[redacted]

Wednesday 7th April 2010

[redacted]
Level 1A, City Tower
Piccadilly Plaza
Manchester
M1 4BD

BY E-MAIL

Re: Single Technology Appraisal – Trastuzumab for advanced gastric cancer

Dear [redacted],

Please find below our responses to the ERG clarificaiton questions. Supplied separately as part of our repsonse are the following items:

- a revised economic model including minor amendment.
- a copy of the CSR (sent on CD due to the size of the file)

Please note the amended model relates to Question 30. This requried the incorporation of reduced monitoring costs post-chemotherapy during maintenance treatment with trastuzumab. Whilst this assumption was described in our submission it was not actually operationalised wihtin the model itself. This amendment reduces the base case ICER's from £53,010 and £52,363 for HCX vs ECX and HCF vs ECF respectively to £51,927 and £50,838 respectively. The full results of the revised base case are provided in the appendix.

Finally it has not been possible to perform the EQ-5D analysis with respect to the FAS population within the timescale, but will be supplied by 14th April.

We hope this feedback helps clarify the issues raised by the ERG. If you require any further clarification or information then please do not hesitate to contact us.

Yours sincerely,

[redacted]

A1. **Priority Question: Please provide the clinical study report for the ToGA trial.**

The CSR will follow this document; sent by post due to the size of the electronic file.

Survival Modeling

A2. **Priority Question:** Please provide the full set of parameter estimates as well as the variance-covariance matrices in an Excel file for the other survival distributions (both overall survival and progression free survival) considered for the model, e.g. the exponential and Gompertz distributions.

The information request is contained within the original model sent to NICE within hidden sheets. The sheets of relevance are titled by the name of the corresponding survival function, eg. Gompertz. These sheets have been unhidden in the revised base case model that accompanies this response.

A3. ***Priority Question:*** *Please provide additional cost-effectiveness results assuming these alternative survival distributions.*

Please find below the deterministic ICER's using alternative survival functions for both PFS and OS. The corresponding plots of the survival curves are provided in the appendix.

Table 1: Mean ICERs (£/QALY) per patient

	Base Case (KM and Weibull)	Exponetial	Gompertz	Log Logistic	Log Normal	Weibul
HCX vs ECX	**£51,927**	**£42,710**	**£57,233**	**£48,951**	**£44,310**	**£52,552**
HCF vs ECF	**£50,838**	**£42,540**	**£54,655**	**£48,487**	**£43,857**	**£51,376**
HCX vs EOX	**£40,711**	**£35,541**	**£46,393**	**£39,544**	**£36,179**	**£41,972**

A4. ***Priority Question:*** *Please clarify whether a proportional hazard model was used to model the progression free survival. Please provide data that justifies the use of a proportional hazard model*.

The progression free survial curve utilises the Kaplan-Meier curves for the start of the curve and is then extrapolated using the Weibull parametric function. Kaplan-Meier curves assume proportional hazards. The Weibull extrapolation uses the parameters that were estimated based on all the data and assumes the same shape parameter for both intervention and comparator; as such it also assumes proportional hazards.

In the clinical analsyis Cox regression was used to estimate the hazard ratios between the two arms of the study. Cox regression will only be used if there is no evidence that the assumption of proportional hazards is violated. A rough check of the proportional hazards assumption was performed by plotting the log negative log of the estimated survivor function against log time. If the proportional hazard assumption holds, they can cross at the beginning and the end of the curves, however they should not cross and then cross again as this would suggest a violation of the proportional hazard assumption. The plot of the log negative log of S(t) vs log of time is one of a number of proportional hazards diagnostics. The other diagnostic plots are the Martingale and Deviance plots.

It was deemed that the proportional hazard assumption held and thus the Cox regression was used to estimate the PFS hazard ratio.

The relevant diagnostic results are provided in the attached document below.

A5. ***Priority Question:*** *The current survival estimates are based on the EMEA approved subgroup. Please provide an Excel file with the equivalent parameter estimates (and variance-covariance matrices) for the full set of survival distributions (overall survival and progression free survival) based on the FAS population.*

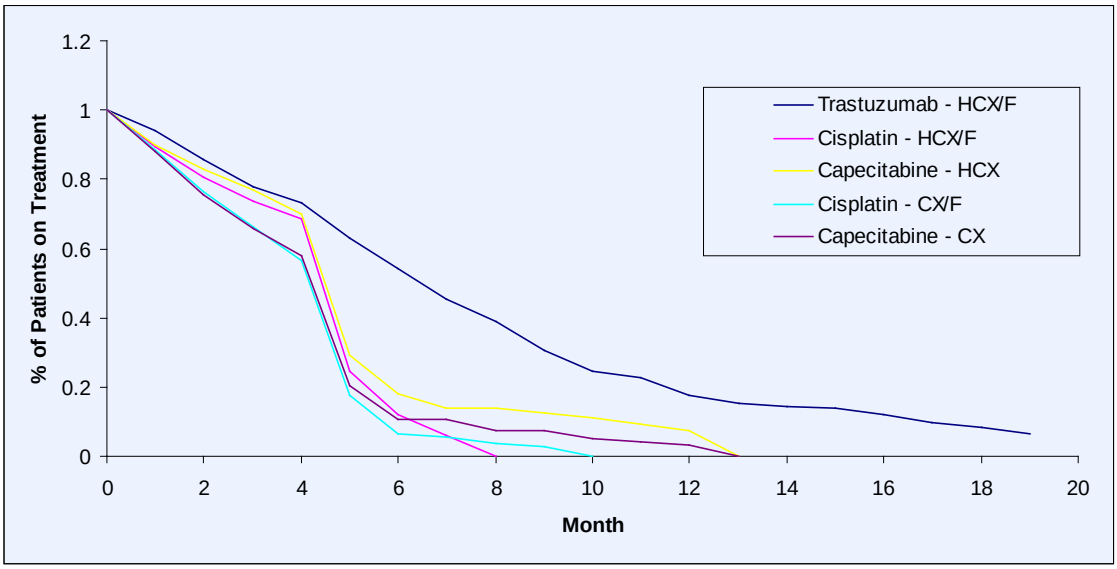
Please find the requested information included in a Excel workbook attached below.

A6. ***Priority Question:*** *Please justify the use of linear regression rather than other approaches to extrapolating the proportion of patients on treatment out of those in progression free survival.*

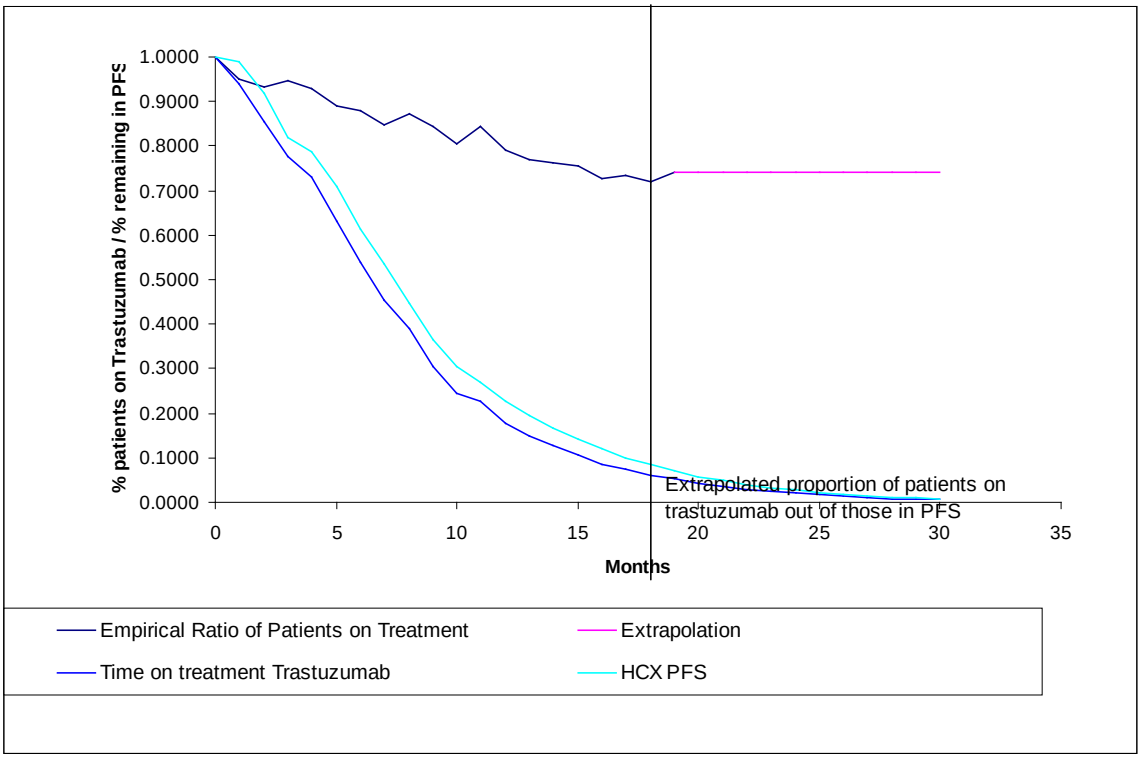
As can be seen from Figure 26 (copied below for ease of reference) in Roche's submission the Kaplan-Meier dose curve for trastuzumab required very little extrapolation. The ratio of patients on treatment over those in PFS declined over time and therefore this ratio was extrapolated assuming a linear continuation of this decline. Sensitivity of the ICER to the assumption that this ratio would continue declining over time was tested in the one-way sensitivity analysis in Roche's submission.

In this alterernative senario it was assumed that the ratio stayed constant from month 19 (the last data point on the dose Kaplan-Meier curve for trastuzumab, see 2nd of two figures below). When assuming that the ratio remains constant from month 19 (at 74%) the ICER only increased by approximately £300 representing only about a 0.6% change from the base case result.

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



Alternative Extrapolation of trastuzumab treatment duration explored in the sensitivity analysis



A7. ***Priority Question:*** *Please provide the full set of parameter estimates as well as the variance-covariance matrices in an Excel file for a parametric fit to the treatment duration of trastuzumab. Please provide the goodness of fit statistics.*

The dose of trastuzumab in the base case model was not based on a parametric fit of the treatment duration of trastuzumab. To incorporate corrolation between dose and PFS, the ratio of patients on treatment out of those in PFS for each month (as estimated for through Kaplan-Meier analysis) was applied to the modelled PFS curve. Since in the base case the Kaplen-Meier for PFS is used until the end of month 12 the assumed dose until the end of month 12 merely represents the area under the Kaplan-Meier dose curve. However since beyond month 12 PFS is exprapolated using the Weibull survival function, dose duration is estimated for this period based on a function of the this Weibull curve. The advantage of this method is that it recognises the relationship between PFS and treatment duration.

Quality of Life

A8. ***Priority Question:*** *Please provide the protocol specifications for the quality of life analysis in the ToGA trial. What was the null hypothesis? Please also provide the results of any statistical analysis of the quality of life data, including any analyses of the EMEA approved subgroup.*

As described in our submission, quality of Life (QoL) was assessed in the two treatment arms as a secondary objective of the ToGA study using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 (Global Health Status, Functioning and Symptom) and QLQ-ST022 (assesses treatment induced changes over time).

Assessments for each questionnaire were made at baseline on day 1 prior to the first dose of study drug and then every three weeks (on day 1 of each cycle prior to dosing) until disease progression. No statistical analysis was planned therefore, no null hypothesis exists. Therefore, the QoL data are of a descriptive nature only.

Descriptive summary statistics for the EMEA approved subgroup are provided below with results comparable to the FAS population.

Figure 1: Global Health Status Score / QoL by cycle (mean +/- SEM) (EORTC QLQ-C30)

Analysis: High HER2 expressing group with extent of disease at screening: recurrent/metastatic

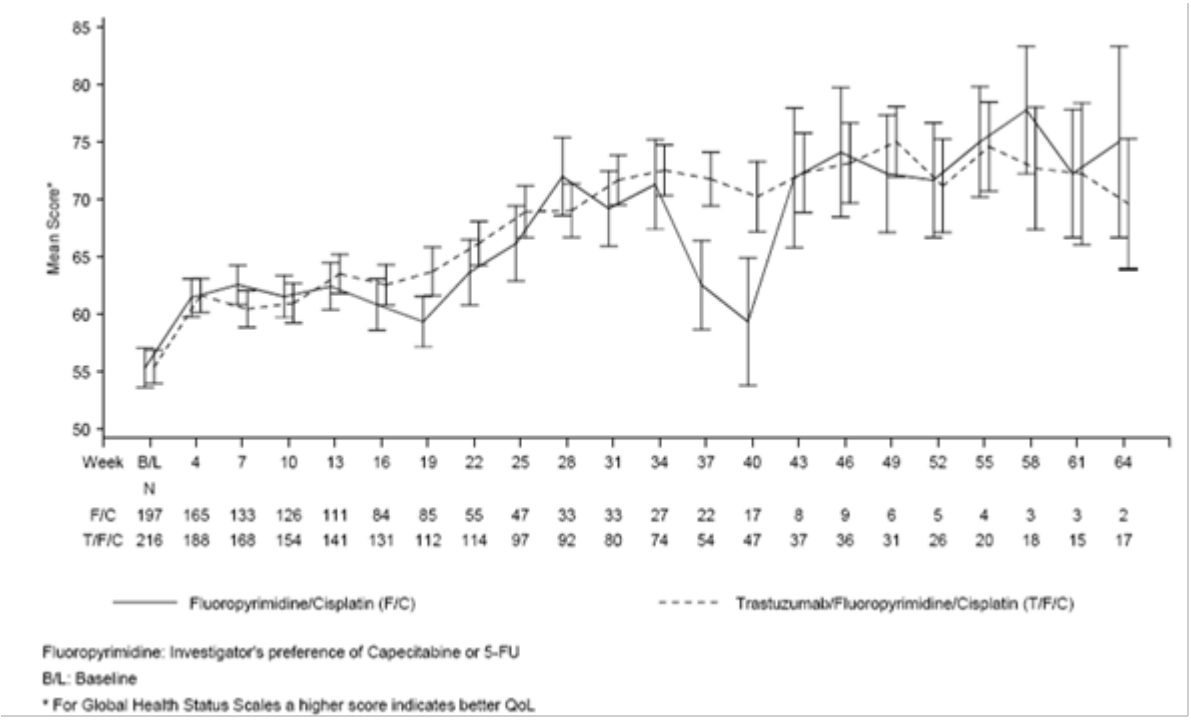


Figure 2: Physical functioning score by cycle (mean +/- SEM) (EORTC QLQ-C30)

Analysis: High HER2 expressing group with extent of disease at screening: recurrent/metastatic

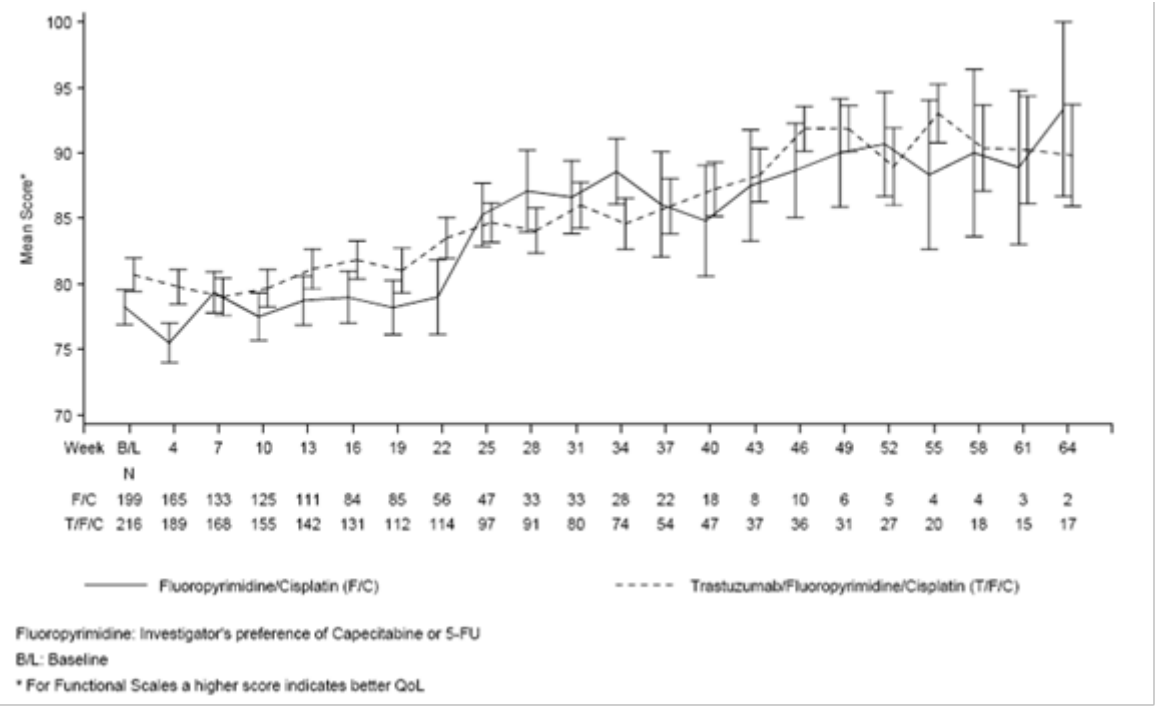
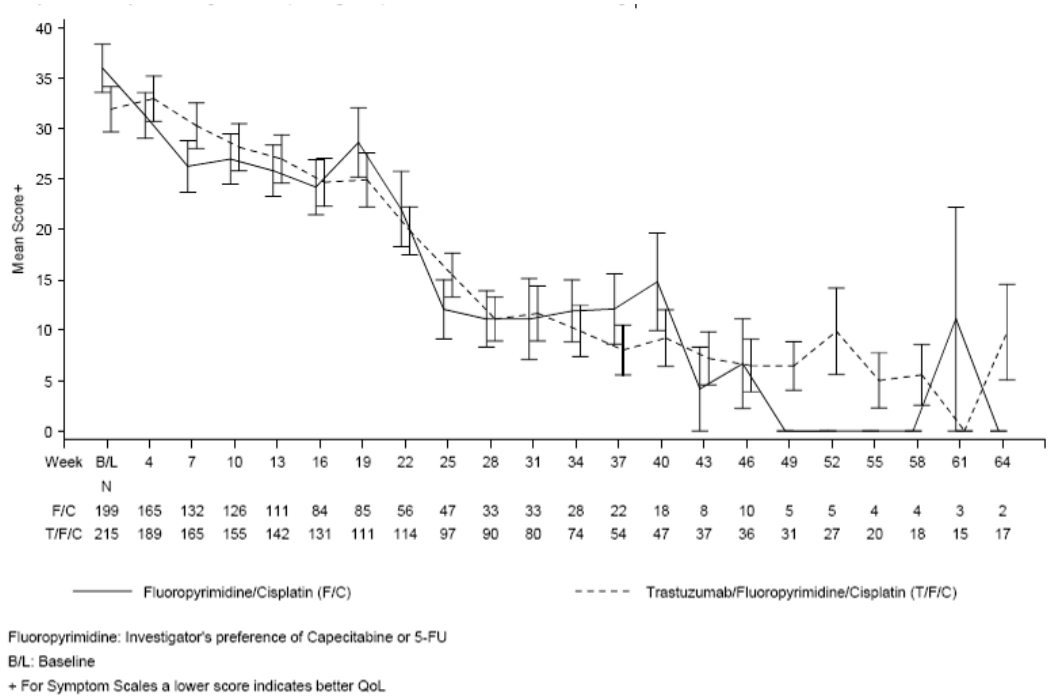


