhere, including as the control arm of ToGA it is important to understand why this is plausible and apparently at variance with the meta-analysis by Wagner.It is generally accepted that cisplatin is the most active single agent in the treatment of gastric cancer with a response rate of up to 30% (DeVita *et al*, 2005). There is also evidence that it has synergy with the fluoropyrimidines that form the background of chemotherapy in

this condition. For these reasons cisplatin and fluoropyrimidines form the basis of chemotherapy for gastric throughout the world. The activity of epiribicin is generally accepted as being lower (single-agent response rate below 20%). However, logic dictates that adding in this agent to a given cisplatin/fluoropyrimidine combination might be expected to increase activity.

However combination chemotherapy always involves a compromise. Although cytotoxic drugs do not all have identical toxicity profiles, they do have overlapping toxicities (most cause anaemia, immunosuppression, thrombocytopenia, mucositis, nausea, vomiting and hair loss). This fact coupled with the total toxicity burden that treatment puts on patients limits the doses of individual drugs that can be used in combination and raises a dilemma in those designing chemotherapy – more drugs or higher doses of the drugs used?

As can be seen in Table 1, the cisplatin+fluoropyrimidine regimens that form the basis of therapy in the ToGA study, and which Roche is suggesting are similar in efficacy to the three drug regimens used in the UK, use a higher dose of cisplatin than was employed in any of those included in the meta-analysis.

Table 1: Chemotherapy doses used studies included in the Wagner et al meta-analysis of chemotherapy for gastric cancer plus the ToGA and Yun (2010) studies

Study	N	Arm A Dose intensity (mg/m^2/week)	Arm B Dose intensity (mg/ m^2/week)
Tobe *et al* (1992)	60	Cis 15 (approx) 5-FU 300 (approx)	As A + Epi 15
Kim *et al* 2001	121	Cis 15 D1; 5-FU 1250	As A + Epi 12.5
Ross *et al* 2002	580	Cis 20; 5-FU 2100; MMC 1.2 D1 q42 days	Cis 20; 5-FU 1400 (Cap 8750)*; Epi 17
Yun *et al* 2010	91	Cis 25 Cap 9333	Cis 25 Cap 9333 Epi 17
ToGA	594	Cis 27; Cap 9333 or 5-FU 1333	Cis 27 Cap 9333 or 5-FU 1222 Tras 6 (per Kg)

*In the ECX regimen devised by this investigational group and now the UK standard

Abbreviations: Cap, capecitabine; Cis, cisplatin; Epirubicin, Epi; 5-FU, 5-fluorouracil; MMC, mitomycin C; Tras, trastuzumab

In the study by Kim *et al* the dose of cisplatin used was 15 mg/m^2/week, approximately the same as that used in the study by Tobe et al (which unusually used flat dosing), whilst in UK version of ECF it is 20 mg/m^2/week

In the ToGA study the cisplatin dose was 27 mg/m^2/week i.e. 33% higher than that in ECF and 80% higher than that in the studies by Kim *et al* and Tobe *et al*, but similar to that used in other recent trials using a two drug combination of a fluoropyrimidine and cisplatin as standard. Using such low doses of what is, probably, the most active agent in gastric cancer, it is unsurprising that Kim et al and Tobe et al managed to enhance total activity by adding in a third agent which has some single agent activity. That the cisplatin/5-FU combinations used in these studies were in adequate is evidenced by the outcomes achieved. For example the median survival in the control (cisplatin and 5-FU) arm of Tobe was approximately 4 months (read from Kaplan Meier curve); this is less than half that seen in the control arm of ToGA and other contemporary studies using adequate cisplatin/fluoropyrimidine combinations

However, when a higher dose of cisplatin 25 mg/m^2 (92% of the ToGA dose) was used by Yun *et a*l, the impact of adding epirubicin at the dose used in the UK was minimal and it seems unlikely that adding epirubicin to the still higher dose of cisplatin in ToGA would add clinically useful additional value (though it would add toxicity).

The disparity in fluoropyrimidine dose intensities is, generally, not so great between studies, with the exception of that by Tobe et al, which used a 5-FU dose schedule which would now be considered extremely inadequate, and a 7% lower capecitabine dose intensity in ECX, than in the control arm of ToGA. Thus, when comparing ECX and the control arm of ToGA, the inclusion of epirubicin in ECX has to compensate for the higher doses of both cisplatin and capecitabine, which may underpin the fact that the *control* arm of ToGA (median survival 11.7 months) has, possibly the longest survival reported for any chemotherapy regimen in an RCT for gastric cancer – certainly longer than has ever been reported for ECF/X (8.7-9.9 months).

Thus a picture emerges of epirubicin adding benefit to treatment regimens when cisplatin and fluoropyrimidine doses are low – in the meta-analysis by Wagner *et al* the epirubicin effect diminishes with increasing cisplatin dose and is by far the greatest in the small study by Tobe where not only is cisplatin dose lowest but 5-FU dose is also very low, resulting in the very poor outcome already described.

However, when adequate doses of fluoropyrimidine and close to maximal doses of cisplatin are used, as in the study by Yun *et al* (2010) the impact of adding in additional epirubicin is minimal and the results achieved without its inclusion are at least as good as those achieved with ECF/X at UK doses (see Figure 1).

In summary, it is reasonable to conclude that there is no evidence that the ECF/X regimen is any more active than a two drug fluoropyrimidine combination *where a higher dose of cisplatin* is used, such as in the ToGA study. Indeed, 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 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/m^2/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.

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.

iii) Does treatment duration in the UK compensate for lower cisplatin doses?

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"*

This thinking is flawed for two reasons:

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

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 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.

Furthermore, as seen in Figure 1, survival in the two drug control arm of the ToGA study where the target treatment duration was 6 cycles was longer than that achieved with the 3 drug combinations used in the REAL 2 study (Cunningham *et al* 2008) where the target was 8 cycles

Conclusions

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 issue of the relative effectiveness of ECF/X as used in the UK and the cisplatin/fluoropyrimidine control arm in the ToGA study is a crucial issue which underpins the ACs decision in Section 4.9 and 4.10 of the ACD to reject the manufacturer's base-case estimate of cost-effectiveness in favour of a higher ICER based on a lower health benefit from trastuzumab.

The possible benefit attributed by the Appraisal Committee to ECF/X over CF/X as used in ToGA (based on the Wagner meta-analysis - see Section 4.12 of the ACD) is not only at odds with the case presented by the manufacturer and the available evidence but also with the guidance given to it by the

independent ERG (who carried out an exploratory analysis assuming a 4% survival benefit from epirubicin based on Yun *et al,* 2010, which still does not adequately account for benefit to both study arms from higher cisplatin and fluoropyrimidine doses than are used in ECF/X) and its clinical experts (who stated that they believed Wagner et al to overestimate the contribution of epirubicin - see Section 4.12 of the ACD).

2.2 Quality of life

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 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)".*

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.

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.

2.3 PFS Utility

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."*

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."*

The ERG originally raised the assumed PFS utility values as an issue for discussion 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

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.

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.

2.4 Cardiac Monitoring

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)

2.5 Degree of Health Gain

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.

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.

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.

Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS

2.6 Interpretation of the EoL criteria

Roche acknowledges that despite offering a very substantial clinical benefit to patients, trastuzumab for the treatment of HER2 positive metastatic gastric cancer is only likely to be considered cost-effective by NICE's criteria if the additional EoL considerations are applied.

According to the ACD the Appraisal Committee agreed that patients with metastatic gastric cancer have a life-expectancy of less than 1 year and can expect to gain at least another 3 months of life from receiving trastuzumab. However, they did not agree that the licensed patient population for trastuzumab met the requirements for a "small patient population"

Roche estimated in its original submission that if all eligible patients with HER2 positive early breast cancer, metastatic breast cancer and advanced gastric cancer received the drug, this would total 7,144 patients per year.

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.

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 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.

