Single Technology Appraisal – Bevacizumab in combination with oxaliplatin and either 5FU or capecitabine for the treatment of metastatic colorectal cancer

PART 1 – RESPONSE TO PRIORITY QUESTIONS

Response to ERG Clarification Questions

Section A: Clarification on Effectiveness Data

A1. **Priority question: Section 6.7.1. Please clarify whether NO16966 trial uses the most effective chemotherapy combination (schedule, dosage and timing) of FOLFOX-4 and XELOX. In addition, do the schedule, dosage and timings in the NO16966 trial reflect current practice in (or outside) the UK for first line therapy?**

1.1 Is the FOLFOX-4 regimen used the optimum one?

FOLFOX-4 represents a globally accepted standard with regulatory approval for the treatment of metastatic CRC (mCRC) which is why it was selected as the control arm of the study. It was accepted during early discussions with the regulatory agencies and at the time of regulatory submission following trial completion and analysis as an acceptable benchmark against which to compare a new therapy i.e. XELOX.

In Roche's regulatory submission, results from Phase III studies of first line chemotherapy regimens in the treatment of mCRC were collated as shown in Table 1.1 From this it can be seen that FOLFOX-4 produces some of the best outcomes of any first-line combination chemotherapy and, furthermore, that the variability in outcomes with FOLFOX-4 between studies is at least as great as the difference between this regimen and the variant FOLFOX-6 described by Tournigand *et al* and often used in the UK.

To our knowledge there has been no direct comparison between FOLFOX-4 and FOLFOX-6 - the two oxaliplatin based regimens most widely used in large trials and in clinical practice. This is unsurprising given that FOLFOX-6 was developed as a more convenient-to-deliver variant of FOLFOX-4 by the researchers who originally pioneered FOLFOX-4 and they concluded (Tournigand *et al.* 2004) after its use in a Phase III study that there are no meaningful differences between the regimens in terms of outcomes. They state that: "*the results of FOLFOX6 and FOLFOX4 first-line were similar despite the higher dose of oxaliplatin in FOLFOX6"*.

More generally, the development of the FOLFOX regimens by the GERCOR group has been reviewed (Reddy *et al.* 2005) and shows no major differences in outcomes between the various versions of FOLFOX.

Roche believes that this reflects the views of UK clinicians who believe commonly used FOLFOX- type regimens to be of similar efficacy.

Table 1.1. Effectiveness of Combination Therapy in Colorectal Cancer

Study/Author	Regimen	No of Pts.	PFS (mos)	RR (%)	OS
First Line Therapy					
Irinotecan-based					
Saltz (2000)	Mayo	226	4.3	21	12.6
	IFL	231	7.0	39	14.8
	Irinotecan	226	4.2	18	12.0
Douillard (2000)	Inf 5-FU/LV	188	4.4*	23	14.1
	I inf 5-FU/LV	199	6.7*	41	17.4
Oxaliplatin-based					
de Gramont (2000)	de Gramont 5 FU/LV	210	6.0	22	14.7
	FOLFOX-4	210	8.2	50	16.2
Goldberg (2004)	IFL	264	6.9*	31	15.0
	FOLFOX-4	267	8.7*	45	19.5
	OX + I	264	6.5	35	17.4
Tournigand (2004)	FOLFIRI	109	8.5	56	21.5
	FOLFOX-6	111	8.1	54	20.6

*TTP not PFS

1.2 Is the XELOX regimen used the optimum one?

The XELOX regimen in the NO16966 study was first tested in the M66016 Phase II study (Scheithauer *et al.* 2003). This trial included 96 patients with previously untreated mCRC. The safety profile of XELOX was very similar to that of the FOLFOX-4 regimen. Responses were consistently >50% in all subgroups studied. Median PFS was 7.7 months (95% CI: 6.5-8.5 months). Median OS was 17.4 months with a minimum follow-up of 12 months, with 1-year survival being 72% (at the time of analysis, 59% patients were still alive). This study formed the basis of the hypothesis tested in the NO16966 study that the XELOX regimen used in M66016 was of similar efficacy to FOLFOX-4.

One of the two primary objectives of the NO16966 study was to determine whether the assumption that the XELOX regimen tested in trial M66016 was non-inferior to FOLFOX-4. As presented in this submission, the study confirmed that this was the case and the EMEA accepted that the XELOX regimen used in NO16966 represents a useful alternative to a widely used current standard and modified the Marketing Authorisation of

Xeloda (capecitabine) accordingly. A similar result was obtained from the NO16967 study which demonstrated the non-inferority of this XELOX regimen compared to FOLFOX-4 in patients with relapsed mCRC (Rothenberg *et al.* 2007). The XELOX regimen used in NO16966 is the only one which Roche promotes and to the best of our knowledge is the only combination of capecitabine and oxaliplatin with significant use in the UK or elsewhere

In summary, there is no reason to believe that any other regimen of oxaliplatin plus 5-FU offers clinical benefits over the FOLFOX-4 control used in the NO16966 study, though the FOLFOX-6 regimen is more convenient (and sometimes used in the UK as a result) and will therefore have different costs associated with it. These are considered in the cost-effectiveness part of our original NICE STA submission.