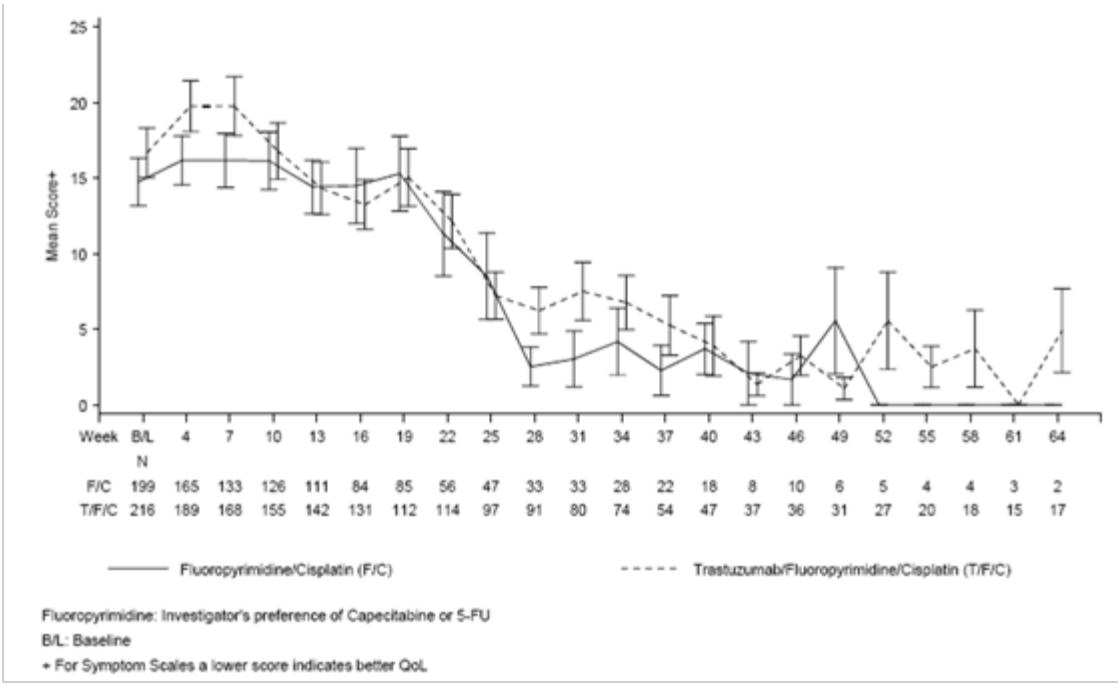
Figure 3: Symptom scores over time (a) appetite loss, (b) nausea/vomiting and (c) constipation (mean +/- SEM)

Analysis: High HER2 expressing group with extent of disease at screening: recurrent/metastatic

a)

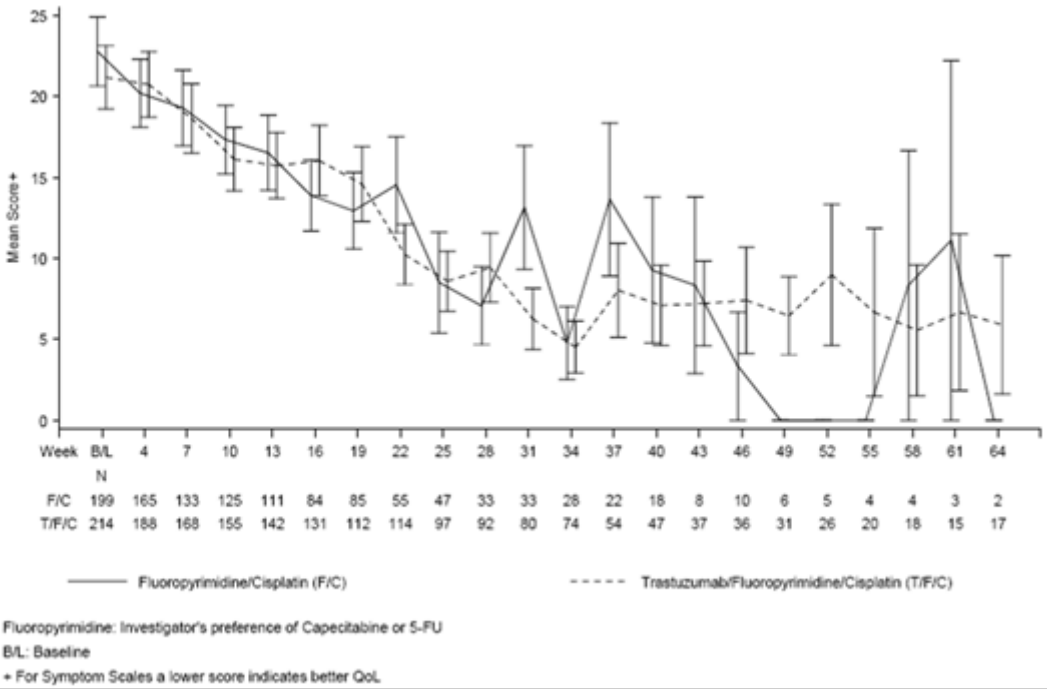


b)



Fluoropyrimidine: Investigator's preference of Capecitabine or 5-FU
B/L: Baseline
+ For Symptom Scales a lower score indicates better QoL

c)



Fluoropyrimidine: Investigator's preference of Capecitabine or 5-FU
B/L: Baseline
+ For Symptom Scales a lower score indicates better QoL

A9. ***Priority Question:*** *Please provide the EQ-5D scores from the ToGA trial over time in both tabular and graphical formats, by treatment for the EMEA approved subgroup and FAS populations. For the tabulated data, please report the mean (and standard error) for each time point.*

The requested plot of the EQ-5D data for the licensed subgroup is shown below. The corresponding information in tablular form is provided in the attached file below.

[redacted]

It has not been possible to perform the FAS analysis of the EQ-5D data in addition to other requested information in the timescale provided. Given that the licensed subgroup is the population under consideration by NICE and forms the primary basis of the submission, provision of this was given priority over the FAS analysis.

Figure 4: EQ-5D by Treatment and Progression Free Assessment Week

A10. ***Priority Question:*** *Please provide tabulated data on the number of censored patients and reasons for censoring over time for the EQ-5D data.*

A mixed model does not utilise censoring and hence no patients were censored from the EQ-5D analysis.

A11. ***Priority Question:*** *Please provide additional results from a complete case analysis of the EQ-5D estimates for the patient sample that was measured at all time points. Please report the mean (and SE) for each time point.*

Please find these results in the file attached in the response to quesiton A9

A12. ***Priority Question:*** *Please describe the mixed model fitted to the utility data in more detail, including model coefficients and output. Please provide goodness of fit test results for alternative models if any were fitted.*

<u>The Analysis of EQ-5D in Study BO18255 (ToGA)</u>

Patients were administered the EQ-5D questionnaire at baseline and there after, every 3 weeks until either disease progression, death or lost to follow-up, which ever occurs first. Patients' EQ-5D raw values for each non-missing assessment were scored using UK tarrifs (The EuroQoL Group [1,2]). Patients that progressed were given the EQ-5D questionnaire on their day of progression. This assessment was excluded when estimating the PFS utility.

<u>Models</u>

Two random slope models using Proc Mixed, SAS version 8.2, were developed to assess the utility value for the progression free and progressed health states:

Model # 1 EQ-5D score = intercept + day of assessment + treatment

Model # 2 EQ-5D score = intercept + day of assessment

The day of assessment and the intercept were incorporated into the model as random effects with patient establishing the block diagonality of the Random matrix. A number of covariance structures for the random matrix were assessed for goodness of fit (Table 2 and 3) by the Akaike Information Criteria (AIC).

Results

The EQ-5D is an instrument designed to measure health states as reported by patients irrespective of treatment. A treatment effect however cannot be ruled out and thus an additional analysis was conducted adding treatment as a fixed effect to the random slope model (Model #1). A treatment effect on patient's EQ-5D scores was not found to be significant (p=0.1429). Therefore, the final utility used for PFS was generated using the unstructured covariance matrix (Table 3).

Table 2: Summary of Covariance Structures and Goodness of Fit (Model # 1)

Utility Estimate	Covariance Structure	Goodness of Fit (AIC)
0.7437	Unstructured	-2076.7
0.7439	Variance Components	-2077.6
0.7589	Autoregressive (1)	-1066.4
0.7437	Heterogeneous Autoregressive (1)	-2076.7
0.7589	Compound Symmetry	-1066.4
0.7578	Toeplitz	-1201.4
0.7437	Heterogeneous Toeplitz	-2076.7

Table 3: Summary of Covariance Structures and Goodness of Fit (Model # 2)

Utility Estimate	Covariance Structure	Goodness of Fit (AIC)
0.7292	Unstructured	-2080.5
0.7296	Variance Components	-2081.4
0.7478	Autoregressive (1)	-1067.1
0.7292	Heterogeneous Autoregressive (1)	-2080.5
0.7478	Compound Symmetry	-1067.1
0.7484	Toeplitz	-1203.6
0.7292	Heterogeneous Toeplitz	-2080.5

References

1. (Nr.ref1). The EuroQol Group. EuroQol-a new facility fort he measurement of health-related quality of life. Health Policy 1990; 16(3): 199-208

2. (Nr.ref2). Szende Á, et al. Psychometric and Utility-based Measures of Health Status of Asthmatic patients with Different Disease Control Level. Pharmacoeconomics 2004; 22(8): 537-547

ToGA trial

A13. Baseline Data:

a) Please provide all data on the baseline characteristics of the EMEA approved subgroup of patients comparable to that provided for the FAS population for factors used in the stratification and other prognostic factors.

Please find below data on the patient demographics, baseline characteristics, and stratification factors for the EMEA licensed subgroup (high HER2 expressors: IHC2+/FISH+ or IHC3+) excluding those patients with locally advanced disease. There were only 10 patients per arm with locally advanced disease in the EMEA license subgroup. The inclusion and exclusion criteria plus the randomisation process used produced two well-balanced patient treatment groups (see Table 4 below).

Table 4: Summary of patient demographics: FAS population compared with high HER2 expressing group (recurrent/metastatic at screening)

	FAS population		EMEA license subgroup (recurrent/metastatic at screening)	
Characteristic	CX/F n=290	CX/F plus trastuzumab n=294	CX/F n=210	CX/F plus trastuzumab n=221
Sex, % Male / Female	75 / 25	77 / 23	72 / 28	76 / 24
Age, median (range) years	59.0 (21-82)	61.0 (23-83)	59.5 (21-82)	61.0 (23-83)
Weight, median (range) kg	60.3 (28-105)	61.5 (35-110)	61.0 (28-101.8)	61.0 (38-105)
Region, n (%) Asia C/S America Europe Other	 166 (56) 26 (9) 95 (32) 9 (3)	 158 (53) 27 (9) 99 (33) 14 (5)	 115 (55) 18 (9) 71 (34) 6 (3)	 116 (52) 22 (10) 72 (33) 11(5)
Type of GC (central assessment) Intestinal Diffuse Mixed	 74.2[a] 8.7[a] 17.1[a]	 76.8[b] 8.9[b] 14.3[b]	 77.8 6.3 15.9	 79.1 7.3 13.6
Prior gastrectomy	21.4	24.1	20.5	24.4

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

As this was an international study, just over 50% of patients were from Asian countries and 33% of patients were from Europe, including the UK.

Although there were more males than females in the study, this is reflected in UK clinical practice as more males than females are diagnosed with stomach cancer (CRUK 2009a) and approximately 80% of the patients recruited into each arm of the REAL-2 study were male (Cunningham 2008).

Baseline characteristics were well balanced across both arms (Table 5).

Table 5: Summary of baseline characteristics: High HER2 expressing group with extent of disease at screening: recurrent/metastatic

	Fluoropyrimidine/ Cisplatin N=210	Trastuzumab/Fluoro- pyrimidine/Cisplatin N=221
Time from First Diagnosis of Gastric Cancer to Randomisation (months)		
n	210	221
Median	1.2	1.5
Range	0.2-65.6	0.3-309.3
Time from Diagnosis of Locally Advanced or Recurrent/Metastatic Disease to Randomisation (months)		
n	210	221
Median	0.9	1.0
Range	0.3-7.5	0.2-26.7
Extent of Disease at Study Entry		
n	210	221
Locally Advanced	0 (0.0%)	0 (0.0%)
Metastatic	210 (100.0%)	221 (100.0%)
Primary Site		
n	210	221
Stomach	180 (85.7%)	180 (81.4%)
GE Junction	30 (14.3%)	41 (18.6%)
Type of Gastric Cancer (assessed by local laboratory)		
n	210	221
Intestinal	101 (48.1%)	105 (47.5%)
Diffuse	60 (28.6%)	75 (33.9%)
Not Assessed	49 (23.3%)	41 (18.6%)
Type of Gastric Cancer (assessed by central laboratory)		
n	207	220
Intestinal	161 (77.8%)	174 (79.1%)
Diffuse	13 (6.3%)	16 (7.3%)
Mixed	33 (15.9%)	30 (13.6%)
Measurability		
n	210	221
Measurable	196 (93.3%)	204 (92.3%)
Non-measurable	14 (6.7%)	17 (7.7%)
Prior Radiotherapy		
n	210	221
Yes	5 (2.4%)	3 (1.4%)
No	205 (97.6%)	218 (98.6%)
Prior Anthracycline Therapy		
n	210	221
Yes	2 (1.0%)	2 (0.9%)
No	208 (99.0%)	219 (99.1%)
Prior Chemotherapy		
n	210	221
Yes	10 (4.8%)	17 (7.7%)
No	200 (95.2%)	204 (92.3%)
Prior Gastrectomy		
n	210	221
Yes	43 (20.5%)	54 (24.4%)
No	167 (79.5%)	167 (75.6%)
ECOG Performance Status		
n	210	221
0	78 (37.1%)	82 (37.1%)
1	116 (55.2%)	120 (54.3%)
2	16 (7.6%)	19 (8.6%)

Fluoropyrimidine: Investigator preference of Capecitabine or 5-FU

Prior Gastrectomy includes Preferred Terms: Gastrectomy and Oesophagogastrectomy

	Fluoropyrimidine/ Cisplatin N=210	Trastuzumab/Fluoro- pyrimidine/Cisplatin N=221
Number of Lesions per Patient		
n	210	221
1-4	75 (35.7%)	96 (43.4%)
>4	135 (64.3%)	125 (56.6%)
Median	6	5
Range	1 - 16	1 - 20
Number of Sites per Patient		
n	210	221
1-2	103 (49.0%)	108 (48.9%)
>2	107 (51.0%)	113 (51.1%)
Median	3	3
Range	1 - 8	1 - 7
Visceral (Lung or Liver) Metastases		
n	210	221
Yes	131 (62.4%)	131 (59.3%)
No	79 (37.6%)	90 (40.7%)

Fluoropyrimidine: Investigator preference of Capecitabine or 5-FU
* Identical sites will be counted only once per patient

The two groups were well balanced in terms of the stratification factors.

Table 6: Summary of stratification factors: High HER2 expressing group with extent of disease at screening: recurrent/metastatic

	Fluoropyrimidine/ Cisplatin N=210	Trastuzumab/Fluoro- pyrimidine/Cisplatin N=221
Extent of Disease		
n	210	221
Metastatic	210 (100.0%)	221 (100.0%)
Primary Site		
n	210	221
Stomach	180 (85.7%)	180 (81.4%)
GE Junction	30 (14.3%)	41 (18.6%)
Measurability		
n	210	221
Measurable	196 (93.3%)	204 (92.3%)
Non-measurable	14 (6.7%)	17 (7.7%)
ECOG Performance Status		
n	210	221
0-1	194 (92.4%)	202 (91.4%)
2	16 (7.6%)	19 (8.6%)
Chemotherapy Regimen		
n	210	221
Capecitabine	183 (87.1%)	193 (87.3%)
5-FU	27 (12.9%)	28 (12.7%)

Fluoropyrimidine: Investigator preference of Capecitabine or 5-FU

b) Please provide a breakdown of the CF/CX ratio for each arm of the trial in the EMEA approved subgroup.

The CF/CX ratio in the EMEA approved subgroup is in line with the overall FAS population (

Table **7**).