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.

Taking into account the restricted IHC 3+ population now being proposed by Roche and falling gastric cancer rates, the eligible patient population for trastuzumab is comfortably below the 7,000 that has been suggested to define a “small patient population”.

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.

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.

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.

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.

3 Are there any equality related issues that need special consideration that are not covered in the ACD?

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).

Whilst this point was raised by the clinical expert in the meeting it appears to have been omitted from the ACD.

In addition trastuzumab produces a similar health gain in mGC which is a predominantly male disease, but has been given provisional negative guidacance, whilst it has been funded in a predominantly female disease – mBC.

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Appendix 1: New Evidence; IHC 3+ subgroup analysis of trastuzumab in HER2+ve metastatic gastric cancer

Background

Trastuzumab is a monoclonal antibody directed against HER2, a cell surface protein and growth factor receptor controlling cell growth. Once bound it works in at least two ways: Firstly, by interfering with the function of the receptor it switches off the aberrant growth signal that drives tumour cell proliferation in patients with HER2 over-expression and, secondly, by marking out cells for attack by the patients immune system.

In cells with higher levels of HER2 on the surface it is reasonable to suppose that there is more HER2 mediated aberrant signalling and so the consequences of "turning it off" with trastuzumab will be greater, whilst the higher the levels of bound trastuzumab, the stronger the signal to the immune system to seek out and destroy tumour cells.

Thus, theoretically, the trastuzumab treatment effect would be expected to be greater in patients with higher levels of HER2. This is the reason why, from early in its development , trastuzumab studies have generally only recruited patients expressing HER2 at the 2+ and 3+ levels on the 3 point scale used to describe cell surface HER2 levels during immunohistochemical testing.

In breast cancer there is also a clear gradation of trastuzumab efficacy between patients with 2+ and 3+ overexpressing tumours. For example, in the Phase II study HO649g where heavily pre-treated patients with HER2 overexpressing breast cancer were treated with trastuzumab monotherapy, treatment benefits were greater in the 3+ subgroup as shown in Table 2

Table 2: Summary of clinical outcomes for study H0649g of trastuzumab in heavily pre-treated HER 2 positive breast cancer

Parameter	All patients (n=222)		+3 HER overexpressors (n=172)	
		95% CI or Range		95% CI or range
Response rates based on REC assessment (%)				
Overall response rate	34 (15%)	11% - 21%		
Complete response	8 (4%)			
Partial response	26 (12%)			
Response rates based on investigator assessment (%)				
Overall response rate	46 (21%)	16% - 27%	(18%)	12.59-24.6%
Complete response	9 (4%)		(3%)	
Partial response	37 (17%)		(15%)	
Time to disease progression (median)	3.1 months	Range 0 – 28+	3.2 months	Range 2.6-3.5
Duration of response (median)	9.1 months	Range 2 – 26+	9.1 months	Range 5.6-10.3
Time to treatment failure (median)	2.4 months	Range 0 – 28+		
Survival (median)	12.8 months	Range 0.5 - 30+	16.4 months	Range 12.3-ne

Sources: Final Study Report H0649g, Table 11, page 40, Table 12, page 40, Table 13, page 41, SPC August 2000
"Ne" indicates that this figure could not be calculated or had not yet been reached

As detailed in Roche's submission to NICE on trastuzumab+chemotherapy in advanced breast cancer (TA107) the relationship between the degree of overexpression and trastuzumab benefit is a consistent one.

Therefore, when the ToGA study was begun it was assumed that this relationship could be expected in gastric cancer and the protocol specified that a sub-group analysis be conducted looking at the patients with a different HER2 status. This analysis showed (see Figure 12 of Roche's original submission for this appraisal) that the relationship did indeed hold good with IHC 0+ and 1+/FISH+ patients apparently getting no benefit, with the licensed population (IHC2+ Fish+ and IHC3+) receiving substantial benefit with the most prominent benefit in the IHC3+ patients.

Clinical Evidence

In Roche's original submission the summary hazard ratio for the pre-planned of analysis of the IHC3+ subgroup was presented however below present in greater detail the clinical results for this subgroup and limited to the metastatic patient population (8 patients in the original analysis had locally advanced rather than metastatic disease however the license is for metastatic disease only)

Characteristics of the IHC 3+ subpopulation from the ToGA study

When examining a subgroup from a study, it is important to confirm that the balance of characteristics between the study arms that should have been achieved by randomisation in the larger trial population is preserved, so that any difference in treatment effect can be confidently attributed to real differences in sensitivity to the drug and not to imbalances in baseline risk between trial arms.

As shown in Table 3 although the sub-population of 279 patients from the ToGA study Full Analysis Set (FAS; ITT population) with HER2 3+ recurrent/metastatic gastric cancer (62% of licensed population) is generally well-balanced for prognostic characteristics at baseline, there is an imbalance with respect to ECOG performance status. The control had approximately half the number of ECOG 2 (least fit) patients and 20% less ECOG 0 (fittest) patients. This imbalance would be expected to favour survival in the control arm and reduce the apparent treatment benefit of trastuzumab if uncorrected.

Table 3: Baseline characteristics of the IHC 3+ subpopulation of patients from the FAS population of the ToGA study

	Fluoropyrimidine +cisplatin N=135	**Trastuzumab +cisplatin +fluoropyrimidine N=144**
Time from first diagnosis of gastric cancer to randomisation (months)	1.2	1.4
Median	0.2-65.6	0.3-309.3
Range		
Time from diagnosis of recurrent/metastatic disease to randomisation (months)	1.0	1.0
Median	0.3-4.1	0.2-13.2
Range		
Primary site		
Stomach	122 (90.4%)	114 (79.2%)
Gastro-oesophageal junction	13 (9.6%)	30 (20.8%)
Histology (local assessment)		
Intestinal	64 (47.4%)	63 (43.5%)
Diffuse	38 (28.1%)	48 (33.3%)

Not assessed	33 (24.4%)	33 (22.9%)
Histology (central assessment)		
Intestinal	103 (78.0%)	115 (80.4%)
Diffuse	5 (3.8%)	8 (5.6%)
Mixed	24 (18.2%)	20 (14.0%)
Number of lesions per patient		
1-4	46 (34.1%)	64 (44.4%)
>4	89 (65.9%)	80 (55.6%)
Median	6	5
Range	1-15	1-20
ECOG Status		
0	51 (37.8%)	43 (29.9%)
1	77 (57.0%)	86 (59.7%)
2	7 (5.2%)	15 (10.4%)
Number of sites per patient		
1-2	68 (50.4%)	70 (48.6%)
>2	67 (49.6%)	74 (51.4%)
Median	2	3
Range	1-6	1-5
Visceral (lung or liver) metastases		
Yes	81 (60.0%)	88 (61.1%)
No	54 (40.0%)	56 (38.9%)