Similarly, there is no evidence that any variation on the XELOX regimen used in NO16966 and elsewhere and promoted by Roche would offer any clinical benefit, nor that such variants have any significant use in clinical practice.

A2. **A2 Priority question: Section 6.7.5.1. The validity of combining the two parts of the study may be questioned. Please provide the statistical rationale for pooling of patients receiving chemotherapy alone (XELOX or FOLFOX) in the two arm open label study with those receiving FOLFOX or XELOX plus placebo in the 2x2 factorial design. In addition, please clarify how you have accounted for between study variability in the estimate for the baseline treatment mean for patients receiving chemotherapy alone (XELOX or FOLFOX) with those receiving FOLFOX or XELOX plus placebo and how you have preserved the randomisation of the two study designs (two arm design and 2x2 factorial design) when estimating population treatment effects.**

See A3 below

A3. **Priority question: Section 6.8.1.1. Although a statistically significant treatment action (p=0.7025) was ruled out in the 2x2 factorial trial, a high p-value could reflect low power and so cannot be taken as evidence for no interaction (Montgomery et al BMC Medical Research Methodology 2003, 3.26; available at http://www.biomedcentral.com/1471-2288/3/26). Did the N016966 trial have sufficient power to detect an interaction between each treatment group? If the trial had sufficient power to detect a difference between treatments, could you please provide a power curve and further details on the test for interaction including 95% confidence intervals etc.**

2/3.1 Pooling of data from the two parts of NO16966 was pre-planned

Question A2 and A3 both relate to the pooling of data from different study arms and the test of heterogeneity used to justify this. Pooling of data from the first and second parts of

the study was pre-planned and allowed for in the power calculations for the study. Therefore answers to both questions A2 and A3 are covered simultaneously below.

Section 13 of the Study Data Reporting and Analysis Manual (DRAM) provides further details on these methods and states the following:-

13. POWER CALCULATIONS

13.1 Final Analysis

1200 events in the eligible patient population of all randomized patients are necessary to ensure 90% power for the non-inferiority testing as outlined in section 9.2.2.1.1.1. However, in case of interaction, 900 events in the eligible patient population of patients randomized either to the initial 2-arm part or the placebo containing arms of the 4-arm factorial part of the study will still ensure 80% power for the non-inferiority testing as outlined in section 9.2.2.1.1.2.1. To achieve this number of events, it was decided to recruit an additional 300 patients to the initial 2-arm part of the study and so increase the planned sample size of 1620 patients to 1920 (600 patients to initial 2-arm part and 1320 patients to the factorial 4-arm part). The required number of 900 events in the non-bevacizumab treatment groups will occur later than the 1200 events among all patients. The time-point of the final analysis will therefore be determined by the 900 events in the eligible patient population of arms A', A, B' and B [XELOX, B-XELOX, FOLFOX, B-FOLFOX] (expected to occur approximately 26 months after start of enrolment into the factorial 4-arm part).

The approach to interaction testing as a precursor to pooling study arms for analysis was prospectively defined and described within the Study Data Reporting and Analysis Manual (DRAM) along with the statistical power of the interaction test to be applied. Sections 9.2.1-9.2.1.2 of the DRAM are reproduced as follows:-

9.2.1 ASSESSMENT OF HETEROGENEITY

An interaction test will be performed on the primary endpoint TTP or death to detect any kind of interaction between the different regimens (FOLFOX-4, XELOX, placebo, bevacizumab). Independent of the results of the interaction test, clinical assessment of the treatment effect in the subgroups will also be investigated for XELOX+bevacizumab vs. XELOX+placebo, FOLFOX-4+bevacizumab vs. FOLFOX-4+placebo, XELOX/XELOX+placebo vs. FOLFOX-4/FOLFOX-4+placebo and XELOX+bevacizumab vs. FOLFOX-4+bevacizumab. The overall assessment of whether a clinically and statistically relevant interaction exists will take into consideration the results of all the interaction tests as well as the magnitude of the point estimates of the treatment effect in the various treatment groups. An interaction between the different regimens (XELOX, FOLFOX-4, placebo and bevacizumab) cannot be ruled out if either the statistical interaction test is significant or the subgroup comparison shows a clinically relevant difference.

9.2.1.1 Testing for Interaction

The interaction test will primarily focus on the primary endpoint, TTP or death, but the results of the assessment applied to the endpoints overall survival as well as overall response rate will also be presented. To achieve maximum power for the test, the anlysis will be performed on cohort A and ITT population. For time to disease progression, the interaction test will be based on Cox proportional hazards regression with binary covariates for

• type of chemotherapy (XELOX versus FOLFOX-4),
• treatment with bevacizumab (YES versus NO),
• interaction term (cross product of above factors).