Table 7: CF/CX ratio for each study arm of the FAS population and EMEA subgroup (recurrent/metastatic)

Chemotharepy regimen	Fluoropyrimidine / cisplatin	Trastuzumab / fluoropyrimidine / cisplatin
FAS population		
n	290	294
Capecitabine	255 (87.9%)	256 (87.1%)
5-FU	35 (12.1%)	38 (12.9%)
EMEA license subgroup		
n	210	221
Capecitabine	183 (87.1%)	193 (87.3%)
5-FU	27 (12.9%)	28 (12.7%)

c) Please confirm that there was no maximum age for enrolment in the trial.

According to the trial protocol, patients ≥ 18 years were eligible for inclusion in the ToGA trial and there was no upper age limit that prohibited entry.

d) Please provide the number of participating UK centres and the number of patients enrolled from the UK

A total of 594 patients were randomised in the ToGA study at 122 centres in 24 countries (range 1-16 centres per country), including six centres from the UK. Out of all European patients (n=194), 23 patients were recruited from the UK; 13 patients (4.4%) were randomized to the CX/F arm, and 10 patients (4.3%) to the HCX/F arm.

A14. Please provide all results data for the EMEA approved subgroup of patients comparable to that provided for the FAS population.

The results for the primary and secondary endpoints (OS, PFS, TTP, DoR, ORR, CBR) for the EMEA approved high HER expressing subgroup, excluding the 10 patients with locally advanced disease in each arm, are provided below (Tables 8-13). The results clearly demonstrate that the addition of trastuzumab to CX/F chemotherapy improves the primary endpoint of overall survival and all secondary efficacy parameters analysed in patients whose tumours express high levels of HER2 (IHC2+/FISH+ or IHC3+).

Table 8: Hazard ratios and 95% Confidence Interval by subgroup for overall survival for patients with recurrent/metastatic disease at screening

		Fluoropyrimidine/ Cisplatin			Trastuzumab/Fluoro- pyrimidine/Cisplatin				
Subgroup		Patients per group	N Events	Median time	Patients per group	N Events	Median time	Hazard Ratio	95% CI for Hazard Ratio
All		280	179	11.0	284	161	13.8	0.73	[0.59;0.90]
HER2 Result	FISH+/IHC0 or 1+	68	45	8.6	58	40	10.0	1.01	[0.66;1.56]
	FISH- or + or no result/IHC2+ or 3+	210	133	11.7	221	117	16.0	0.65	[0.50;0.83]

Fluoropyrimidine: Investigator preference of Capecitabine or 5-FU

Table 9: Hazard ratios and 95% Confidence Interval by subgroup for time to progression for patients with recurrent/metastatic disease at screening

		Fluoropyrimidine/ Cisplatin			Trastuzumab/Fluoro- pyrimidine/Cisplatin				
Subgroup		Patients per group	N Events	Median time	Patients per group	N Events	Median time	Hazard Ratio	95% CI for Hazard Ratio
All		280	213	5.6	284	201	6.9	0.70	[0.57;0.85]
HER2 Result	FISH+/IHC0 or 1+	68	56	4.8	58	46	5.5	0.97	[0.66;1.44]
	FISH- or + or no result/IHC2+ or 3+	210	156	5.7	221	152	7.8	0.64	[0.51;0.80]

Fluoropyrimidine: Investigator preference of Capecitabine or 5-FU

Table 10: Hazard ratios and 95% Confidence Interval by subgroup for progression-free survival for patients with recurrent/metastatic disease at screening

		Fluoropyrimidine/ Cisplatin			Trastuzumab/Fluoro-pyrimidine/Cisplatin				
Subgroup		Patients per group	N Events	Median time	Patients per group	N Events	Median time	Hazard Ratio	95% CI for Hazard Ratio
All		280	230	5.4	284	219	6.6	0.71	[0.59;0.85]
HER2 Result	FISH+/IHC0 or 1+	68	60	4.6	58	48	5.3	0.97	[0.66;1.42]
	FISH- or + or no result/IHC2+ or 3+	210	169	5.5	221	166	7.5	0.65	[0.52;0.80]

Fluoropyrimidine: Investigator preference of Capecitabine or 5-FU

Table 11: Hazard ratios and 95% Confidence Interval by subgroup for duration of response for patients with recurrent/metastatic disease at screening

		Fluoropyrimidine/ Cisplatin			Trastuzumab/Fluoro-pyrimidine/Cisplatin				
Subgroup		Patients per group	N Events	Median time	Patients per group	N Events	Median time	Hazard Ratio	95% CI for Hazard Ratio
All		99	80	4.8	134	97	6.9	0.55	[0.40;0.74]
HER2 Result	FISH+/IHC0 or 1+	22	18	4.5	20	15	4.7	0.76	[0.38;1.52]
	FISH- or + or no result/IHC2+ or 3+	76	61	4.9	113	81	7.0	0.52	[0.37;0.72]

Fluoropyrimidine: Investigator preference of Capecitabine or 5-FU

Table 12: Hazard ratios and 95% Confidence Interval by subgroup for overall tumour response for patients with recurrent/metastatic disease at screening

		Fluoropyrimidine/ Cisplatin			Trastuzumab/Fluoro-pyrimidine/Cisplatin				
Subgroup		Patients per group	N Responder	%	Patients per group	N Responder	%	Odds Ratio	95% CI for Odds Ratio
All		280	99	35.36	284	134	47.18	1.63	[1.16;2.29]
HER2 Result	FISH+/IHC0 or 1+	68	22	32.35	58	20	34.48	1.10	[0.52;2.31]
	FISH- or + or no result/IHC2+ or 3+	210	76	36.19	221	113	51.13	1.84	[1.25;2.71]

Fluoropyrimidine: Investigator preference of Capecitabine or 5-FU

Table 13: Hazard ratios and 95% Confidence Interval by subgroup for clinical benefit rate for patients with recurrent/metastatic disease at screening

Subgroup		Fluoropyrimidine/ Cisplatin Patients per group	N Responder	%	Trastuzumab/Fluoro-pyrimidine/Cisplatin Patients per group	N Responder	%	Odds Ratio	95% CI for Odds Ratio
All		280	194	69.29	284	224	78.87	1.65	[1.13;2.42]
HER2 Result	FISH+/IHC0 or 1+	68	46	67.65	58	45	77.59	1.66	[0.74;3.68]
	FISH- or + or no result/IHC2+ or 3+	210	147	70.00	221	176	79.64	1.68	[1.08;2.60]

Fluoropyrimidine: Investigator preference of Capecitabine or 5-FU

e) Please clarify the definition of the primary analysis; page 55 states that the FAS population is used but page 56 defines the primary analysis as being based on the per protocol population. Where analyses of the per protocol rather than the ITT population are used, please supply the ITT data.

We apologise for any confusion caused on this point. As described on page 55 of our submission, the primary patient population analysed was the full analysis set (FAS) and the analyses provided in the submission were based on the FAS unless otherwise stated. A Per Protocol analysis (based on the FAS but excluding randomised patients with major protocol violations) was also carried out. The results of this analsyis [redacted]

Indirect Comparison

A15. Please clarify the systematic review process for the indirect treatment comparison including the following issues:

i) How were the interventions in the inclusion criteria selected?

ii) What were the treatment regimens "of interest"?

iii) Why was quality of life not considered as an outcome?

The interventions initially included were selected through consultation with multiple Roche affiliates to determine which regimens are used in each of the countries. Hence there are regimens listed as intervnetions on page 78 of Roche's submission that are not of relevance to the UK NHS. The regimens of interests specified by the UK affiliate are those identified as relevant comparators based on current usage in the UK NHS (ie primarily ECX and ECF and to a less exstent EOX)

On page 79 of Roche's submission where it states "of interest" this refers to the comparators of interest to the appraisal ie ECX, ECF and EOX and the comparators in the ToGA study (CX and CF).

The purpose of the literature search was to inform the relative efficacy in terms of survival assumed in the economic analysis. Hence we did not consider including quality of life as it would not have answered this question.

A16. Please provide a list of the studies excluded at each stage during the indirect comparison review process (p 79).

The list of studies is provided in the attached files below

A17. Please provide data for all arms of each trial used to illustrate the efficacy of each chemotherapy regimen; this should include numeric and statistical information as well as graphical illustration.

Figure 5: Overview of the design of included studies (n=4)

Study	Treatment arms	Study design	Patient population	Inclusion criteria	Exclusion criteria	Survival	Trial duration	Length of follow-up	Dose, frequency and duration of treatment
Cunningham (2008, REAL2)	ECF ECX EOF EOX	Randomised, multicenter study	adenocarcinoma, squamous-cell carcinoma, or undifferentiated carcinoma of the esophagus, gastroesophageal junction, or stomach	locally advanced (inoperable) or metastatic; ECOG of 0 to 2; and adequate renal, hepatic, and hematologic function.	previous chemotherapy or radiotherapy, uncontrolled cardiac disease	OS, PFS	June 2000 and May 2005	Median: 17.1 months	on day 1 of every 3-week cycle, epirubicin (50 mg/m2); cisplatin (60 mg/m2) given with hydration in the ECF and ECX groups, and oxaliplatin (130 mg/m2) intravenously in the EOF and EOX groups. Fluorouracil (at a daily dose of 200 mg /m2) and capecitabine (at a twice daily dose of 625 mg /m2) were given throughout treatment in the appropriate groups
Kim (2001)	FP	Randomised phase III trial	gastric cancer	Nr	nr	OS, PFS	Mar 1997 to Apr 2000	nr	5FU 1,000 mg/m2 IV on days 1 to 5, and cisplatin 60 mg/m2 IV on day 1 every 4 weeks
	ECF								epirubicin 50 mgIm2 on day 1, cisplatin 60 mg/m2 on day 1, and 5-FU 1,000 mg/rn2 IV on days 1 to 5 every 4 weeks
Yun (2010)	XP	randomised phase II study	gastric cancer	Confirmed, measurable AGC. ECOG <=2, adequate bone marrow, hepatic, cardiac and renal functions. Only adjuvant chemotherapy that had been completed more than 6 months before registration and no radiotherapy within 4 weeks before registration.	Severe comorbid illness, including cardiac dysfunction, or a history of anaphylaxis.	PFS	During 2008	Median treatment duration: 4.4 months in the XP arm, 4.2 months in the ECX arm	cisplatin 75 mg/m2 on day 1, and oral capecitabine 1000 mg/m2 twice daily as an intermittent regimen of 2 weeks of treatment followed by a 1-week rest, every 3 weeks
	ECX								epirubicin 50 mg/m2 was administered on day 1 in addition to regular XP regimen every 3 weeks
Tobe (1992)	FP	Phase II, randomised, multicenter	gastric cancer	recurrent or metastatic, ECOG<3 (ECOG scale), progressive disease with lesions that could be measured or evaluated	ECOG score 4, prior chemotherapy, heart disease or a concomitant malignant disease	OS, PFS	January 1990 and September 1991	nr	50 mg of CDDP on day 1 and 250 mg of 5-FU on days 2-5 repeated every 2 weeks until PD
	ECF								30 mg/m2 of EPIR on day 2 in addition to the regular FP regimen repeated very 2 weeks until PD

Figure 6: Overview of the patient characteristics of included studies (n=4)

Study	Treatment arm	Male	Median age (years, range)	Intestinal GC	Diffuse GC	Prior surgery	Metastatic disease	Primary site: stomach	Primary site: GE junction	Primary site: esophagus	ECOG PS 0	ECOG PS 1	ECOG PS 2	KPS 90	KPS 80	KPS 70	1 organ involved	2 organs involved	>2 organs involved	HER-2 positive	Randomized population (N)	ITT population (N)	Per protocol population
Cunningham (2008, REAL2)	ECF	81	65 (22-83)	nr	nr	7.6	79.5	36.1	28.9	34.9	88.4 (0-1)	11.6	nr	nr	nr	nr	nr	Nr	nr	263	263	249
	ECX	81	64 (25-82)			7.5	76.8	42.3	28.2	29.5	87.6	12.4								250	250	241
	EOF	81	61 (33-78)			7.7	77	37	23.4	39.6	91.5	8.5								245	245	235
	EOX	83	62 (25-80)			8.8	75.7	43.5	22.2	34.3	90	10								244	244	239
Kim (2001)	FP	70	56.5	nr	nr	nr	95.0	nr	nr	nr	88.3 (0-1)	nr	nr	nr	nr	nr	nr	nr	nr	nr	60	60	nr
	ECF	75	55				95.0				90										61	60	
Yun (2010)	XP	72	58 (33-75)	nr	nr	34	nr	nr	nr	nr	87	8	nr	nr	nr	nr	nr	nr	nr	nr	47	45	nr
	ECX	64	55 (35-71)			36					91	2									44	44	
Tobe (1992)	FP	54	nr	nr	nr	nr	nr	nr	nr	nr	46.2 (0-1)	38.5 (2-3)	nr	nr	nr	nr	nr	nr	nr	nr	29	26	21
	ECF	67									50 (0-1)	40 (2-3)								31	30	22	

(Data reported is the percentage of the total patient population in each trial arm, unless otherwise stated)

Figure 7: Overview of the outcomes reported in the included studies (n=4)

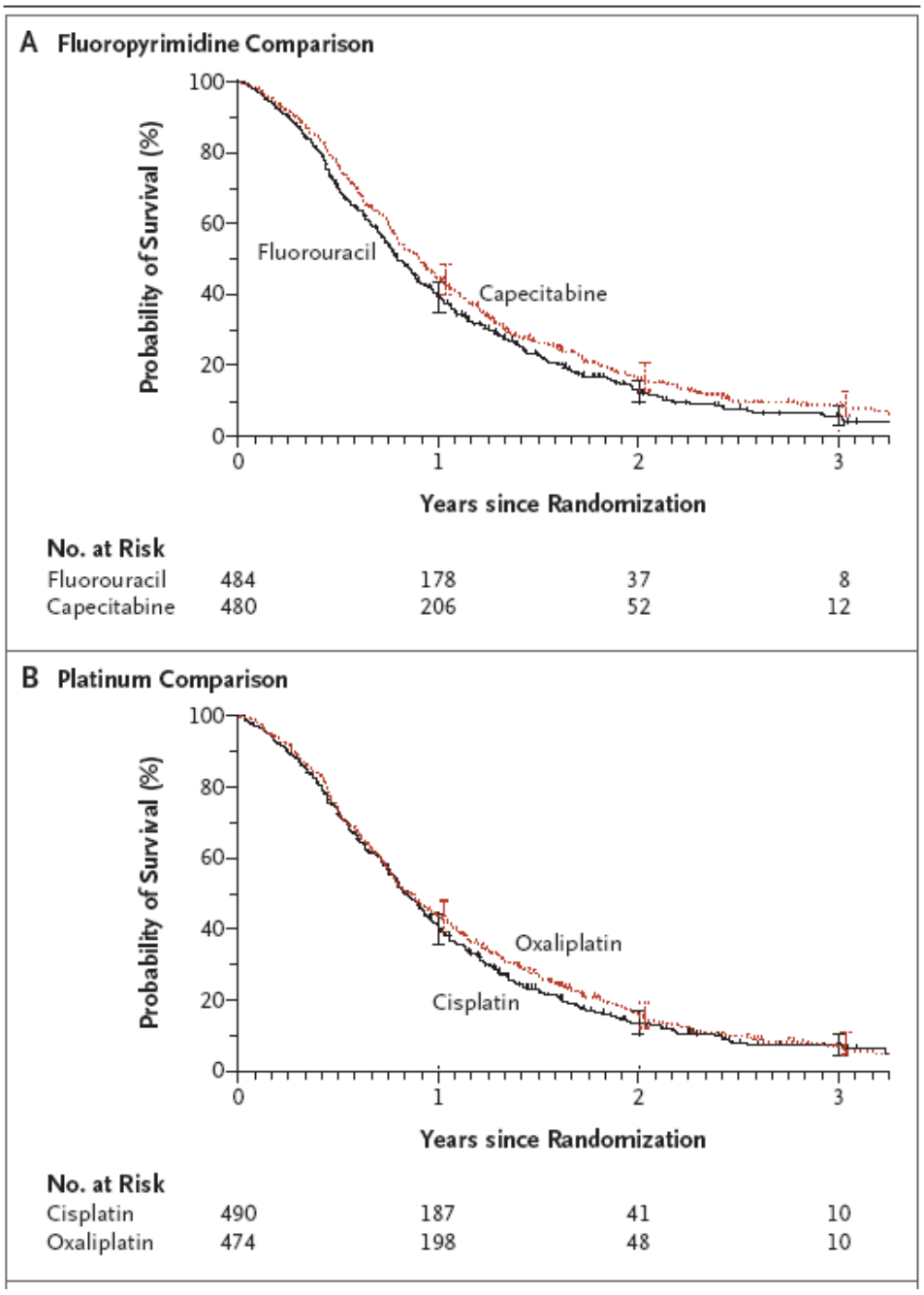
Study	Treatment arms	Hazard Ratio for OS	95% CIs	OS at one year (%)	OS at 1 year (n/N)	Hazard Ratio for PFS	95% CIs	PFS at 6 months (%)	PFS at 6 months (n/N)
Cunningham (2008, REAL2)	EOX and EOF	0.92 (O vs C)	0.80 - 1.10	43.9	215/489	0.92 (O vs C)	0.80 - 1.04	nr	nr
	ECX and ECF			40.1	196/513			nr	nr
	EOF and ECF	0.86 (X vs F)	0.80 - 0.99	44.6	221/495	0.92 (X vs F)	0.81 - 1.05	nr	nr
	EOX and ECX			39.4	195/494				
Kim (2001)	FP	0.83 (ECF vs FP taken from Wagner 2005)	0.42-1.61	nr	nr	nr	nr	nr	nr
	ECF								
Yun (2010)	XP	nr	nr	nr	nr	0.96 (ECX vs XP)	0.58-1.57	56	25/45
	ECX							59	26/44
Tobe (1992)	FP	0.57 (ECF vs FP, taken from Wagner 2005)	0.27-1.20	13	3/22	nr	nr	nr	nr
	ECF			27	7/25				

Graphical overview of the outcomes reported in the included studies

Cunningham (2008, REAL2):

The Kaplin-Meier plots for the REAL-2 sudy are shown below. Panel A shows overall survival according to a two by two comparison in the per-protocol population between the capecitabine and fluorouracil regimens; the hazard ratio for death in the capecitabine groups was 0.86 (95% CI, 0.80 to 0.99). Panel B shows overall survival according to a two-by-two comparison in the per-protocol population between the oxaliplatin and cisplatin regimens; the hazard ratio for death in the oxaliplatin groups was 0.92 (95% CI, 0.80 to 1.10).