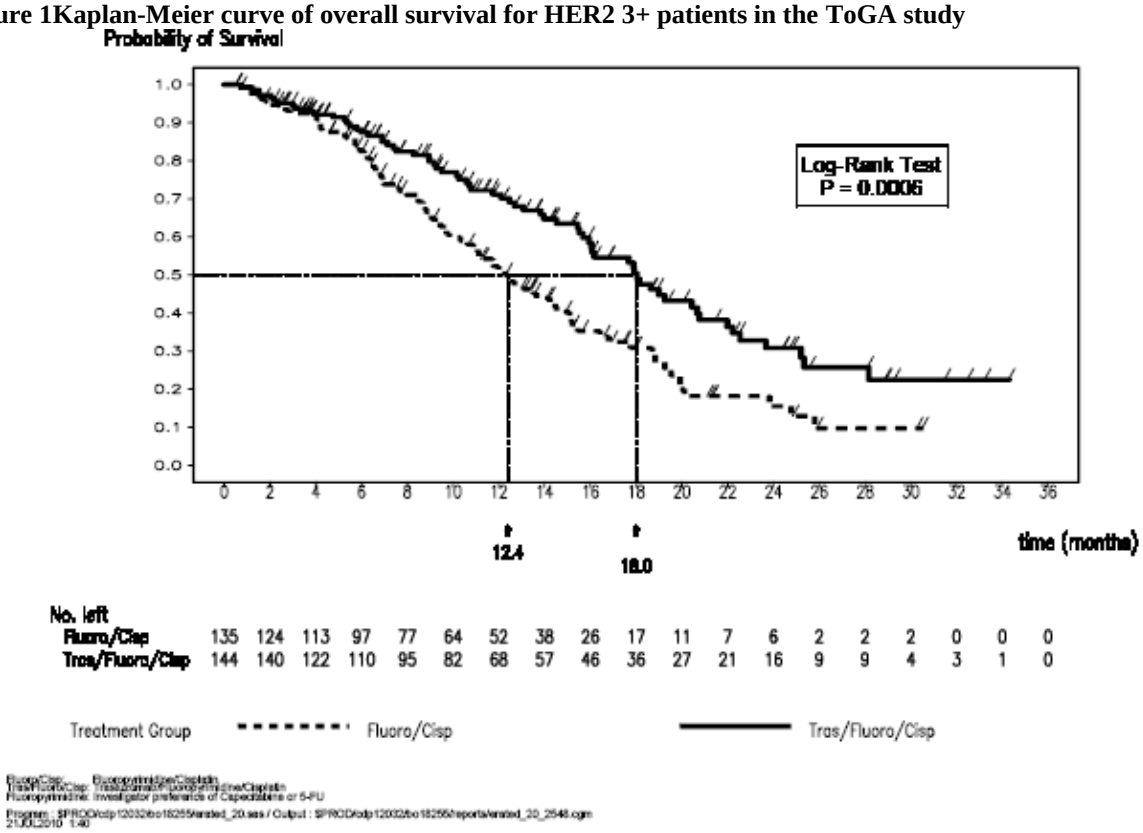
Clinical outcomes in HER2 3+ subgroup

Primary study end-point: overall survival (OS)

As shown in Figure 1 the addition of trastuzumab to standard platinum-fluoropyrimidine chemotherapy in patients whose tumours were IHC 3+ resulted in an early, sustained and dramatic separation of the Kaplan-Meier survival curves. The risk of death was reduced by 43% (HR 0.57; 95% CI 0.41,0.79; p=0.0008) with median OS increased by 45.2% from 12.4 (95% CI 10, 15) months to 18.0 (95% CI 16, 21) months. Stratification for extent of disease, primary site, measurability, ECOG performance status and fluorpyrimidine choice reduced the hazard ratio slightly (HR 0.51; 95% CI 0.36, 0.72; p=0.0001).

Although this survival benefit is clearly consistent with (in fact, the two groups (IHC3+/FISH any result and IHC2+/FISH+) that represent the licensed population do not have a statisticially significant different treatment effect), but slightly greater than, that reported for the entire licensed patient population in Section 6.4.7.1 of Roche’s original submission

Figure 1Kaplan-Meier curve of overall survival for HER2 3+ patients in the ToGA study

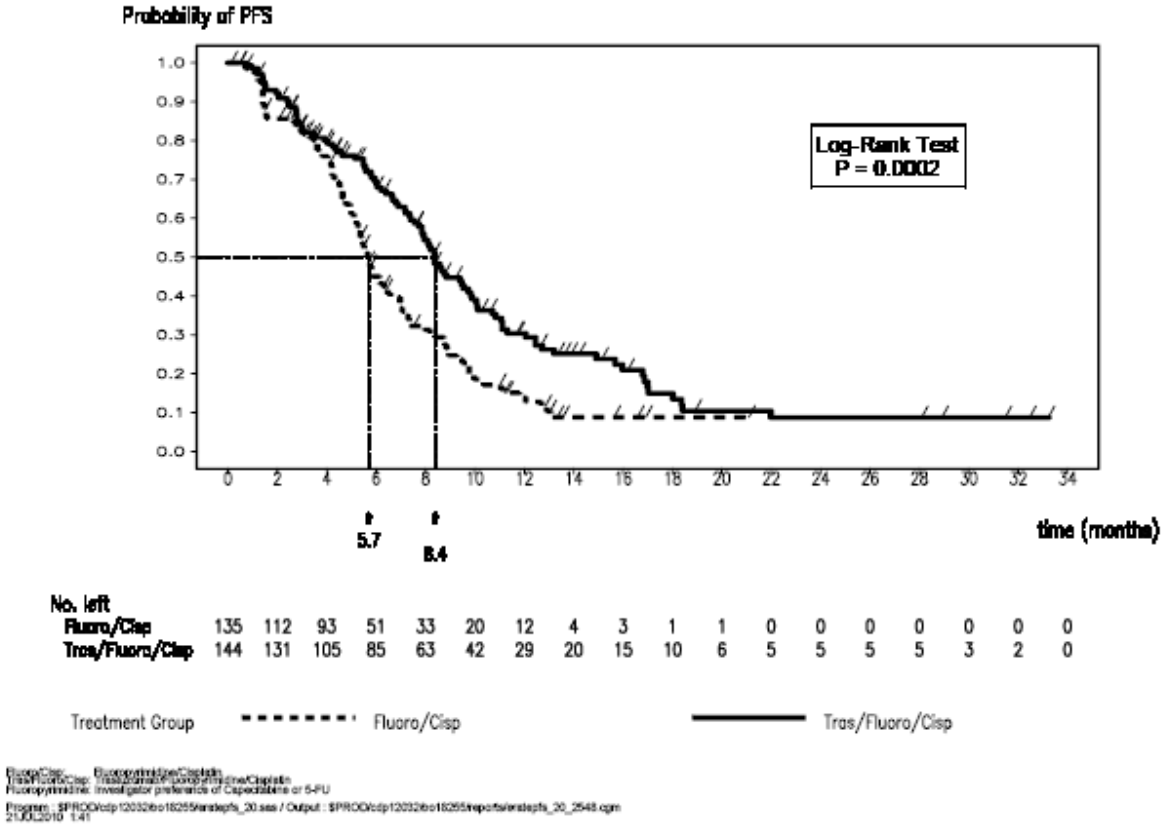


Progression-free survival (PFS)

Figure 2 shows that as for OS, the addition of trastuzumab to standard platinum-fluoropyrimidine chemotherapy in patients who tumours were IHC 3+ resulted in an early, sustained and dramatic separation of the Kaplan-Meier PFS curves. The risk of progression was reduced by [redacted] with median PFS increased by [redacted] from [redacted] months to [redacted] months. Stratification for extent of disease, primary site, measurability, ECOG performance status and fluoropyrimidine choice had little impact on this result [redacted].

Again, this PFS benefit is clearly consistent with, but greater than, that reported for the entire licensed patient population in Section 6.4.7.1 of Roche's original submission.

Figure 2: Kaplan-Meier curve of progression-free survival (PFS) for HER2 3+ patients in the ToGA study



Time to progression (TTP)

As expected the PFS results were mirrored by those for TTP. Addition of trastuzumab to chemotherapy improved median TTP by [redacted] from [redacted] to [redacted] with the risk of progression reduced by [redacted] in an unstratified analysis and [redacted] in an analysis stratified for the factors described above.