Figure 8: Kaplan-Meier Estimates of Overall Survival from main study publication



Kim (2001): data only reported as abstract, no graphical display of efficacy was provided

Figure 9: Yun (2010): Kaplan-Meier estimates for Progression-Free survival from the study publication. Overall survival data were not reported

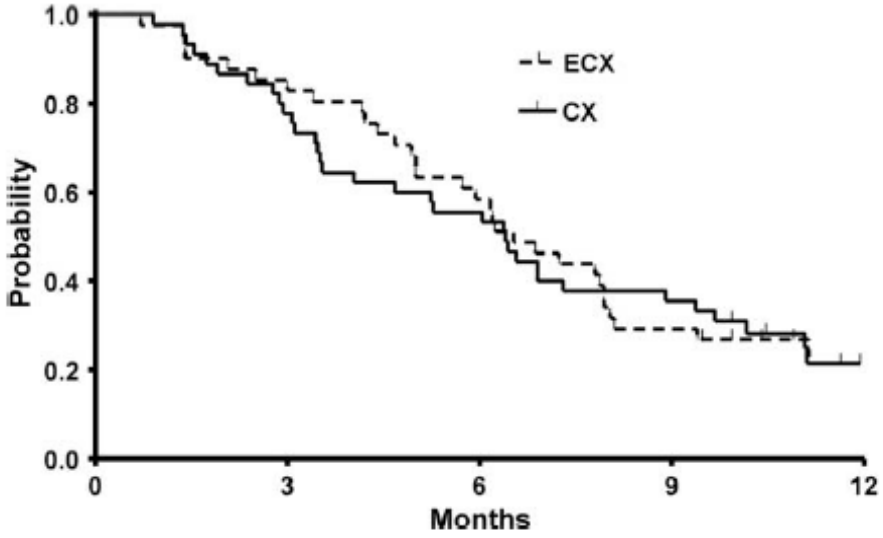


Fig. 1 – Kaplan–Meier estimates for progression-free survival by the treatment arm.

Figure 10: Tobe (1992): OS curves from main study publication

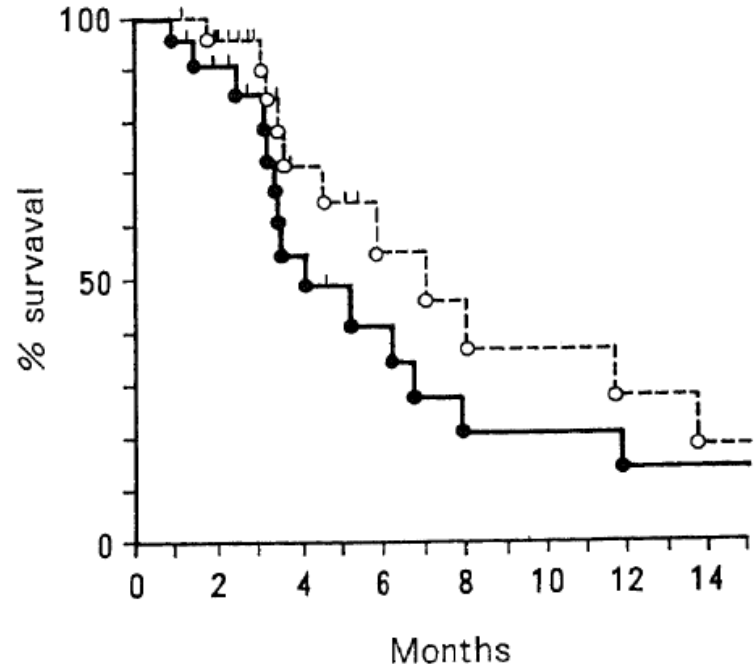


Figure 1. *Overall survival curves.* ●–●, *group A (FP, n=22);* ○–○, *group B (FPEPIR, n=25). The 6 month and 1 year survival rates, and median survival periods were 34%, 13% and 120 days for group A, and 55%, 27% and 210 days for group B, respectively.*

A18. The network diagram supplied (p80) does not appear to reflect the comparisons assessed by the included studies, including ToGA. Were separate analyses of HCF versus CF and HCX versus CX conducted? If so please supply these.

Separate analyses of HCX versux CF and HCX versus CF were not conducted however given that capecitabine has been demonstrated to provide a survival advantage compared to 5-FU it is nessessary to split out CF and CX and HCF and HCX in the network. There was no significant interaction observed in the ToGA study between the base chemotherapy and treatment (p-value: 0.6328) hence it was considered reasonable to assume that the treatment effect of adding trastuzumab is the same when added to either CF or CX.

A19. The overall survival hazard ratio for EOX in comparison with ECX in the sensitivity analysis quoted in Table 32, page 147, was 0.92. In the REAL II publication, this hazard ratio was the result of comparing the two oxaliplatin groups with the cisplatin groups. It was not the result of comparing EOX with ECX. Please provide the progression free survival and overall survival hazard ratios and confidence intervals for EOX in comparison with ECX or additional support for the current assumption.

The REAL-2 study had a 2 by 2 design. The primary endpoint was to demonstrate non-inferiority of overall survival for the therapies containing capecitabine as compared with fluorouracil (a comparison of ECX and EOX vs ECF and EOF) and for those containing oxaliplatin as compared with cisplatin (a comparison of EOF plus EOX vs ECF and ECX).

A pairwise comparason between EOX vs ECX represents a subgroup analysis and has the disadvantage of analysing only half of the patients in the study. This subgroup analysis would be appropriate if it was believed an interaction existed between the fluoropyrimidine and platinum groups, however the test among the treatment variables in the pooled two-by-two comparisons did not reveal any such interaction (P = 0.36). Hence the results of the primary analysis (ie from the 2 by 2 comparisons) are considered the most robust.

A20. Search strategies:

a) Was a search for non-randomised trials conducted? If so please supply details.

No search was made for non-randomised trials

b) Please confirm that the search strategy on pages 215-216 (Appendix C2) is that which is referenced on page 77 as section 10.8 in Appendix 3.

Yes, that is correct, apologies for the confusion.

c) Please supply the following information relating to this search:

i) Search strategies for the other databases (EMBASE, SciSearch, Cochrane Library).

ii) Confirm which interface was used to conduct the search

iii) Explain lines 15-17 of the strategy: do these relate to database search including other databases?

The search was conducted in data star. The search strategy on pages 215-216 (Appendix C2) was adapted for the other databases mentioned and results were combined in lines 15-17 of the search strategy.

Current UK Practice

A21. In Table 17, page 113 it is reported that 17.8% of metastatic gastric cancer patients are estimated to be eligible for trastuzumab (IHC2+ FISH+ or IHC3+) and 66% of eligible patients are IHC2+ and require a FISH test. Please provide a summary of factors known to influence the positivity rate in clinical practice and provide any additional supporting evidence on the potential range around these estimates from other sources.

The ToGA trial assessed almost 3,812 tumour samples for HER2 status in a central laboratory and therefore provides the most robust data set of HER2 positivity rates in patients with mGC. Furthermore, ToGA is the first phase III trial to provide information on the incidence of HER2 positivity in a prospective manner in this patient population.

Based on the results from the ToGA study the rate of HER2 positivity for the high expressing groups (IHC2+/FISH+ or IHC3+) is 17.8% (Bang 2009), this may vary according to the tumour site (stomach or GOJ) and histological subtype (Bang 2009). It is reasonable to assume that the rates of HER2 positivity in the UK are comparable to the ToGA trial as this provides the largest and most comprehensive data-set and there are insufficient data to suggest otherwise.

A22. Please provide additional data on the percentage of tests for each of IHC and FISH that needed to be repeated (i.e. test failures due to inadequate tissue sample) in the ToGA study. Please provide any additional data available on the rate of IHC/FISH test failures from other metastatic gastric cancer studies.

Retest incidence from the ToGA screening phase

Patients were eligible for ToGA if assessed as either HER2 positive by an IHC score of 3+ or a positive FISH result. Hence the two tests (IHC and FISH)- were conducted in parallel. In case of failure, one repeat test was performed for the respective assay. The failure rate as given below describes the total failure i.e. primary and repeat tests failed. The number of tests that failed initially but were succesfull upon repetition has not been captured.

For ToGA in total 3,815 patients have been registered for screening at the central pathology lab "TARGOS" in Kassel Germany. 3 patients had to be excluded from ToGA resulting in a total of 3812 samples from 3803 patients being screened (9 patients had double entries). The breakdown for testing failures is given below:

FISH failures:

485 in total, 125 due to insufficient or no tumour tissue and 360 due to sample specific technical failure.

IHC failures:

176 in total, 156 due to insufficient or no tumour tissue and 20 due to sample specific technical failure

The failure rate due to insufficient/no tumour material is to a large extent artificial as it is mainly caused by the fast turn around time that was mandated by the ToGA protocol (results had to be reported within two subsequent working days). This turn around time required that often histopathological assessments were conducted in parallel not sequentially, i.e. H&E staining, IHC and FISH tests were processed simultaneously. Routinely H&E staining is done first to assess tumour tissue and the amount of tumour cells present. If the first H&E staining reveals tumour material as insufficient for further testing fresh slices would be cut from the tissue block. This was often not feasible in ToGA hence in several cases insufficient tumour material lead to test failure that could be avoided when applying sequential staining steps as done in routine setting.

Taking this into account the failure rate for FISH and IHC was calculated based on technical failures only, these are 9.4% for FISH and 0.6% for IHC. The relatively high rate of technical failure for FISH (e.g. signal too weak, background staining) might in part be due to pre-analytical processes at the local site e.g. suboptimal fixation procedures.

Retest results from pre-validation study

At Roche there is only one additional data set available providing data on HER2 test failures. These data came from the pre-validation study that was set up before ToGA was initiated with the objective to validate the HER2 testing procedure on gastric cancer tissue (see Hofmann et al., histopathology 2008). In this prevalidation trial the failure rate was 5.6%. In total 10 out of 178 samples failed either IHC or FISH HER2 tests for the following reasons: technical failure with FISH (N=3), insufficient tumour material (N=4) and being an inappropriate sample type for the study (N=3). As Roche did not conduct phase I nor phase II trial evaluating trastuzumab in mGC prior to ToGA we cannot provide further data on HER2 test failure rates.

UK Clincal Practice

Source BioScience (*http://www.sourcebioscience.com/default.aspx;* One of the main suppliers of the IHC and FISH testing in the UK) estimate that around 1% of IHC and between 3%-5% of FISH tests require retesting due to a technical error. The cost of any such retesting is absorbed by the company. In addition they indcated that only very infrequently did they receive inadequate tissue sample requireing a replacement specimin.

Summary

The rate of testing failures due to insufficient/no tumour material was recorded in ToGA as 3% and 4% for FISH and IHC respectively. However in clincal practice this rate is expected to be lower. Indeed one of the main suppliers of HER2 testing in the UK, Source Bioscience, confirm that they very infrequently receive inadquate/ no tumour samples.

The rate of technical falure reported in ToGA for the IHC test was <1% which is consistented with that estimated by Source BioScience who say they currenly need to retest only around 1% of the time with the IHC test.

The rate of retesting for the FISH test is expected to be slight greater than that of the IHC test however it is still expected to be low. In addition it is worth noting that only 12% of patients tested would require a FISH test (ie those reporting IHC2+). In ToGA the rate of technical falure for the FISH test was 9.4% however the UK based testing team at Source Bioscience estimate that they require only around 3-5% of FISH tests to be retested due to technical failure.

So in conclusion the number of retests required due to an inadequate/no tumour sample is expected to be nominal. Retests due to technical errors are also infrequent and the cost of retesting in this instance would be absorbed by the company perfoming the test and so would not impact the estimated cost of testing to the NHS.

A23. Please provide an indication of average delay in routine clinical practice between the time at which a decision is made to test a patient for HER2 status and the availability of IHC and confirmatory FISH results.

HER2 testing has been a standard diagnostic test in the treatment of breast cancer for ten years. From receipt of the tissue, a reporting time of 5-7days could be expected, the difference reflecting variance between labs and samples that have an equivocal IHC2+ result and therefore require a confirmatory FISH test. Approximately, 12% of tumour samples in the ToGA trial required confirmation of HER2 status with FISH. Her2 testing is likely to run concurrently with other patient assessments being made to inform the treatment decision e.g. oral or IV fluoropyrimidine, LVEF and renal function.

A24. Please provide the proportion of patients HER2 eligible for trastuzumab that record an LVEF of 50% or more in the ToGA trial.

LVEF of <50% was an exclusion criteria of the ToGA study, however there were a few patient in the FAS population that violated this criterion; 2 pts in CX/F arm and 1 pt in HCX/F had an LVEF < 50% at baseline.

During the screening phase of ToGA, tumours from 810 patients were diagnosed as HER2-positive (defined as IHC3+ or FISH+). 17 of these patients were not randomized into ToGA because their LVEF was <50%, representing 2% of the HER2-positive population (as defined as IHC3+ or FISH+). The proportion of patients with an LVEF <50% in the licensed population (IHC2+/FISH+ or IHC3+) is not readily availible from the dataset though is expected to be similar (around 2%).

A25. Please clarify whether LVEF eligibility would be assessed before or after HER2 eligibility.

The comparators of interest to the decision problem contain epirubicin and as such cardiac function should be assessed as part of current routine clinical practice prior to receiving treatment. Cardiac function would also be assessed prior to treatment with trastuzumab (SmPC trastuzumab 2010). Therefore, it is probable that cardiac function and HER2 would be assessed in parallel for patients considered eligible to receive chemotherapy.

Patients cardiac function should be assessed as part of current routine clinical practice prior to receiving epirubicin-based chemothrapy or treatment with trastuzumab as per the SmPC for these drug. It is expected that the HER2 test would be requested at the same time as the test for LVEF so that all the results could be considered at the following consultation to determine the most suitable course of treatment.

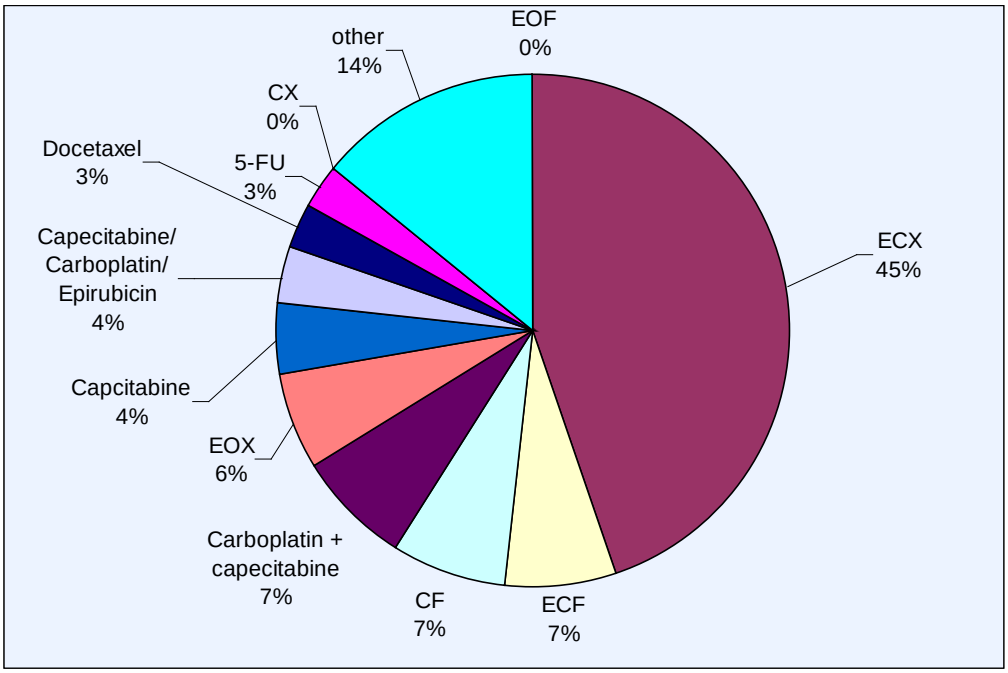
A26. Please supply further information on the market research conducted on current treatment practice in the UK; Appendix E6 does not contain sufficient information. In particular please clarify the sources of the data, including patient numbers, provide a clearer version of Figure 5, and confirm which two regimens are at 0%.

The regimens which are marked as 0 in Figure 5 are CX and EOF. A revised version of figure 5 is provided below.

The market research presented was not commission by Roche but is purchasable data from Synovate. Further details on the methods used to select the sample are provided in the presentation from the supplier below attached below.

[redacted]

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



Resource Use

A27. Please report the mean number of cycles for each treatment regimen assumed in the model and also the mean (and standard error) number of cycles from the ToGA trial.

Please find the mean number of cycles in the model shown in the table below alongside the truncated arithmetic means observed in ToGA.

	Economic Model		*ToGA*	
	Fluoropyrimidine/Cisplatin	*Trastuzumab+ Fluoropyrimidine/Cisplatin*	*Fluoropyrimidine/Cisplatin*	*Trastuzumab+ Fluoropyrimidine/Cisplatin*
Trastuzumab		*10.2*		*9.2 (0.51)*
Cisplatin	*4.7*	*5.2*	*4.6 (0.16)*	*4.8 (0.14)*
Capecitabine	*5.1*	*6.2*	*4.8 (0.20)*	*5.1 (0.19)*
5-FU	*7.1*	*6.9*	*4.4 (0.51)*	*5.1 (0.31)*

A28. Please clarify if the cardiac monitoring frequency numbers are correct in Appendix E1 (page 218) and Excel spreadsheet 'Admin-pharm-mon'. If they are, please explain the derivation. Please justify the lower cardiac monitoring frequency in the trastuzumab arms.

We can confirm that the frequency of cardiac monitoring is correct in the model and Appendix E1. The frequency of cardiac monitoring is incorporated in the analysis in accordance with the recommended frequency of monitoring specified in the SmPCs for epirubicin and trastuzumab (at baseline for both agents, then every cycle with Epirubicin; every 3 months with trastuzumab).

The relevant sections of the SmPC for each drug has been quoted below for ease of reference:

Epirubicin SmPC (section 4.4)

"Initial treatment calls for a careful baseline monitoring of various laboratory parameters and cardiac function "….."It is recommended that an ECG before and after each treatment cycle should be carried out. Alterations in the ECG tracing, such as flattening or inversion of the T-wave, depression of the S-T segment, or the onset of arrhythmias, generally transient and reversible, need not necessarily be taken as indications to discontinue treatment."

Trastuzumab SmPC (section 4.4)

"Formal cardiological assessment should be considered in patients in whom there are cardiovascular concerns following baseline screening. Cardiac function should be further monitored during treatment (e.g. every three months)."

A29. Please provide the sources and/or calculation of the smallest dose/vial quantities given in Excel spreadsheet 'Regimen drug costs' in column K titled 'smallest', and please confirm that they are correct. Is 9000mg the smallest capecitabine quantity?

The smallest dose / vial represents the number of mg in the smallest vial or pack (for capecitabine) listed in the latest BNF as of January 2010 (BNF58). A list of all the vial / pack sizes is provided in table 54 of Roche's submission.

9000 mg is the number of mg contained in the smallest whole pack of capecitabine available (150mg * 60 tablets). It was conservatively assumed that in centres that do not use vial sharing would also not split packs of capecitabine to minimize wastage. Though this is probably a conservative assumption given that packs are split for patinet safety as well as to minimise wastage. The model is however not sensitive to changes to this assumption; reducing the minimum dose to zero only changes the ICERs by £31 for HCX either EOX or ECX.

Costs

A30. Page 139 of the report indicates that the frequency of monitoring varies according to whether the monitoring is during chemotherapy and trastuzumab or during trastuzumab but post-chemotherapy. Please clarify how the model accounts for the different costs of monitoring.

There was an error in the model previously submitted such that it was not incorporating this aspect of clinical practice. The model has now been amended with the following revisions:

1. the 'Admin-pharm-mon' sheet has been corrected (see reply to question A33 below for amended table).
2. in each of the sheets in the model that are entitled by the name of the interventions and comparators eg, HCX, ECX etc, the formulae in the 'supportive care costs of PFS' column has been amended to incorporate the difference in monitoring costs between treatment on chemotherapy and post-chemotherapy with trastuzumab monotherapy.

Textual clarifications and additional points

A31. Please clarify test prices on page 142 as the total prices are not the same as in the model (£542.49 vs. £466.67).

We can confirm that the figure of £466.67 in the model and in table 17 is correct. On page 142 the test result should indicate £466.67 (5.61*£68 + 0.66*£133)

A32. Please clarify why the numbers of cycles per month in Appendix E1 and in the Excel spreadsheet 'Admin-pharm-mon' are different to those in Table 17, page 114, and Table 29, page 137, and the Excel spreadsheet 'Dose Table'.

The number of cycles was captured for each drug in the ToGA study and not each regimen. The administration costs are not calculated for each drug individually but rather by regimen hence the average cycle duration across all the drugs was taken to model the cost of administration.

A33. Please clarify why the total admin, pharmacy and monitoring costs in Appendix E1 are different to those in the Excel spreadsheet 'Admin-pharm-mon' (£655 vs. £746, £905 vs. £996, etc.).

We can confirm that the figures in the model are correct and that the figures were misrepresented in the appendix E1. Please find the amended version of the table in appendix E1 provided below.

Appendix E1: Resource use

Unit cost (£'s)		ECX	EOX	ECF	HCX	HCF	H mono	HX	X Mono	HF	F Mono
	Cycles per month	1.29	1.29	1.29	1.29	1.29	1.29	1.29	1.29	1.29	1.29
	Per cycle pharmacy preparation and dispensing										
9	Pharmacy Infution	2	2	3	2	3	1	1		2	1
9	Pharmacy oral	1	1		1			1	1		
	Pharmacy cost per cycle (£'s)	**28**	**28**	**28**	**28**	**28**	**9**	**19**	**9**	**19**	**9**
	Per cycle administration:										
30	patient transport	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
38.5	Ambulatory pump			3		1				1	1
125.5	Monitoring additional to admin visit										
39	District Nurse Visit			2		1				1	1
268	Day case	1	1	1	1	1					
159	5-FU + Trastuzumab									1	
133	Administration Trastuzumab / 5-FU Monotherapy						1	1			1
1,989	Administration overnight visits										
	Administration cost per cycle (£'s)	**277**	**277**	**472**	**277**	**355**	**142**	**142**	**9**	**246**	**220**
	Total: admin and pharmacy cost / month	**393**	**393**	**644**	**393**	**494**	**197**	**209**	**24**	**344**	**297**
	Monthly Monitoring during treatment										
125	Consultation OP appointment in PFS	1.44	1.44	1.44	1.44	1.44	0.72	1.44	1.44	1.44	1.44
133	cardiac monitoring	1.29	1.29	1.29	0.33	0.33	0.33	1.33		0.33	
	Monthly monitoring cost (£'s)	**352**	**352**	**352**	**225**	**225**	**134**	**267**	**91**	**134**	**91**
	Total admin, pharmacy and monitoring cost / month	**746**	**746**	**996**	**618**	**719**	**331**	**476**	**114**	**478**	**388**

A34. *Please clarify why the figures in Table 26 (page 134) are different to those in Excel spreadsheet 'Regimen drug costs' (207 vs. 216, 6674 vs. 6689, etc.).*

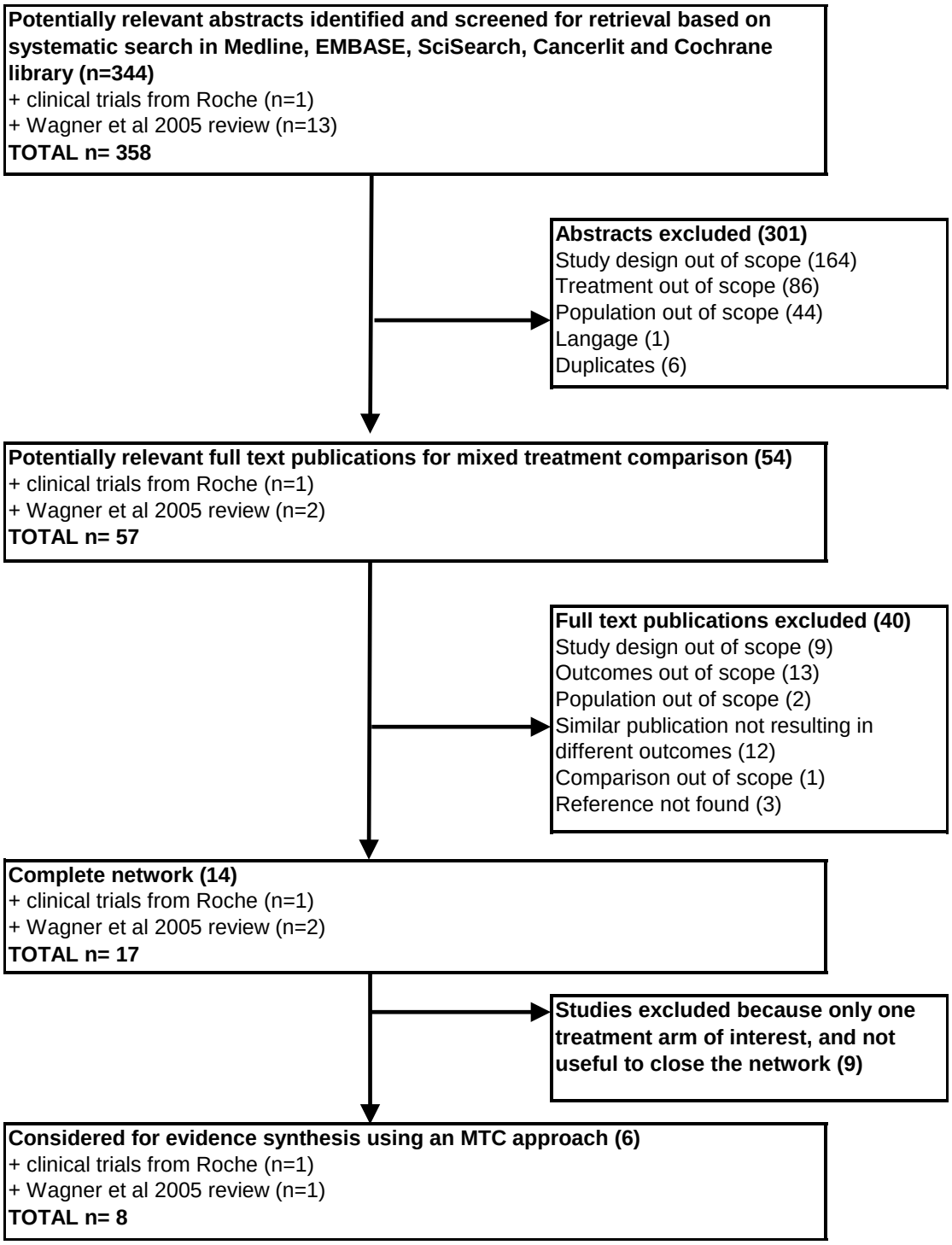
The figures in the model are correct as they account for wastage, those in the table 26 need to be updated as assume no wastage. Please find the amended table 26 below.

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

	ECX	EOX	ECF	HCX	HCF
5-FU	-	-	6,689	6,689	-
Capecitabine	40,854	40,854	-	-	40,419
Cisplatin	96	-	95	-	118
Epirubicin	77	77	80	80	-
TrastuzumabLD	-	-	-	-	512
Trastuzumab	-	-	-	-	392
Oxaliplatin	-	216	-	216	-

A35. *In Figure 16 (page 83) the numbers do not add up – the box on full-text publications sums to 32 instead of 40. Please clarify.*

Please find the corrected flow chart below



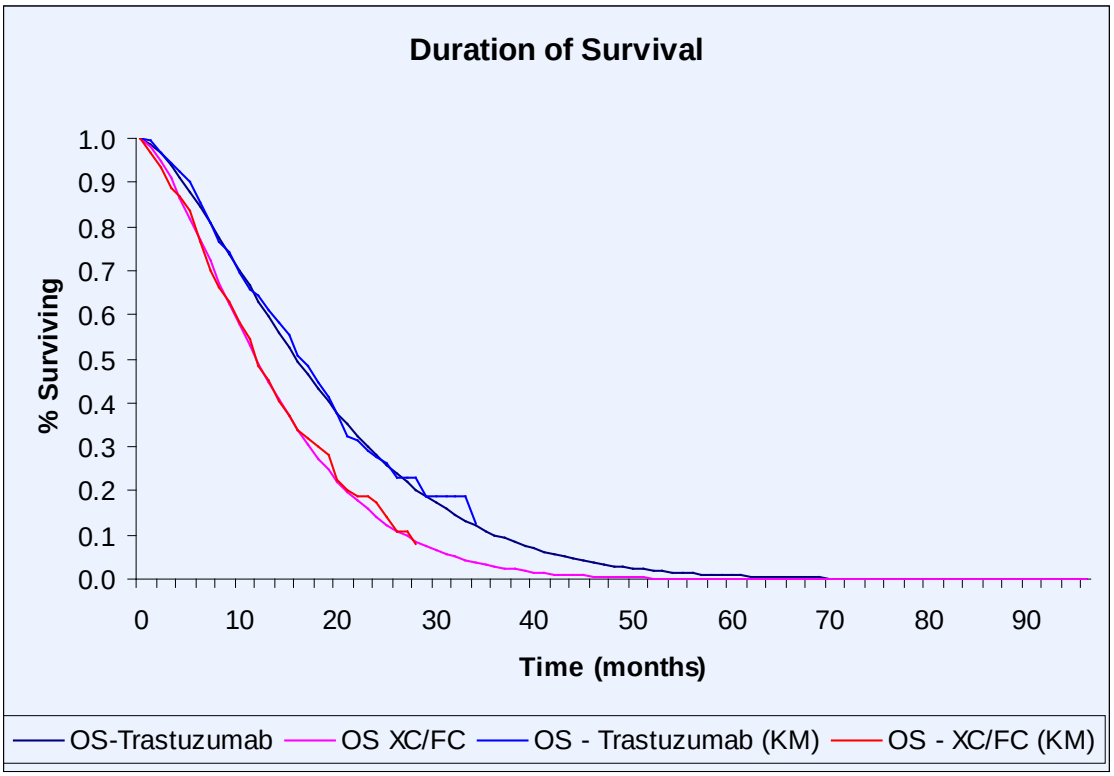
A36. In Figure 6 (page 43) the numbers do not add up (should it be 60 abstracts rather than 57?); please clarify the correct figures for each stage of the review process.

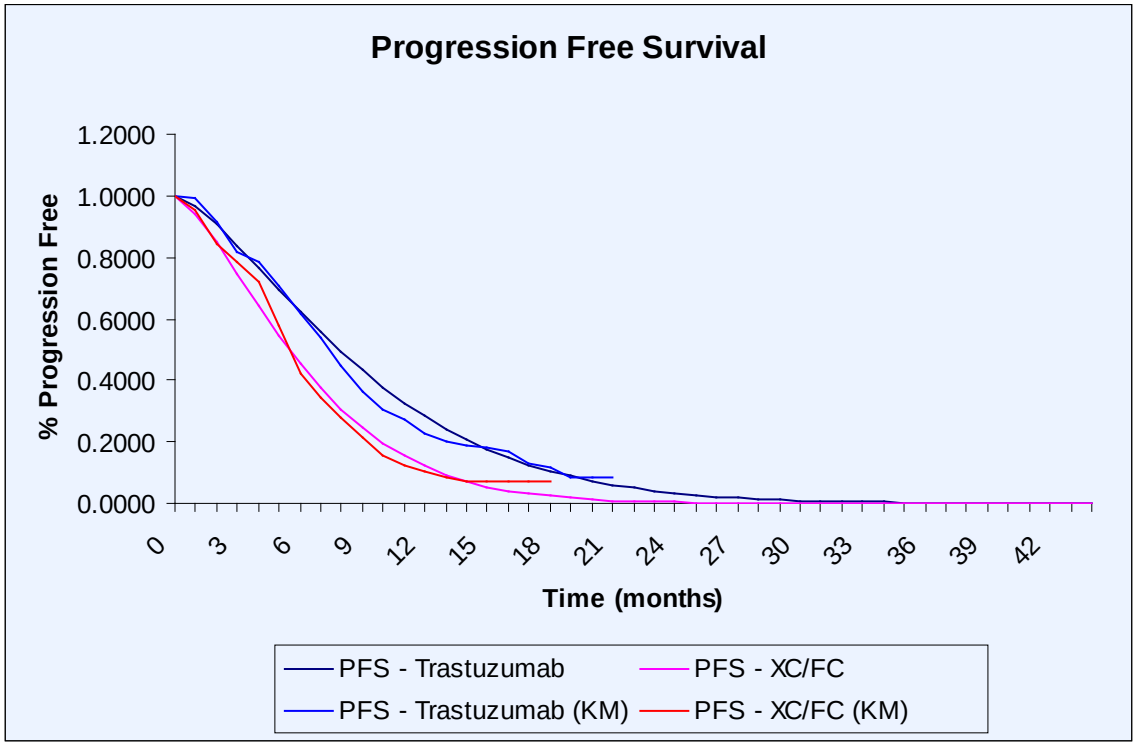
This is correct the figure should be 60 not 57.