Tumour response

The improvements seen in OS, PFS and TTP were a reflection of both an increase in the proportion of patients responding to treatment following the addition of trastuzumab (as shown in Table 4) and the duration of response in those patients who did respond, as shown in Table 5

Table 4: Tumour response rates for IHC 3+ patients in the ToGA study

	Fluoropyrimidine+ Cisplatin	**Fluoropyrimidine+ Cisplatin+**

	N=135	Trastuzumab N=144
Response		
Non-response		
95% CI for Response Rate[1]		
Difference in Response Rates		
95% CI for difference in Response Rates[2]		
p-Value (Chi-squared test)		
Odds Ratio		
95% CI for Odds Ratio		
Complete Response (CR)		
95% CI for Complete Response Rate[1]		
Difference in CR Rates		
95% CI for difference in CR Rates[2]		
p-Value (Chi-squared test)		
Odds Ratio		
95% CI for Odds Ratio		
Clinical Benefit[3]		
No Clinical Benefit		
95% CI for Clinical Benefit Rate[1]		
Difference in Clinical Benefit Rates		
95% CI for difference in Clinical Benefit Rates[2]		
p-Value (Chi-squared test)		
Odds Ratio		
95% CI for Odds Ratio		

1. 95% CI for one sample binomial using Pearson-Clopper method

2. Approximate 95% CI for difference of two rates using Hauck-Anderson method

3. Clinical Benefit defined as Complete Response, Partial Response or Stable Disease as best response to treatment

Table 5: Response duration for IHC 3+ patients in the ToGA study

	Fluoropyrimidine+ Cisplatin N=135	**Fluoropyrimidine+ Cisplatin+ Trastuzumab N=144**
Patients included in analysis	[redacted]	[redacted]
Patients with event	[redacted]	[redacted]
Patients without event	[redacted]	[redacted]
Time to event (months)		
Median[1]	[redacted]	[redacted]
95% CI for Median[1]	[redacted]	[redacted]
Range[2]	[redacted]	[redacted]
p-Value (Log-Rank test)	[redacted]	
Hazard Ratio	[redacted]	
95% CI	[redacted]	

Safety in the IHC 3+ population

Since any adverse effects arising from trastuzumab use are the result of interactions between the drug and normal tissue rather than tumour, the extent of abnormal HER2 expression in the tumour will not affect the safety profile of trastuzumab and the analysis of safety and tolerability in Section 6.7 of Roche's original submission for this appraisal is equally applicable to any consideration of the IHC 3+ subgroup.

IH3+ Cost Effectiveness Analysis

Methods Overview

Roche's original base-case was modified by replacing the following elements of the model with those pertaining specifically to the IHC3+ subgroup:

i) PFS and OS Kaplan Meier curves
ii) Weibull parameter estimates
iii) Time to treatment cessation Kaplan-Meier curves
iv) Cost per treated patient of HER2 testing

The economic model was also amended to reflect criticisms of the original base-case analysis by the ERG in their report, and also discussions in the first Appraisal Committee Meeting. All of the assumptions incorporated by the ERG in their alternative base-case were incorporated in this subgroup analysis except with regards to PFS utility values for the reasons detailed in section 2.2 and 2.3. In addition, the probabilistic sensitivity analysis was adapted to incorporate uncertainty around the comparative effectiveness estimates of the comparators in the economic model *versus* the doublet regimens used in the ToGA study.

In this revised base-case model a benefit is assumed for ECX vs CX and also EOX vs ECX as per the ERG alternative scenario analysis. Given that we consider it equally if not more plausible that there is no efficacy advantage for the three drug regimens over the high intensity cisplatin/fluoropyrimidine regimen used in the ToGA study, regimens (see section 2.1) we consider this revised base case represents a conservative approach.

Extrapolation of Survival Data

Despite there being a relatively mature follow-up of patient outcomes and 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.

29.9% and 22.2% of patients remained in PFS for the trastuzumab+chemotherapy and chemotherapy-alone arms respectively; 53.5% and 38.5% of patients were still alive in the trastuzumab-containing arms and chemotherapy alone arms respectively.

The parameters for the endpoints PFS and OS, under the assumption of a parametric survival function, were estimated using the clinical data for the IHC3+ subgoup. 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.

Progression Free Survival

Table 6: Summary of Parametric Functions' Goodness of Fit for PFS

Parametric Model	AIC	BIC
llogistic	623.31573075	634.20936609
lnormal	627.83131335	638.7249487
Weibull	636.77704963	651.30189676
exponential	669.64381555	676.90623911
Gompertz	670.75520615	681.64884149

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, as per the analsyis of the licensed population, 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 3 and Figure 4 below). Hence, consistent with the original submission, the Kaplan-Meier PFS curves were used up to the end of month 12. and from month 13 the Weibull function 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 5 below.

Figure 3: Extrapolated Progression-Free Survival data from ToGA using the Log Logistic Survival Function (IHC3+ metastatic patients only)

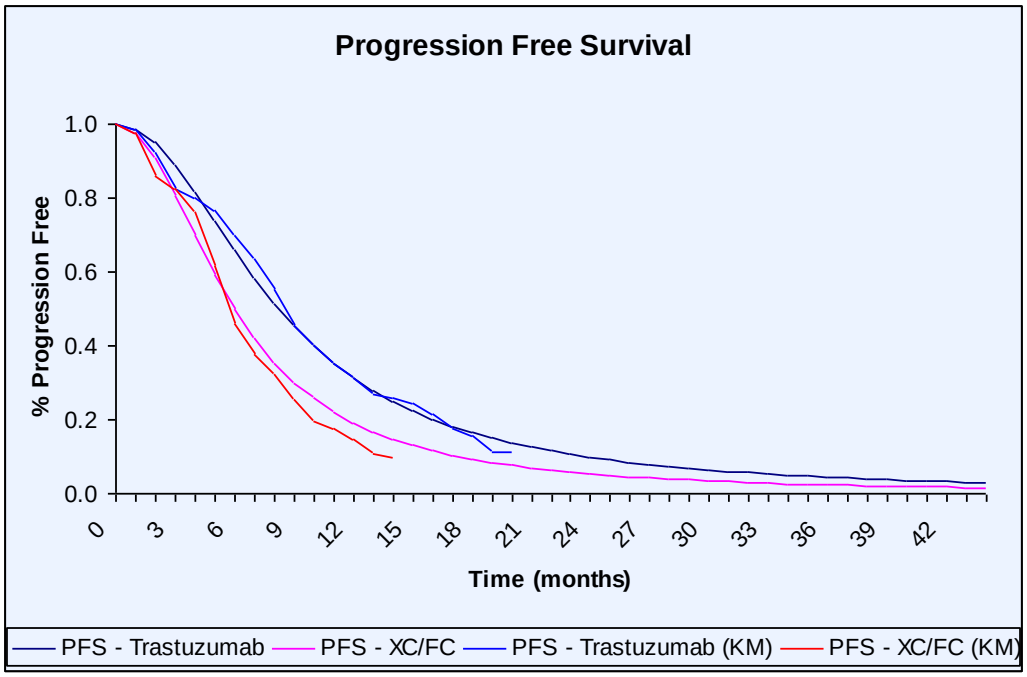


Figure 4: Extrapolated Progression-Free Survival data from ToGA using the Log Normal Survival Function (IHC3+ metastatic patients only)