Appendix

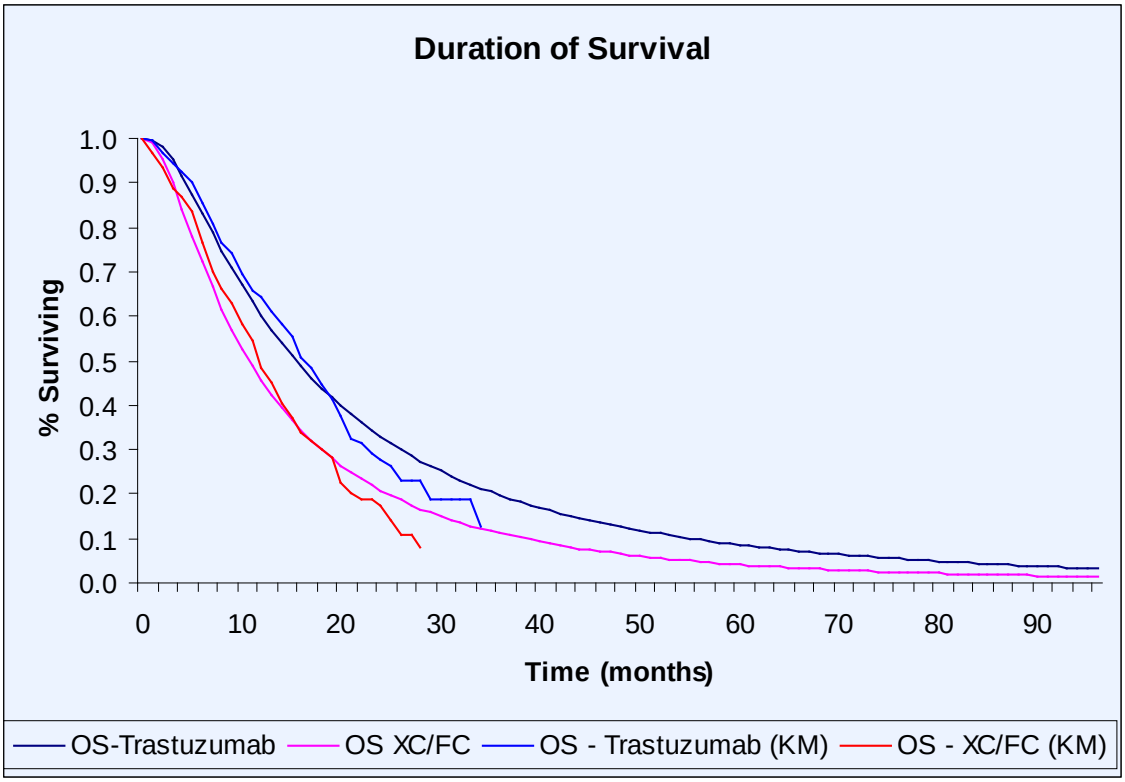
Parametric Survival Plots

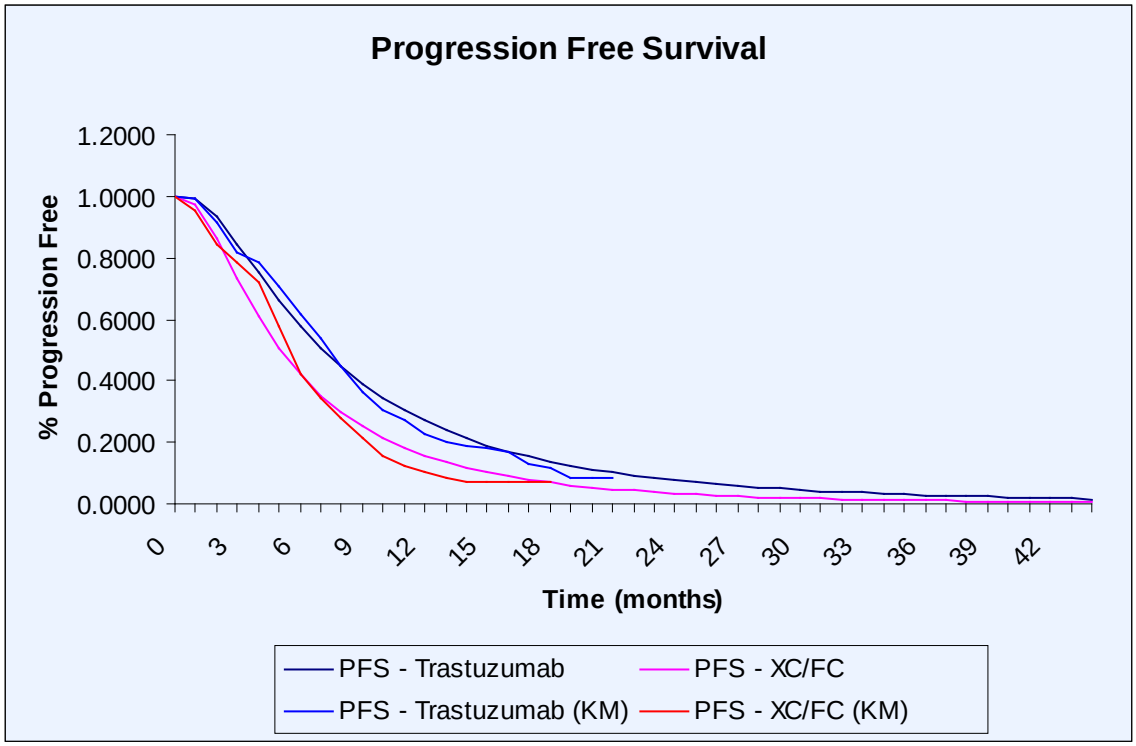
Weibull



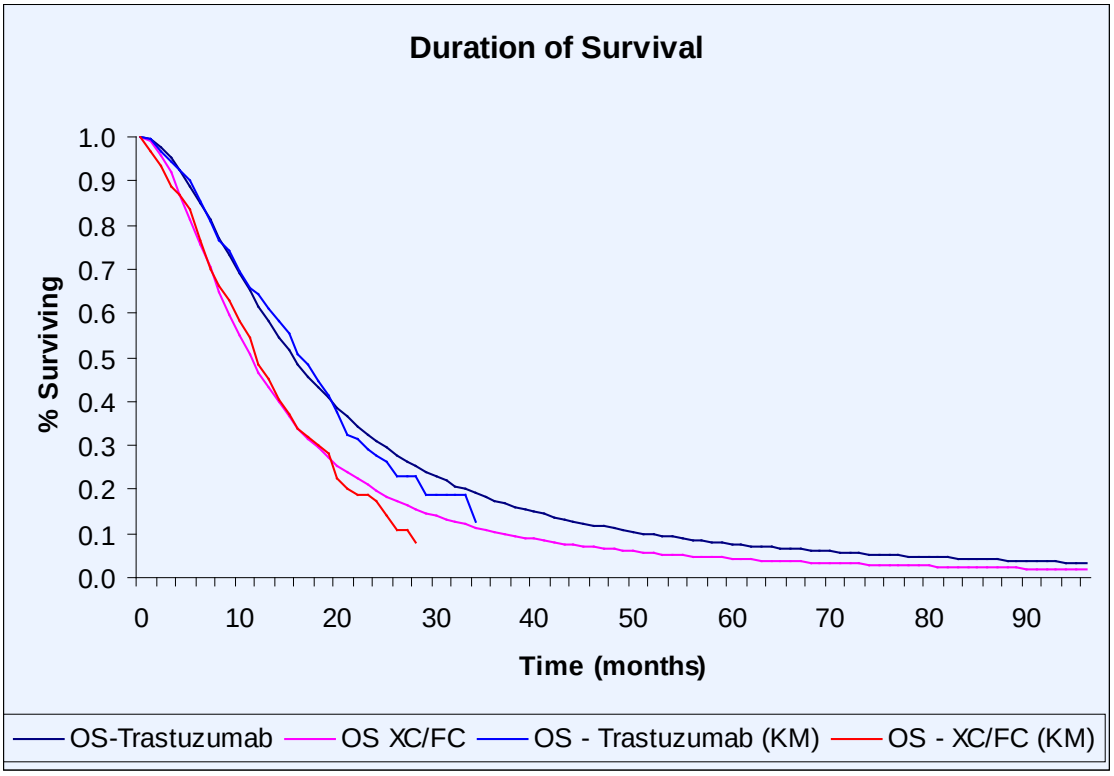


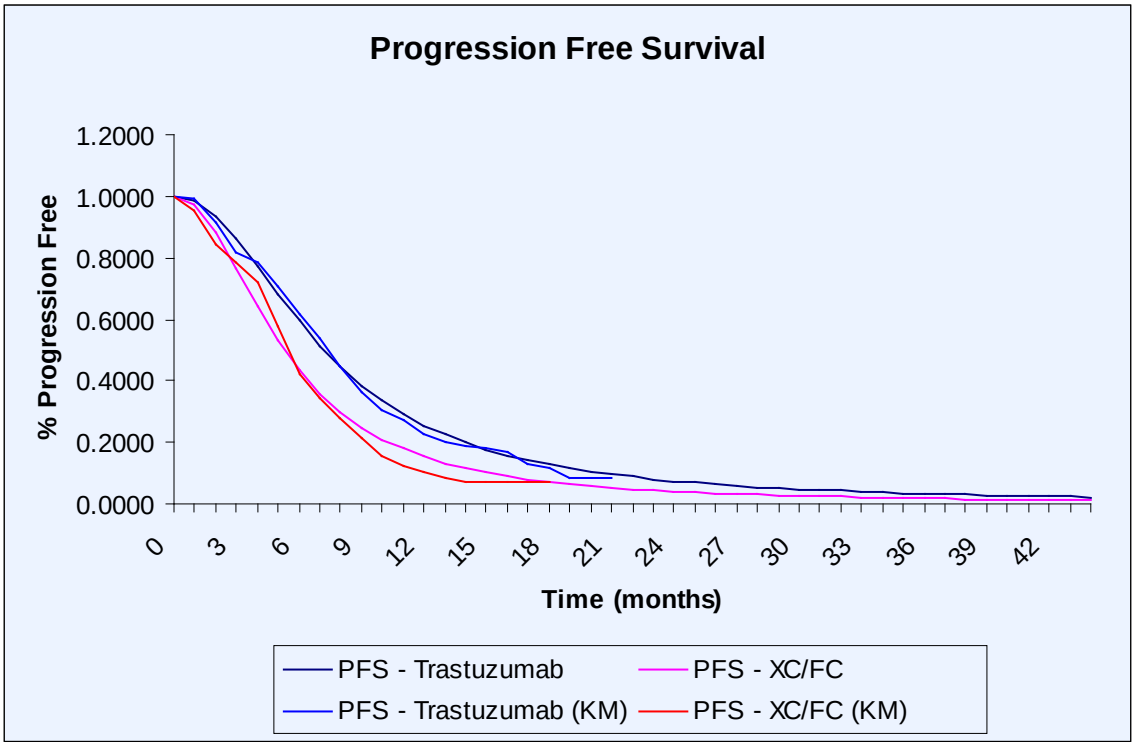
Log Normal


Duration of Survival
% Surviving
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
10
20
30
40
50
60
70
80
90
Time (months)
OS-Trastuzumab
OS XC/FC
OS - Trastuzumab (KM)
OS - XC/FC (KM)

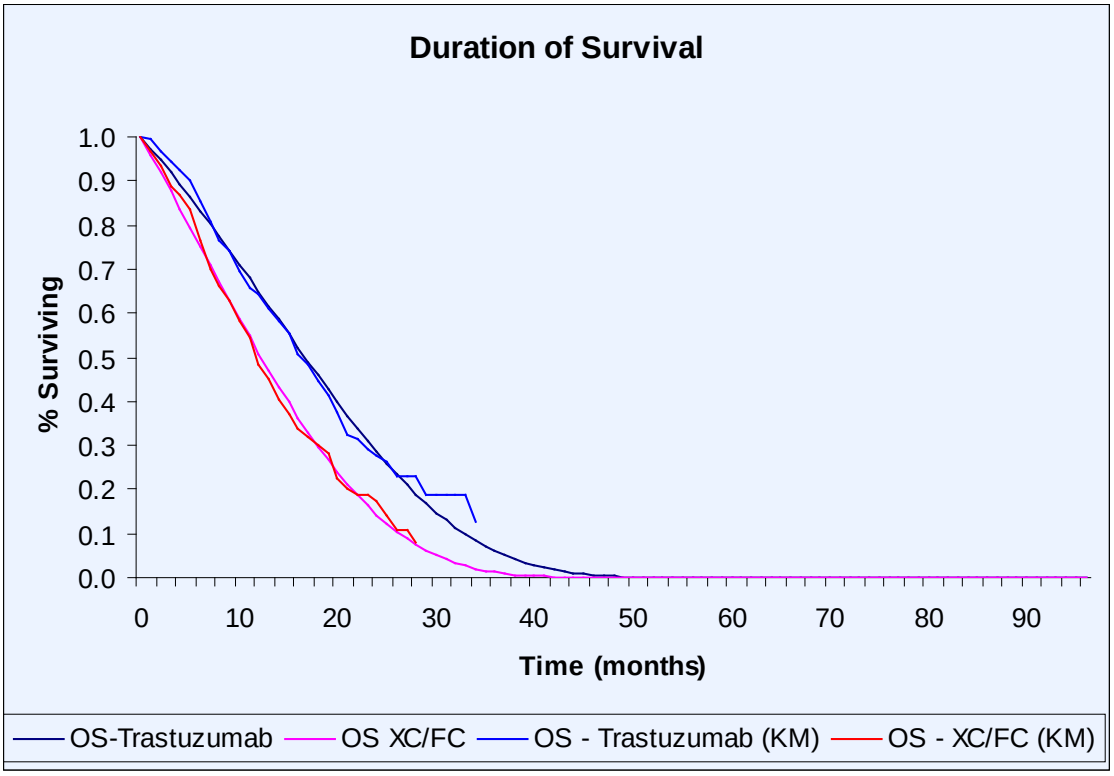

Progression Free Survival
% Progression Free
1.2000
1.0000
0.8000
0.6000
0.4000
0.2000
0.0000
0
3
6
9
12
15
18
21
24
27
30
33
36
39
42
Time (months)
PFS - Trastuzumab
PFS - XC/FC
PFS - Trastuzumab (KM)
PFS - XC/FC (KM)