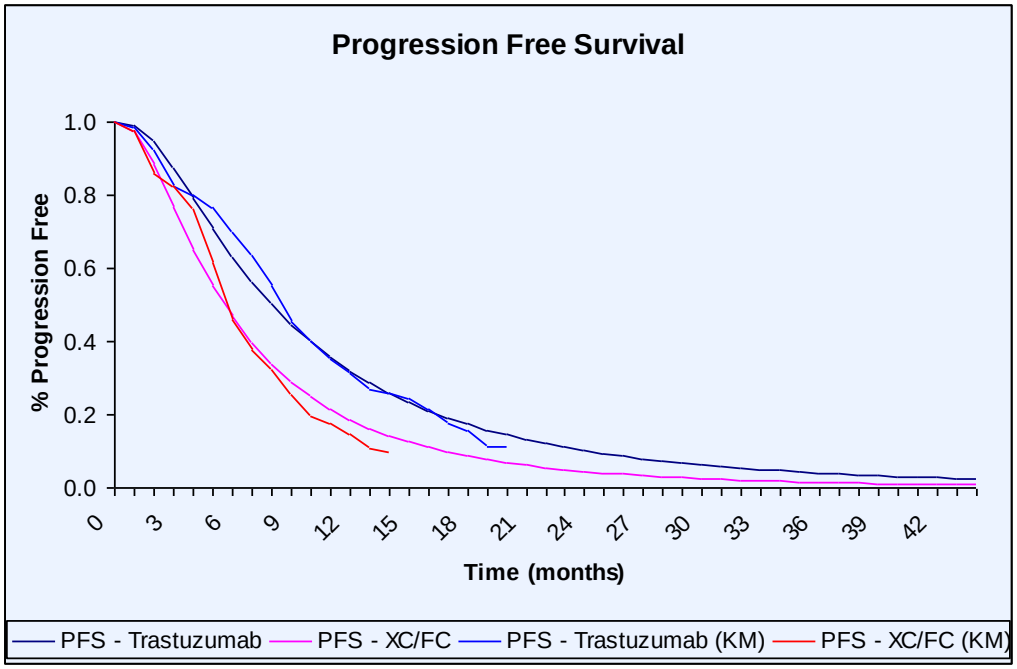
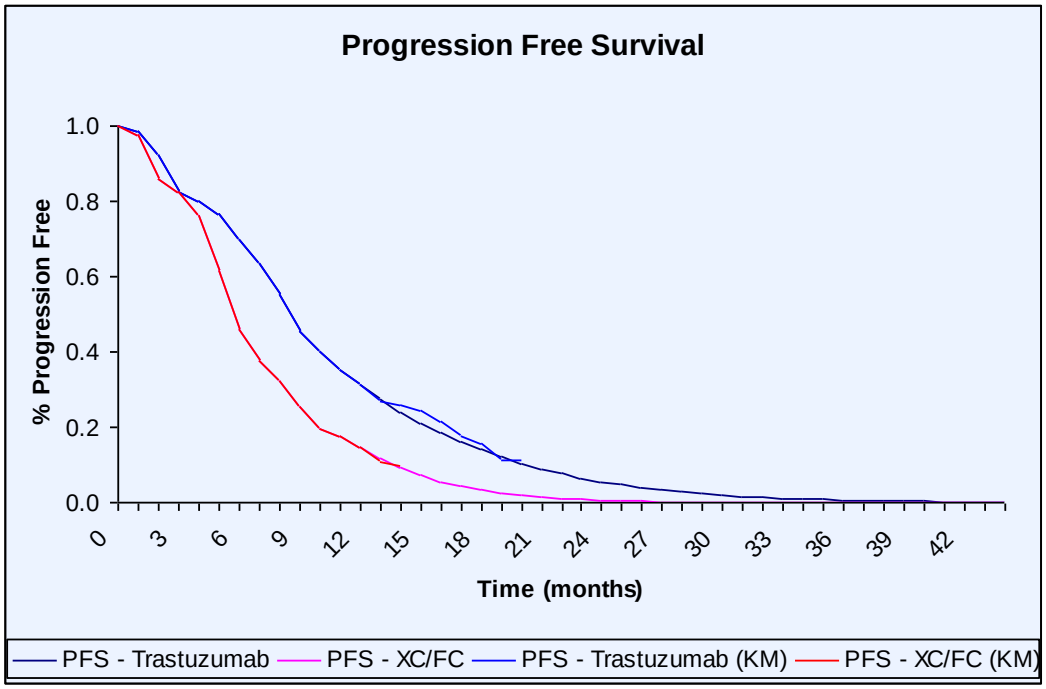


Figure 5: Extrapolated Progression-Free Survival data of ToGA using the KM estimates up to the end of month 12 and extrapolated using the Weibull function from this point on (IHC3+ metastatic only)



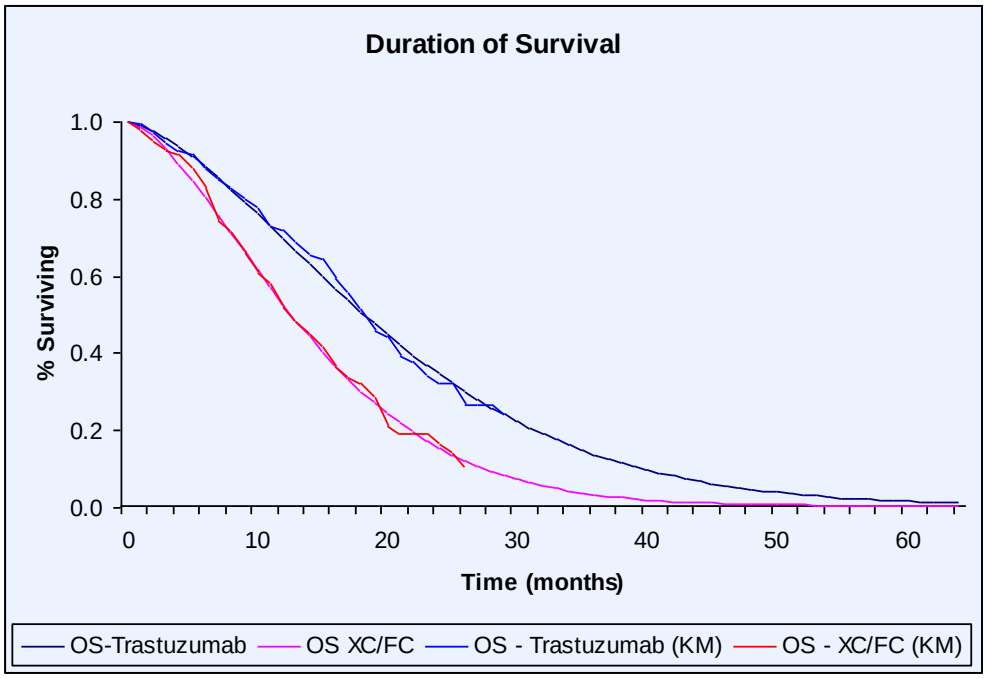
Overall Survival

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 7: Summary of Parametric Functions' Goodness of Fit for OS

Parametric Model	AIC	BIC
Weibull	543.0583051	557.58315222
llogistic	547.32376345	558.21739879
lnormal	558.91518808	569.80882342
exponential	575.76040108	583.02282464
Gompertz	599.12736657	610.02100192

Figure 6: Extrapolated overall survival from ToGA using the Weibull survival function (IHC3+ metastatic only)



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

Table 8: Weibull Parameter Estimates for OS and PFS by Treatment Arm unstratified

Efficacy Endpoint	Trastuzumab + Chemotherapy	Chemotherapy alone
Overall Survival (OS)		
Lambda	0.007754201	0.013708339
Gamma	1.551779098	1.551779098
Progression Free Survival (PFS)		
Lambda	0.029228339	0.05404718
Gamma	1.429900235	1.429900235

The Weibull survival function is defined as

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

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

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

Stratified analysis

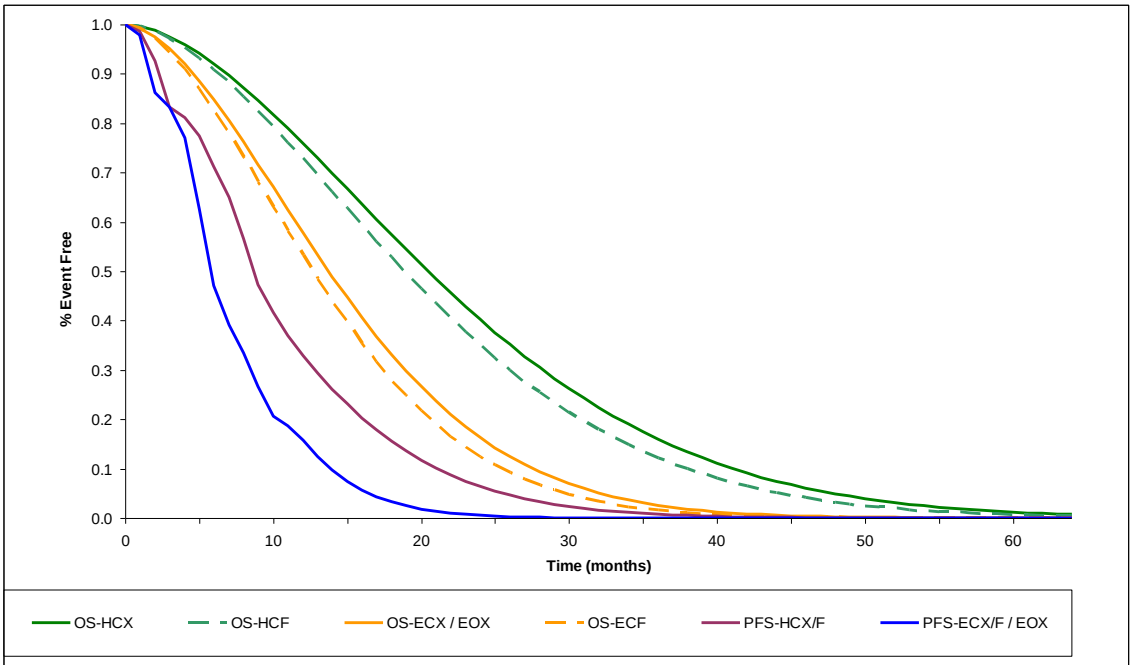
As already stated in the clinical section the hazard ratio for OS and to a lesser extent PFS differed slightly between the stratified and un-stratified analyses possibly due to an imbalance in the performance status of the patients in the comparator arm at baseline. Hence the stratification factors

were set as covariates in the Weibull model to help correct for any potential imbalance in the arms of this subgroup. The resulting parameter estimates for the Weibull function in OS and PFS are shown in the table below and were used to estimate the base case ICER. The variance covariance matrix was expanded to incoporate uncertainty in the additional perameter estimates and updated with the results based on the IHC3+ subgroup. As the KM curve was used to estimate PFS for the first 12 months, this curve was adjusted by applying a hazard ratio of 0.95 to the trastuzumab PFS KM curve (calculated as the unstratified Hazard ratio devided by the stratified hazard ratio).

Table 9: Weibull Parameter Estimates for OS and PFS by Treatment Arm stratified

Efficacy Endpoint	Trastuzumab + Chemotherapy	Chemotherapy alone
Overall Survival (OS)		
Lambda	0.003772149	0.007821893
Gamma	1.726519337	1.726519337
Progression Free Survival (PFS)		
Lambda	0.021182058	0.043662977
Gamma	1.520912548	1.520912548

Figure 7: Extrapolated Survival Curves used in the Base Case Analysis



Indirect treatment comparison

The revised base case conservatively takes the assumptions for the comparative effectiveness of ECX and EOX compared with the comparator arm in ToGA from the ERG's alternative base case scenario where the PFS hazard ratio of ECX vs ToGA CX = 0.96 and EOX vs ECX = 0.87. Multiplying these two hazard ratios gives a hazard ratio for EOX vs CX of 0.84.

Treatment duration

Exactly the same methods as in the original submission were used to estimate the treatment duration. The time to treatment cessation Kaplan-Meier curves were replaced with those based on analysis of the IHC3+ subgroup to calculate the proportion of patients on treatment relative to those remaining in PFS. However using the IHC3+ data made little difference to the results since the average treatment duration on trastuzumab relative to duration in PFS was very similar to that calculated for the licensed population (85% and 88% for the IHC3+ and the licensed populating respectively).

Sensitivity Analysis

In the Appraisal Committee Meeting the following areas of uncertainty were highlighted for discussion (as stated in 4.11 of the ACD):

i) The comparator effectiveness ie the potential variation in effectiveness between the regimens typically used in the UK and those used in the ToGA study
ii) The frequency of cardiac monitoring for epirubicin.
iii) The most relevant HER2 testing strategy.
iv) The change in utility during progression-free survival.
v) The assumption that 80% of centres would share vials of trastuzumab.

The sensitivity of the ICER to changes in the assumptions for each of the areas of uncertainty listed was explored, except for the HER2 testing strategy as this becomes irrelevant for the IHC3+ subgroup as FISH testing would not necessarily be required and also PFS utility as we consider it likely that the PFS utility values would increase as per expectation and the trial data.

In addition to those areas of uncertainty listed above, the committee discussed whether the outcomes in the trial, in which most of the participants were from Asia, would apply to the population of people with HER2-positive metastatic gastric cancer in England in Wales. Whilst the “Committee was persuaded that the population in the ToGA trial could be considered applicable to the UK population” to be consistent with exploring the areas of uncertainty that might potentially increase the ICER it is also appropriate to calculate the impact on the ICER where the available evidence suggests the ICER could decrease. Hence an exploratory analysis was performed looking at the effect on the ICER of using the IHC3+ data limited to only patients treated in Europe. In this analysis the survival curves of the IHC3+ population were replaced with those estimated from the European IHC3+ patient data. The proportion of patients on treatment out of those in PFS was assumed to remain the same as in the IHC3+ base-case analysis.

Sensitivity of the model to variation in the relative effectiveness of ECX vs CX was explored assuming a plausible PFS and OS Hazard ratio range of 1.1 to 0.9. This reflects a much smaller plausible range

of difference between ECX/EOX vs CX than suggested by the committee who indicated that a hazard ratio of 0.77 represented the upper bound and also that in fact the comparator in ToGA could offer equal or slightly better efficacy than the UK regimens (see section 2.1).

Probabilistic Sensitivity Analyis (PSA)

The Bucher method was used to estimate the 95% confidence intervals around the hazard ratios for each of the comparators in the model compared with CX. The resultant confidence intervals for each of the indirect comparisons is listed in the table below (calculations available in the revised model "Model Inputs row 63 to 77).

Table 10: Confidence intervals applied in the model to incorporate uncertainty

Comparison vs CX	Hazard Ratio	Lower CI	Upper CI
HCF	1.15	1.02	1.30
EOX	0.84	0.48	1.46
ECX	0.96	0.58	1.57
ECF	1.10	0.66	1.83

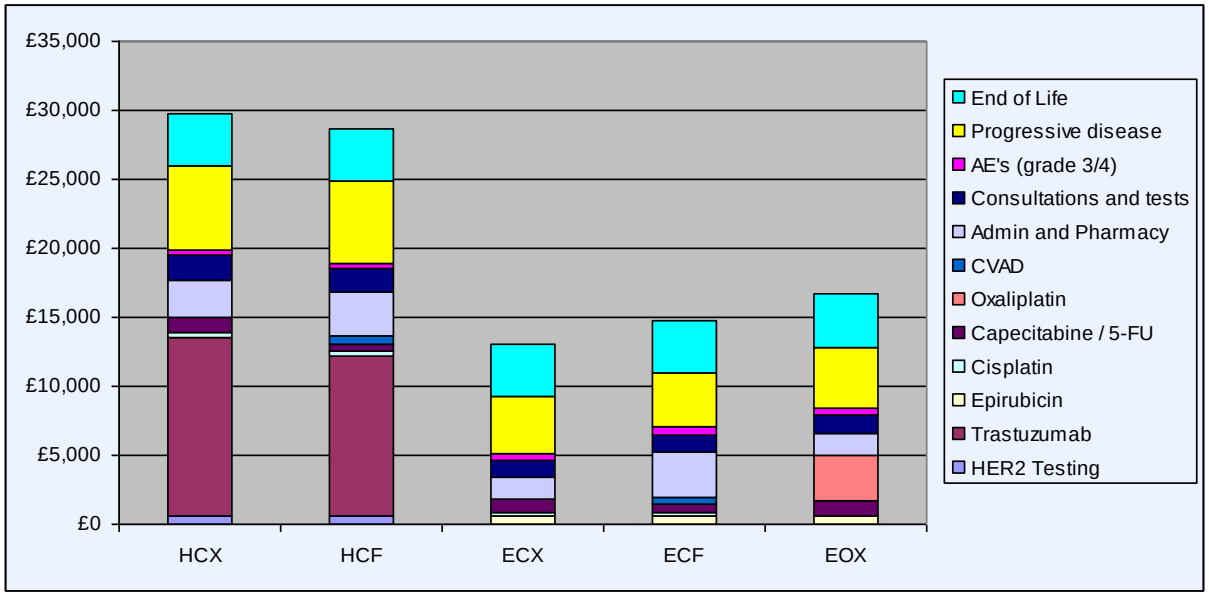
Economic Results (IHC 3+ mGC Subgroup)

The results of the base-case analysis are provided below. The mean results of the probabilistic sensitivity analysis (PSA) were virtually identical to the deterministic results; hence all the figures presented in this section represent the deterministic results. The PSA means are provided alongside the scatter plots in the sensitivity analysis (see appendix 2)

Costs

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

Figure 8: 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.