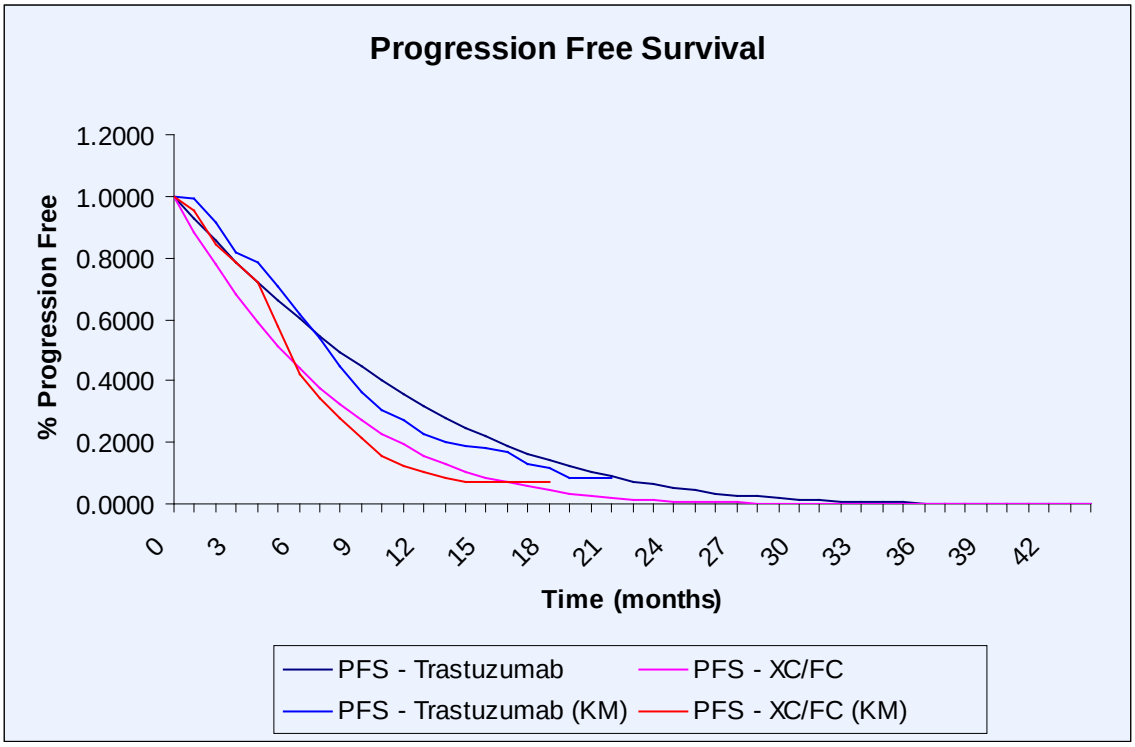
Log Logistic



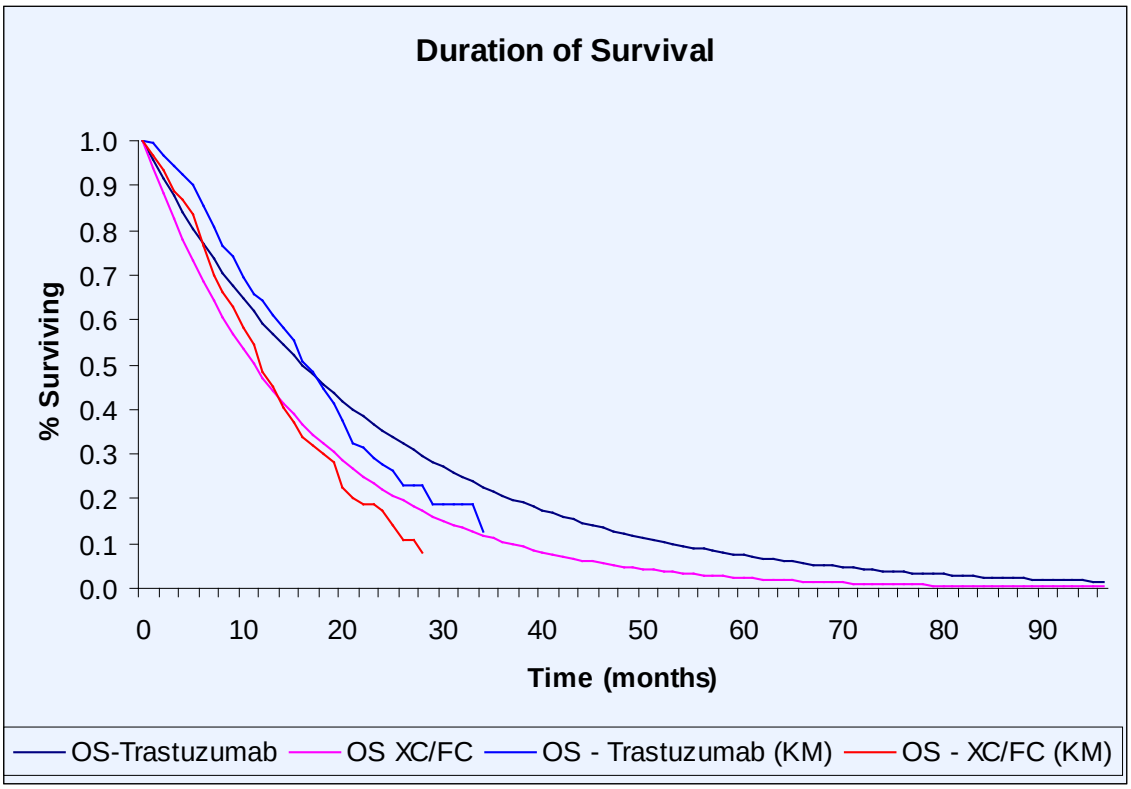


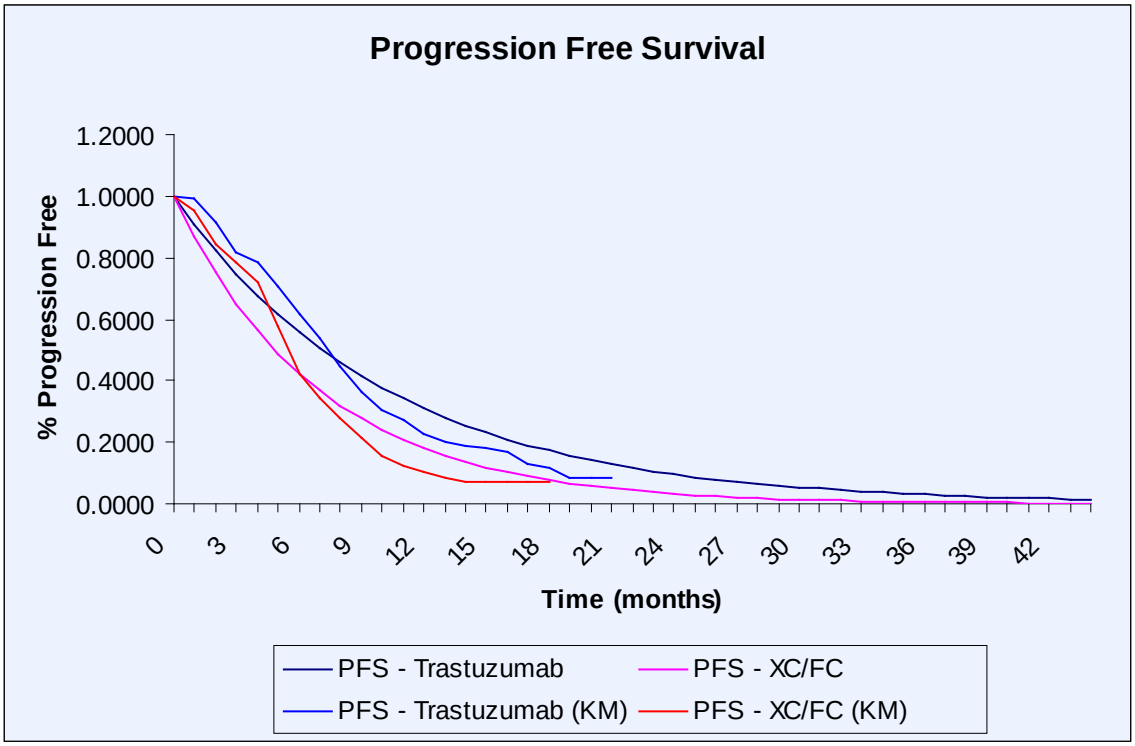
Gompertz


Duration of Survival
% Surviving
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
10
20
30
40
50
60
70
80
90
Time (months)
OS-Trastuzumab
OS XC/FC
OS - Trastuzumab (KM)
OS - XC/FC (KM)


Progression Free Survival
% Progression Free
1.2000
1.0000
0.8000
0.6000
0.4000
0.2000
0.0000
0
3
6
9
12
15
18
21
24
27
30
33
36
39
42
Time (months)
PFS - Trastuzumab
PFS - XC/FC
PFS - Trastuzumab (KM)
PFS - XC/FC (KM)

Exponential





Results for revised base case

Figure 11: Mean total costs per patient

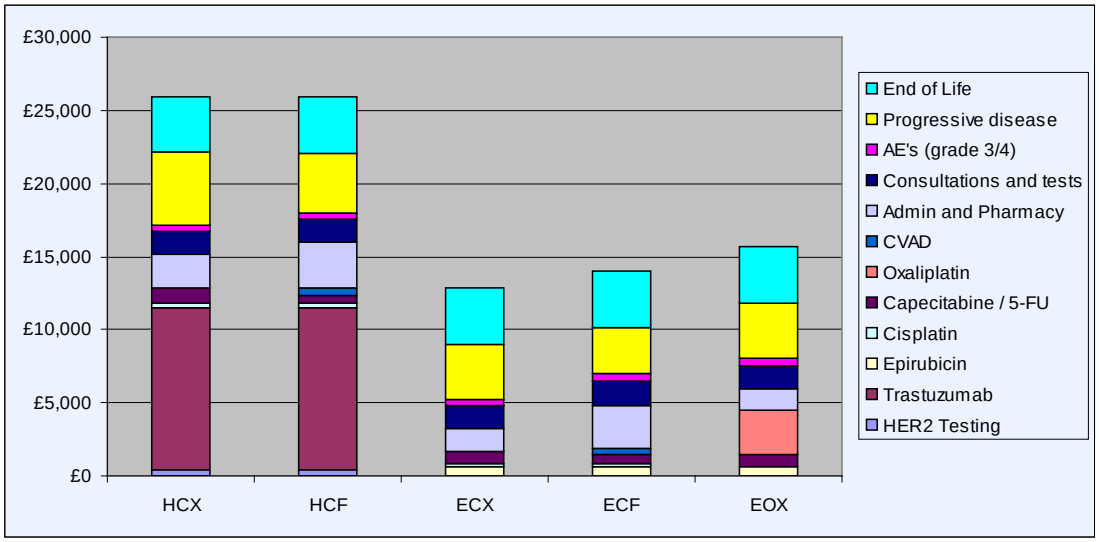


Figure 12: Simultaneous incremental results

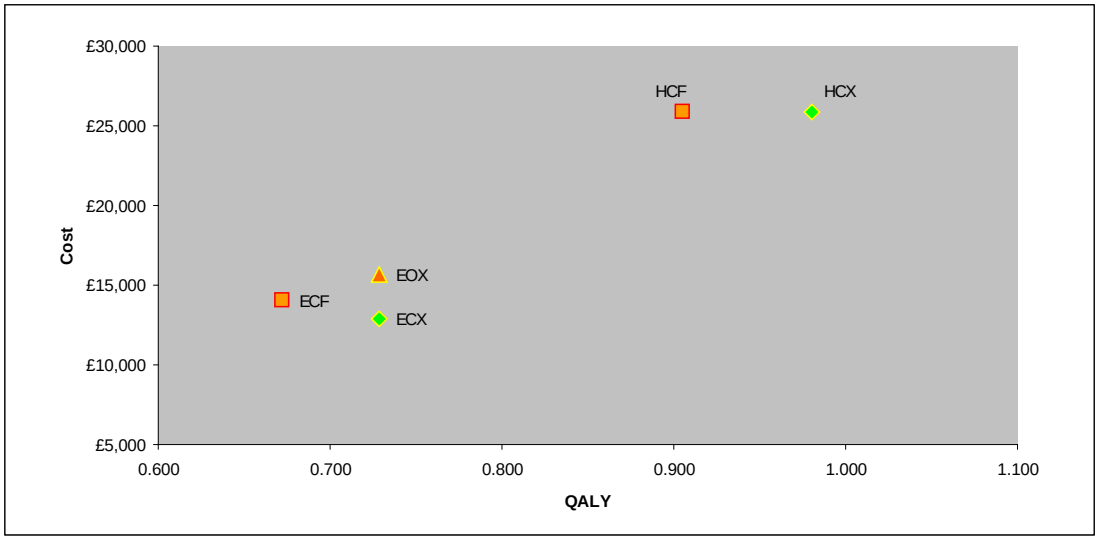


Table 14: Total cost for each intervention per patient

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

Table 15: cost for each comparator per patient

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

Table 16: Mean Incremental cost per patient

	Deterministic	Probabilistic
HCX vs ECX	**£13,064**	**£13,070**
HCF vs ECF	**£11,858**	**£11,860**
HCX vs EOX	**£10,242**	**£10,228**

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

	Deterministic	Probabilistic
HCX vs ECX	**£51,927**	**£51,810**
HCF vs ECF	**£50,838**	**£50,769**
HCX vs EOX	**£40,711**	**£40,544**

Table 18: Mean ICERs (£/LY) per patient (Deterministic)

HCX vs ECX	**£34,063**
HCF vs ECF	**£33,711**
HCX vs EOX	**£26,706**

Sensitivity analysis for revised base case

HCX vs. ECX

One way sensitivity analysis

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

Table 19: One-way sensitivity analysis of HCX vs. ECX to changes to mean parameter estimates (base case £ 51,927)

Parameter modified	Base value	Low value	High value	ICER Low	ICER High
Utility Values					
PFS Utility value	0.73	0.66	0.80	£54,901	£49,258
Include increase in utility with trastuzumab in PFS	0.00	0.00	1.00	£51,927	£48,337
Include increase in utility over time during PFS	1.00	0.00	1.00	£53,813	£51,927
Progression Utility Value	0.58	0.52	0.63	£54,221	£49,818
Survival Analysis					
Weibull or Log Logistic PFS	7	1	3	£52,552	£54,036
Weibull or Log Logistic OS	1	3	1	£46,935	£51,927
OS HR (ECX vs CX)	1	0.96	1.04	£55,009	£49,313
Clinical Practice Assumptions					
% pts requiring hospital transport	30%	0%	50%	£51,768	£52,033
Proportion of centres vial sharing	0.8	50%	100%	£54,433	£50,256
Extrapolation of trastuzumab (number treated at time t / number in PFS) 0 = constant, 1= fit linear regression	1	0	1	£51,927	£52,198
Unit Costs					
Cost of CVAD installation	£505	£303	£707	£51,927	£51,927
Cost of hospital funded transport per visit	£30	£18	£42	£51,863	£51,990
Cost of 5-FU pump	£39	£23	£54	£51,927	£51,927
Cost per consultation with oncologist	£125	£75	£176	£51,491	£52,362
CT scan every 3 months	£0	£0	£106	£51,927	£52,240
End of life cost	£4,000	£0	£4,000	£52,140	£51,927
Cost of Cardiac Monitoring	£133	£80	£186	£52,415	£51,438
Cost of district nurse visit	£39	£24	£55	£51,927	£51,927
Cost of administration day 1 of cycle	£268	£161	£376	£51,759	£52,095
Cost of administration of Trastuzumab monotherapy	£134	£81	£188	£50,968	£52,885
Cost of administration of Trastuzumab in combination with 5-FU	£161	£97	£226	£51,927	£51,927
Pharmacy cost infusion	£9	£9	£23	£51,927	£52,213
Pharmacy cost oral	£9	£9	£12	£51,927	£51,937
Cost of Progressive Disease Health State	£542	£325	£759	£50,019	£53,835
Total ECX Adverse Event costs	£436	£262	£611	£52,620	£51,233
Total ECF Adverse Event costs	£527	£316	£738	£51,927	£51,927
Total EOX Adverse Event costs	£463	£278	£648	£51,927	£51,927
Total trastuzumab Adverse Event costs	£407	£244	£570	£51,279	£52,574

Figure 13: Tornado diagram for HCX vs. ECX

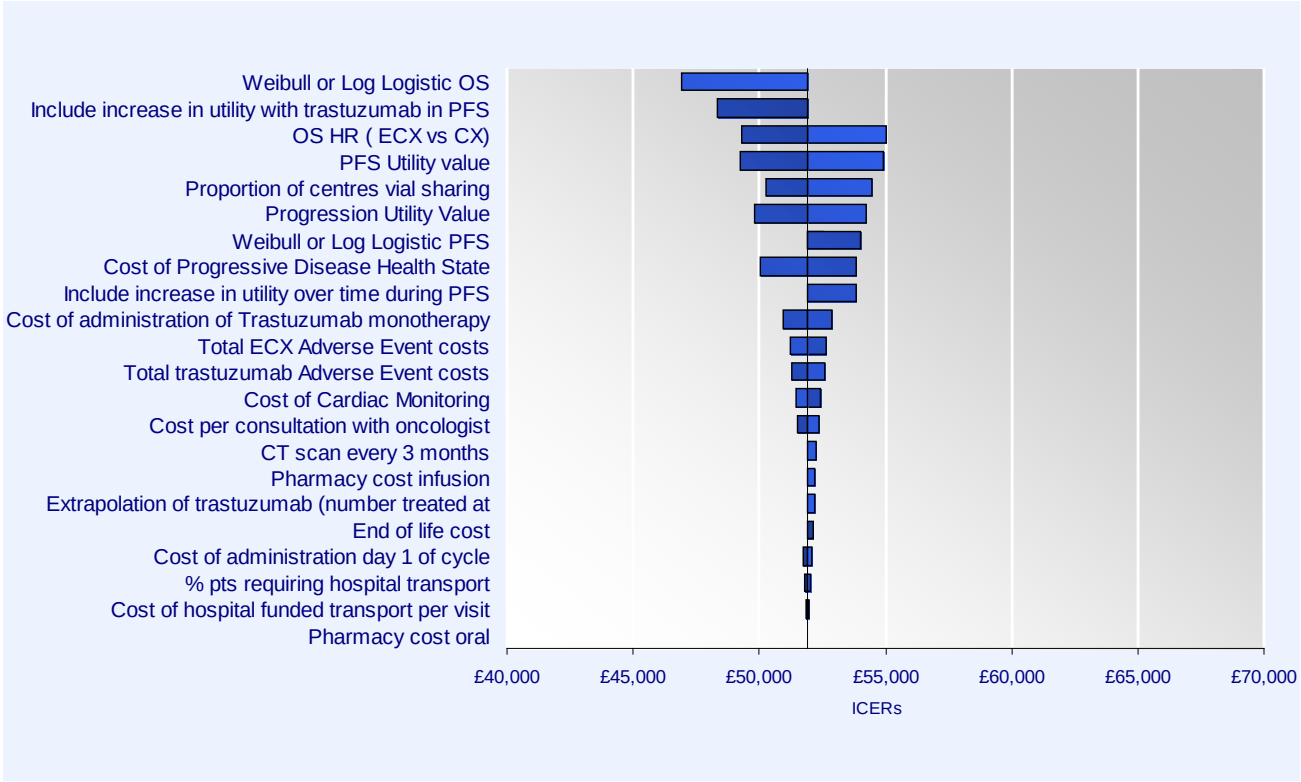


Figure 14: Scatter plot HCX vs. ECX

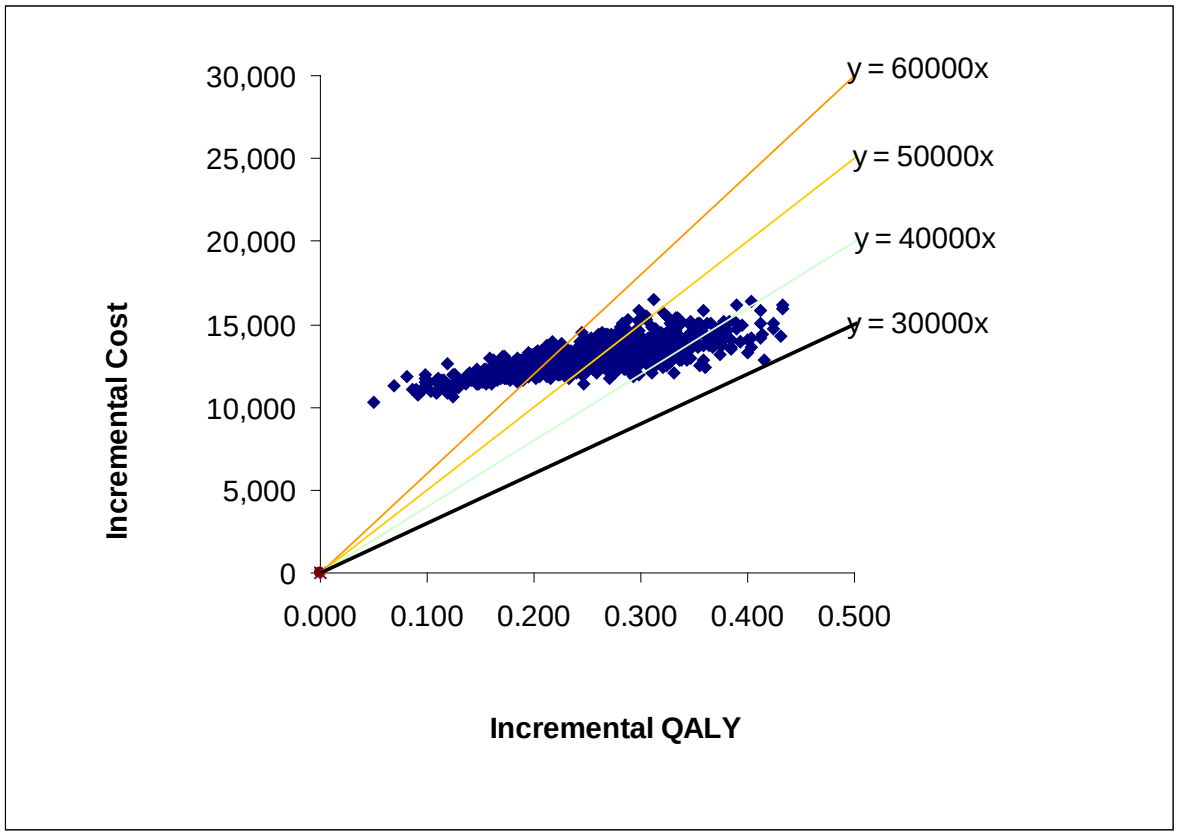
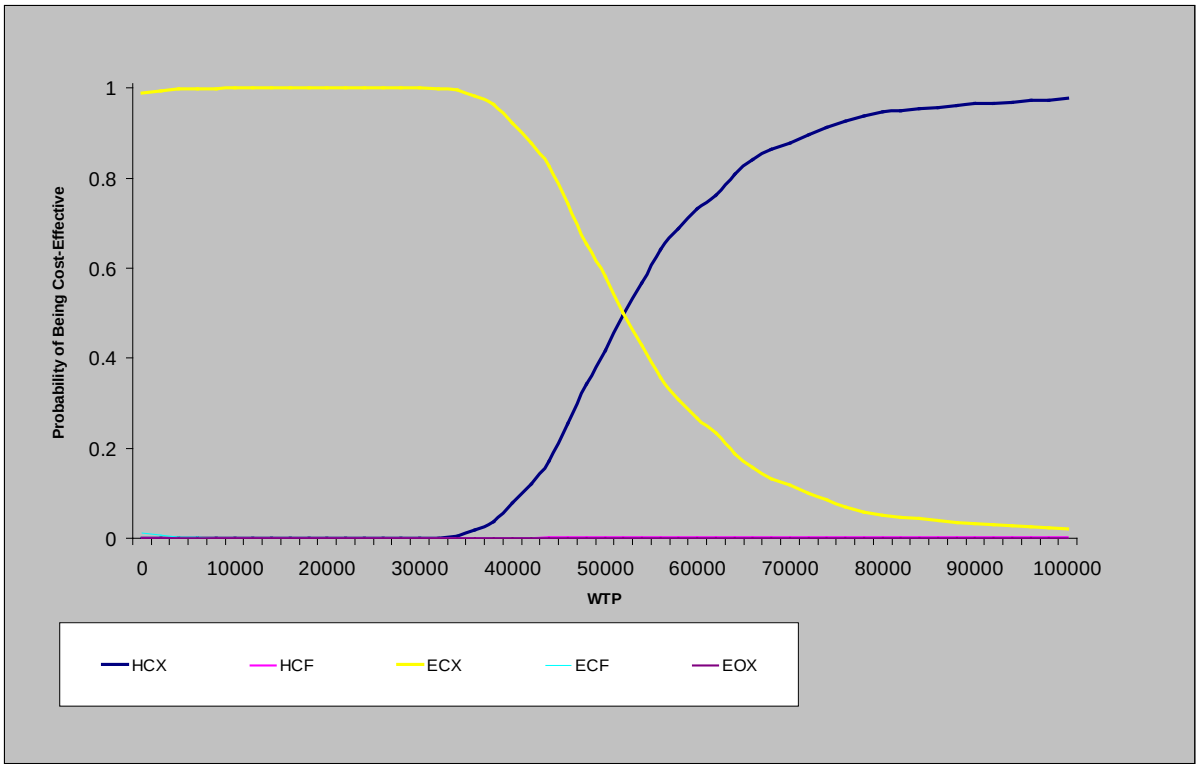