The data displayed above in Figure 8 is represented in tabular format below.

Table 11: Total cost for each intervention per patient

	HCX	HCF
HER2 Testing	£594	£594
Trastuzumab	£12,976	£11,638
Epirubicin		
Cisplatin	£315	£307
Capecitabine / 5-FU	£1,166	£567
Oxaliplatin		
CVAD		£505
Admin and Pharmacy	£2,616	£3,245
Consultations and tests	£1,793	£1,643
AE's (grade 3/4)	£432	£432
Progressive disease	£6,122	£5,938
End of Life	£3,749	£3,768
Total Direct Costs	**£29,761**	**£28,636**

Table 12: cost for each comparator per patient

	ECX	ECF	EOX
Epirubicin	£629	£630	£645
Cisplatin	£244	£234	
Capecitabine / 5-FU	£995	£622	£1,033
Oxaliplatin			£3,347
CVAD		£505	
Admin and Pharmacy	£1,547	£3,251	£1,587
Consultations and tests	£1,210	£1,256	£1,287
AE's (grade 3/4)	£462	£557	£488
Progressive disease	£4,188	£3,910	£4,467
End of Life	£3,831	£3,844	£3,818
Total Direct Costs	**£13,107**	**£14,808**	**£16,671**

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

Table 13 shows that the combination of HCX results in a mean gain of 7.4 months and 6.2 months of life compared with ECX and EOX respectively. HCF results in a mean gain of 6.8 months of life compared with ECF.

Table 13: Time (months) spent in each health state till death per patient (undiscounted)

	HCX	HCF	ECX	ECF	EOX
PFS post treatment	10.58	9.25	7.10	6.49	7.76
Progressive Disease	12.00	11.57	8.05	7.49	8.61
Total	**22.58**	**20.82**	**15.15**	**13.98**	**16.37**

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 0.388 and 0.322 over ECX and EOX respectively and 0.351 for HCF over ECF.

Table 14: QALYs per patient

	HCX	HCF	ECX	ECF	EOX
PFS	0.657	0.572	0.438	0.399	0.479
Progressive Disease	0.537	0.522	0.369	0.345	0.393
Total QALY's	**1.194**	**1.094**	**0.807**	**0.744**	**0.872**

Table 15: Incremental QALYs per patient

	ECX	ECF	EOX
HCX			
PFS	0.219	0.258	0.178
Progressive Disease	0.169	0.193	0.144
Total QALY's	**0.388**	**0.451**	**0.322**
HCF			
PFS	0.135	0.174	0.094
Progressive Disease	0.153	0.177	0.129
Total QALY's	**0.288**	**0.351**	**0.222**

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. EOX was the most challenging comparator regimen hence EOX and HCX make up the efficiency frontier (see Figure 9 below).

Figure 9: Simultaneous incremental results

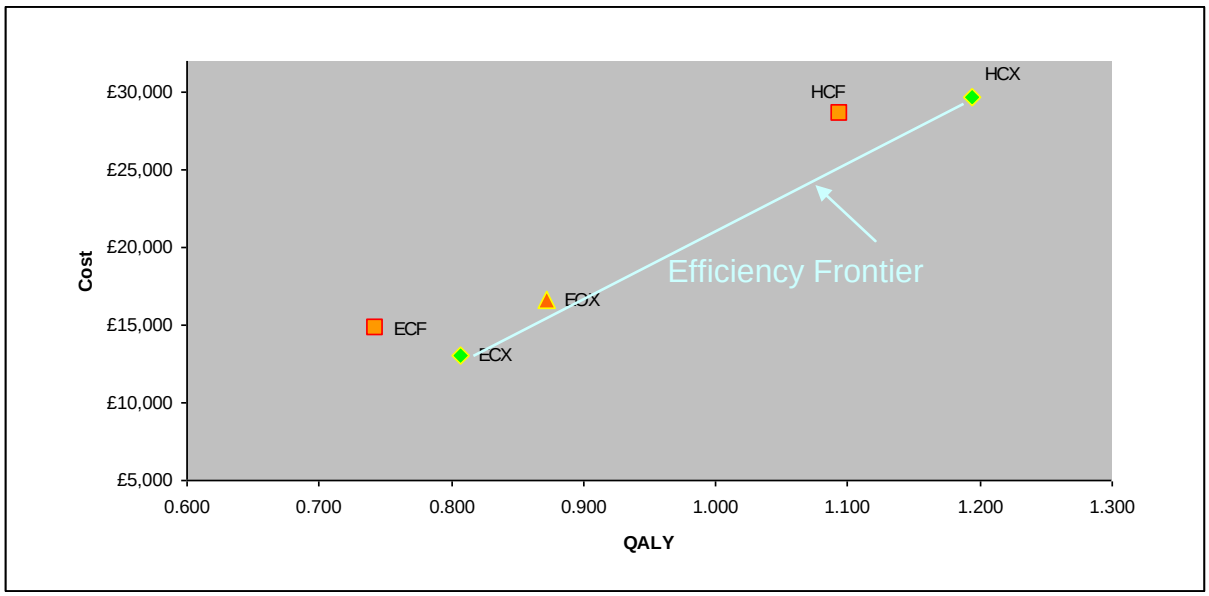


Table 16: Mean Incremental cost per patient

HCX vs ECX	**£16,654**
HCF vs ECF	**£13,090**
HCX vs EOX	**£13,828**

Table 17: Mean ICERs (£/LY) per patient

HCX vs ECX	**£28,109**
HCF vs ECF	**£26,486**
HCX vs EOX	**£25,377**

Table 18: Mean ICERs (£/QALY) per patient

HCX vs ECX	**£42,969**
HCF vs ECF	**£40,608**
HCX vs EOX	**£39,438**

The incremental cost effectiveness ratios (£/QALY) for each of the interventions compared to each of the comparators is provided in Table 18 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 9 above) HCX and ECX results in an incremental cost per QALY of £42,969.

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 £39,438.

Sensitivity Analysis Results

Change to Base-Case Model	ICER
Efficacy:	
Hazard Ratio for HCX/F vs CX/F based on stratified analysis	£49,655
Efficacy based on European subgroup analysis (un-stratified)	£44,598
PFS HR (ECX/EOX) vs CX = 1.1	£38,069
PFS and OS HR (ECX/EOX vs CX) = 0.90	£46,094
Clinical Practice	
Cardiac monitoring only performed at start of treatment for epirubicin but as per SPC for Trastuzumab	£43,080
50% of centres would share vials	£44,874
100% of centres would share vials	£41,696

Probabilistic analysis results at displayed in Appendix 2.

Conclusion

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. As a result the clinical results from the IHC3+ population in ToGA resulted in reduced ICER of approximately £43,000 compared with the licensed population. In addition the ICER was less affected by changes to the key assumptions in the model thus offering greater certainty of it's robustness.

Appendix 2: Result of probabilistic sensitivity analysis

Figure 10: CEAC IHC3+ Analsyis

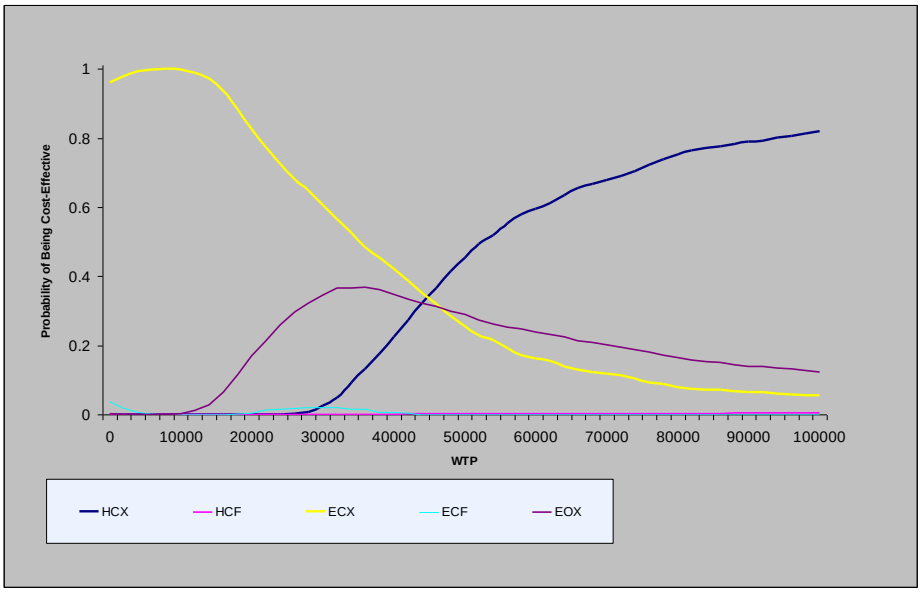
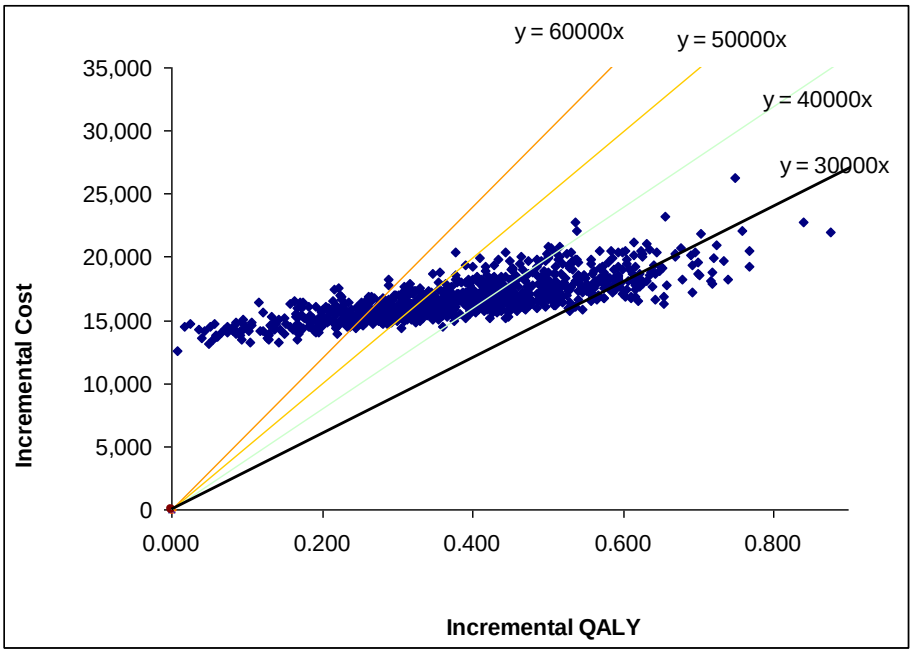
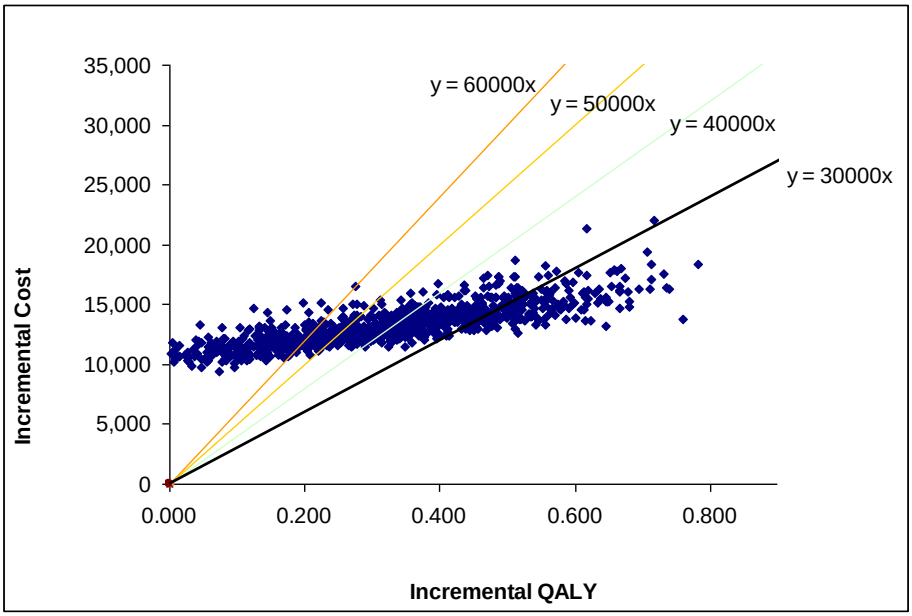


Figure 11: Scatter Plot HCX vs ECX



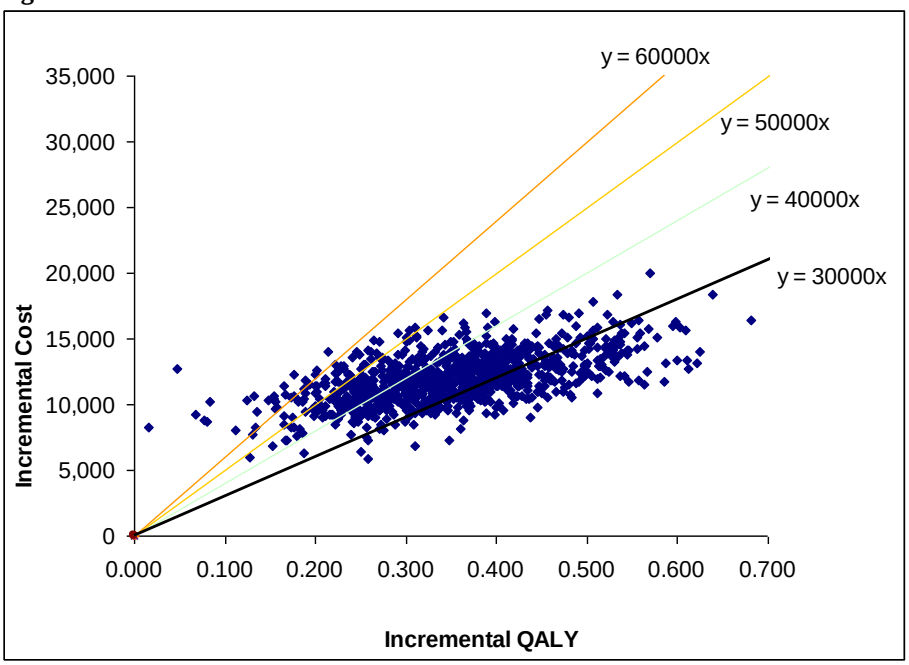
Mean value = 43,970

Figure 12: Scatter Plot HCX vs EOX



Mean value = 42,229

Figure 13: Scatter Plot HCF vs EOF



Mean = £39,623