Figure 15: Cost Effectiveness Acceptability Curve



HCF vs. ECF

Table 20: One-way sensitivity analysis of HCF vs. ECF to changes to mean parameter estimates (base case £ 50,838)

Parameter modified	Base value	Low value	High value	ICER Low	ICER High
Utility Values					
PFS Utility value	0.73	0.66	0.80	£53,993	£48,032
Include increase in utility with trastuzumab in PFS	0.00	0.00	1.00	£50,838	£47,068
Include increase in utility over time during PFS	1.00	0.00	1.00	£52,836	£50,838
Progression Utility Value	0.58	0.52	0.63	£52,835	£48,987
Survival Analysis					
Weibull or Log Logistic PFS	7	1	3	£51,376	£53,082
Weibull or Log Logistic OS	1	3	1	£46,334	£50,838
Clinical Practice Assumptions					
% pts requiring hospital transport	30%	0%	50%	£50,673	£50,949
Proportion of centres vial sharing	0.8	50%	100%	£53,515	£49,054
Extrapolation of trastuzumab (number treated at time t / number in PFS) 0 = constant, 1= fit linear regression	1	0	1	£50,838	£51,131
Unit Costs					
Cost of CVAD installation	£505	£303	£707	£50,838	£50,838
Cost of hospital funded transport per visit	£30	£18	£42	£50,772	£50,904
Cost of 5-FU pump	£39	£23	£54	£51,482	£50,194
Cost per consultation with oncologist	£125	£75	£176	£50,511	£51,165
CT scan every 3 months	£0	£0	£106	£50,838	£51,176
End of life cost	£4,000	£0	£4,000	£51,047	£50,838
Cost of Cardiac Monitoring	£133	£80	£186	£51,365	£50,311
Cost of district nurse visit	£39	£24	£55	£51,173	£50,503
Cost of administration day 1 of cycle	£268	£161	£376	£50,657	£51,019
Cost of administration of Trastuzumab monotherapy	£134	£81	£188	£49,865	£51,811
Cost of administration of Trastuzumab in combination with 5-FU	£161	£97	£226	£50,413	£51,263
Pharmacy cost infusion	£9	£9	£23	£50,838	£51,227
Pharmacy cost oral	£9	£9	£12	£50,838	£50,838
Cost of Progressive Disease Health State	£542	£325	£759	£49,134	£52,542
Total ECX Adverse Event costs	£436	£262	£611	£50,838	£50,838
Total ECF Adverse Event costs	£527	£316	£738	£51,742	£49,934
Total EOX Adverse Event costs	£463	£278	£648	£50,838	£50,838
Total trastuzumab Adverse Event costs	£407	£244	£570	£50,140	£51,537

Figure 16: Tornado diagram for HCF vs. ECF

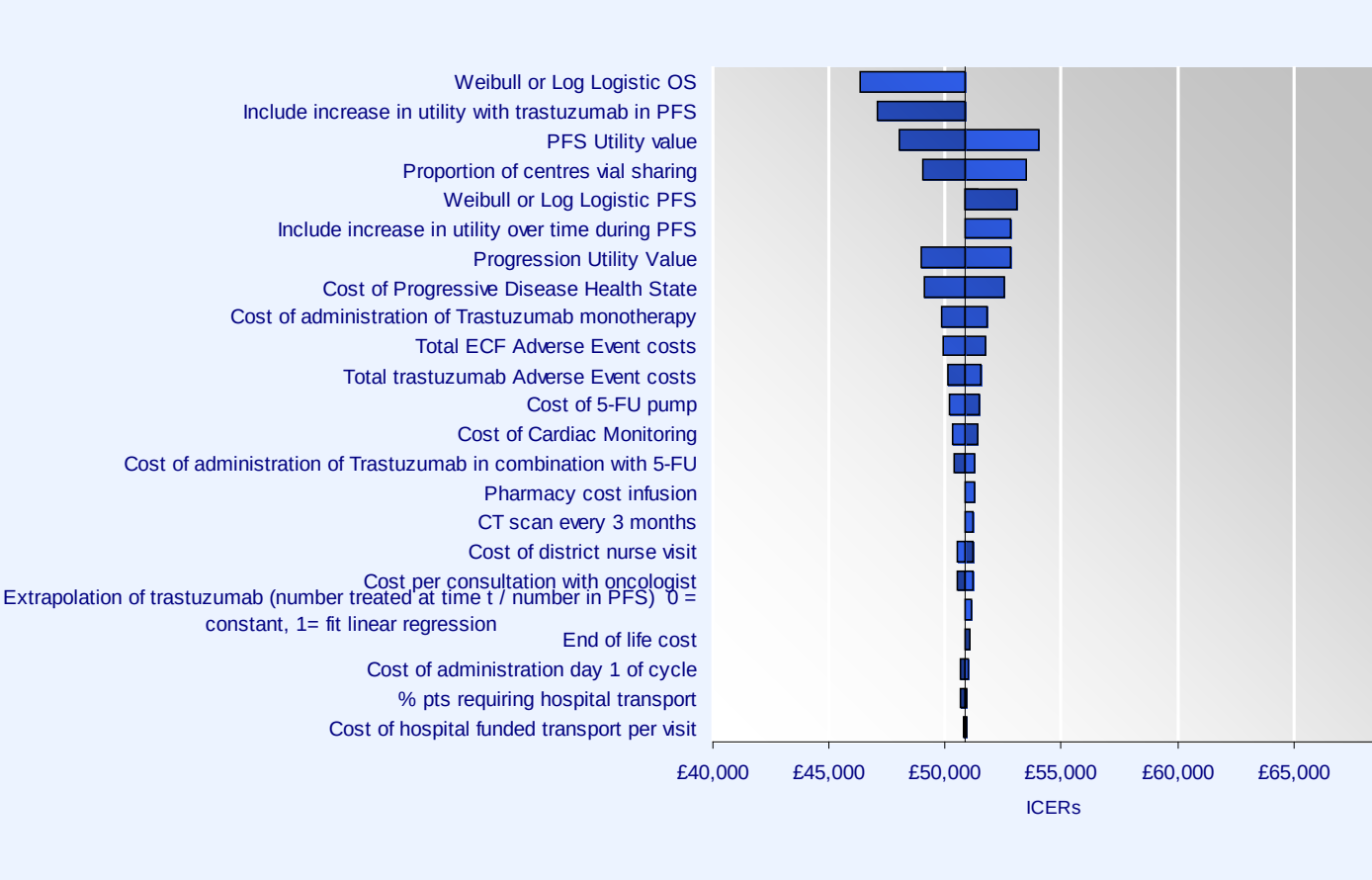
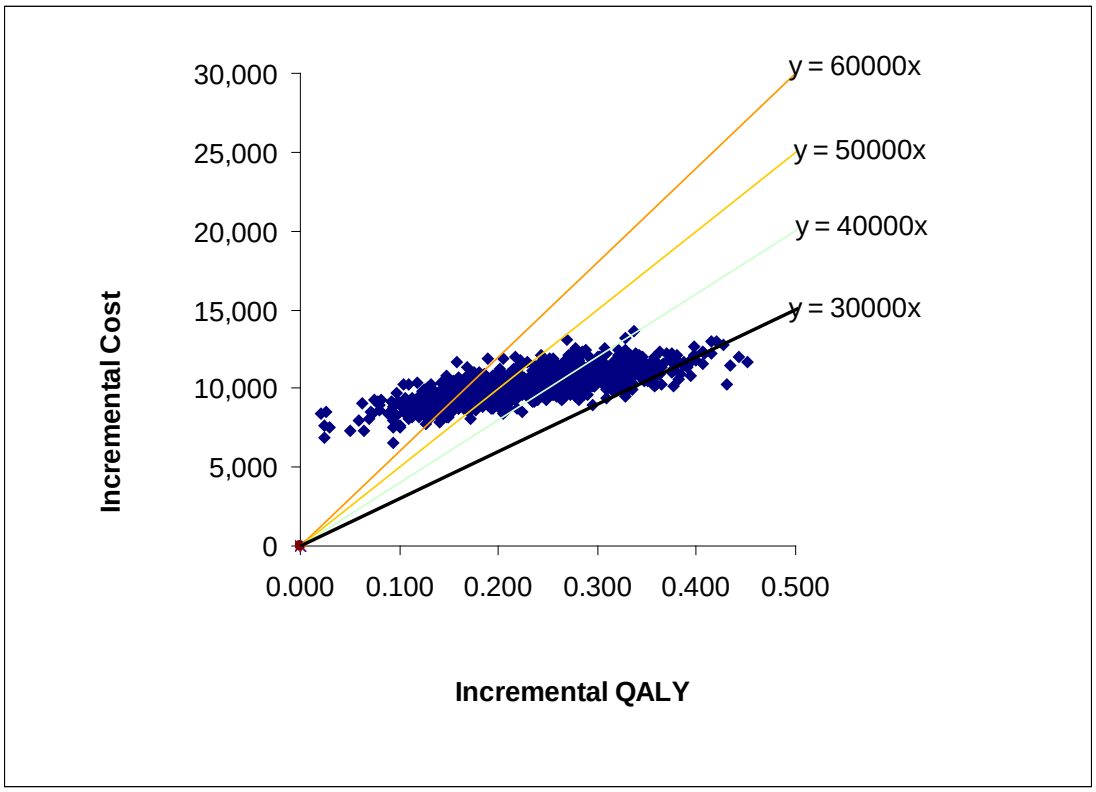


Figure 17: Scatter plot HCF vs. ECF



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paul.catchpole@roche.com

HCX vs. EOX: Base case = £40,717

Parameter modified	Base value	Low value	High value	ICER Low	ICER High
Utility Values					
PFS Utility value	0.73	0.66	0.80	£43,043	£38,619
Include increase in utility with trastuzumab in PFS	0.00	0.00	1.00	£40,711	£37,897
Include increase in utility over time during PFS	1.00	0.00	1.00	£42,190	£40,711
Progression Utility Value	0.58	0.52	0.63	£42,510	£39,059
Survival Analysis					
Weibull or Log Logistic PFS	7	1	3	£41,972	£43,317
Weibull or Log Logistic OS	1	3	1	£37,139	£40,711
OS HR (EOX vs ECX)	1.00	0.92	1.09	£45,752	£37,123
Clinical Practice Assumptions					
% pts requiring hospital transport	30%	0%	50%	£40,553	£40,817
Proportion of centres vial sharing	0.8	50%	100%	£42,522	£39,504
Extrapolation of trastuzumab (number treated at time t / number in PFS) 0 = constant, 1= fit linear regression	0	0	1	£40,711	£40,983
Unit Costs					
Cost of CVAD installation	£505	£303	£707	£40,711	£40,711
Cost of hospital funded transport per visit	£30	£18	£42	£40,648	£40,775
Cost of 5-FU pump	£39	£23	£54	£40,711	£40,711
Cost per consultation with oncologist	£125	£75	£176	£40,276	£41,147
CT scan every 3 months	£0	£0	£106	£40,711	£41,025
End of life cost	£4,000	£0	£4,000	£40,924	£40,711
Cost of Cardiac Monitoring	£133	£80	£186	£41,200	£40,223
Cost of district nurse visit	£39	£24	£55	£40,711	£40,711
Cost of administration day 1 of cycle	£268	£161	£376	£40,543	£40,879
Cost of administration of Trastuzumab monotherapy	£134	£81	£188	£39,753	£41,670
Cost of administration of Trastuzumab in combination with 5-FU	£161	£97	£226	£40,711	£40,711
Pharmacy cost infusion	£9	£9	£23	£40,711	£40,998
Pharmacy cost oral	£9	£9	£12	£40,711	£40,722
Cost of Progressive Disease Health State	£542	£325	£759	£38,803	£42,619
Total ECX Adverse Event costs	£436	£262	£611	£40,711	£40,711
Total ECF Adverse Event costs	£527	£316	£738	£40,711	£40,711
Total EOX Adverse Event costs	£463	£278	£648	£41,447	£39,976
Total trastuzumab Adverse Event costs	£407	£244	£570	£40,064	£41,359

Figure 18: HCX vs. EOX tornado diagram

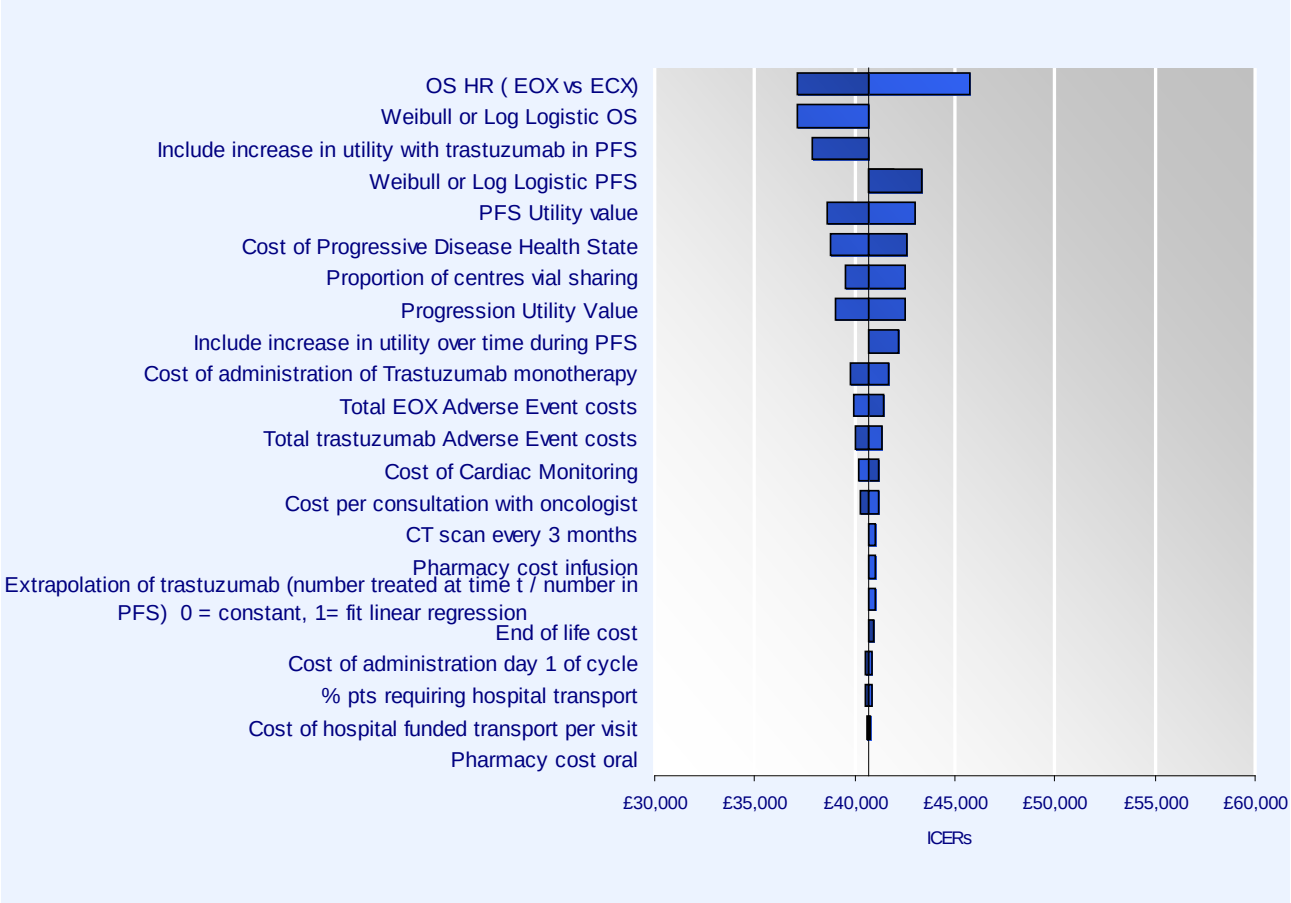

Figure 19: HCX vs. EOX scatter plot