Under the assumption that the addition of bevacizumab adds full benefit to one regimen (either XELOX or FOLFOX-4), but no benefit to the other regimen, the interaction ratio would be 1/0.75 = 1.33 ($HR_{FA/F} = 1$ versus $HR_{XA/X} = 0.75$). With a two-sided significance level of 5%, the test will have 75% power. This is based on the following assumptions:

• Study duration is 35 months, enrolment is 108 patients/month.
• 600 patients are enrolled under the initial 2-arm part.
• 1320 patients are enrolled to the factorial 4-arm part.
• Median TTP or death for FOLFOX-4/XELOX +/- placebo is 8 months.
• Median TTP or death for FOLFOX-4/XELOX + bevacizumab is 10.67 months.
• The interaction effect is measured as $\ln(HR_{XA/X}) - \ln(HR_{FA/F})$ and its standard deviation is approximated by $\sqrt{(1/E_{VX} + 1/E_{VF} + 1/E_{VXA} + 1/E_{VFA})}$.

Table 1 shows the simulated power of the above mentioned interaction test (chance to conclude interaction) for different values of the two-sided significance level α and the assumed underlying interaction ratio (IR).

Table 1 Power of Interaction Test (in %)

α	**IR=1 Median = 8 months**	**1 Median = 10.667 months**	**1.05**	**1.1**	**1.15**	**1.2**	**1.25**	**1.33**
0.05	4.95	4.89	7.31	13.98	24.77	38.92	54.08	76.18
0.10	9.89	9.96	13.18	22.31	36.28	51.23	66.57	84.94
0.15	15.07	14.99	18.92	29.29	44.12	59.64	73.41	88.97
0.2	20	20	24.14	35.67	50.42	66.16	78.51	91.7

The interaction test will be repeated for the two secondary parameters overall survival (based on Cox proportional hazards regression) and overall rate of best response (based on logistic regression). In case of a significant result the null hypothesis of no interaction will be rejected and it will be considered as evidence that there is a statistically relevant interaction. If there is such evidence, the pooling of the subgroups for efficacy may not be appropriate.

9.2.1.2 Clinical Assessment of Interaction

In addition to the statistical interaction testing, a clinical assessment of the treatment effect in the treatment subgroups will also be performed for XELOX+bevacizumab vs. XELOX+placebo, FOLFOX-4+bevacizumab vs. FOLFOX-4+placebo, XELOX/XELOX+placebo vs. FOLFOX-4/FOLFOX-4+placebo and XELOX+bevacizuamb vs. FOLFOX-4+bevacizumab. Point estimates of the median with 95% confidence interval and the hazard ratio with its 97.5% confidence interval form the basis for the clinical assessment. If the overall clinical and statistical assessments lead to the conclusion that no relevant interaction exists, it will be regarded as justification for pooling the two different chemotherapy subgroups in the Bevacizumab / Placebo comparison and for pooling Bevacizumab and non Bevacizumab in the XELOX / FOLFOX-4 comparison".

2/3.2 Application of pre-specified heterogeneity testing permits data pooling

Sections 4.2.1 and Sections 4.2.2 of the Clinical Study Report (CSR) for the NO16966 study report the results of the application of the DRAM specified heterogeneity testing to the results of the NO16966 study and the justification this provides for pooling data:-

4.2.1.4 PFS: Assessment of Treatment Interaction – Non-inferiority

Based on the below results from the statistical and clinical assessments of treatment interaction, the overall comparison of non-inferiority for PFS, XELOX/XELOX+P/XELOX+BV versus FOLFOX-4/FOLFOX-4+P/FOLFOX-4+BV was justifiable as the primary analysis of non-inferiority according to the protocol.

4.2.1.4.1 PFS: Statistical Assessment – Non-inferiority

The statistical test for interaction was based on Cox proportional hazards regression. This is a two-sided test with a significance level of 5%. If there was a statistically significant result, the null hypothesis of no interaction would be rejected and it would be concluded that there was a statistically relevant interaction. The test resulted in a p-value of 0.7025. This result indicated that a statistically significant interaction could be excluded.

4.2.1.4.2 PFS: Clinical Assessment – Non-inferiority

A clinically relevant treatment interaction between bevacizumab and the chemotherapy backbone was ruled out based on the following findings:

- Non-inferiority in terms of PFS was demonstrated in the treatment subgroup comparison of XELOX/XELOX+P versus FOLFOX-4/FOLFOX-4+P (an analysis that excluded patients treated with bevacizumab) and was supported by the exploratory analysis of XELOX compared with FOLFOX-4 in the initial 2-arm part of the study
- The outcome for PFS was similar for FOLFOX-4+BV and XELOX+BV in the prespecified exploratory non-inferiority analysis comparing these treatment subgroups.

Bevacizumab added benefit to both XELOX and FOLFOX-4 in terms of PFS. Although the finding was not statistically significant for the FOLFOX-4 treatment subgroup, the results in both treatment subgroups went in the same direction.

4.2.2.4 PFS: Assessment of Treatment interaction - Superiority

The statistical assessment provided for testing of non-inferiority applies as well to testing for superiority. The statistical test for treatment interaction resulted in a p-value of 0.7025. Any clinically relevant treatment interaction was ruled out based on the non-inferiority of XELOX/XELOX+P versus FOLFOX-4/FOLFOX- 4+P, non-inferiority of XELOX+BV versus FOLFOX-4+BV and added benefit by BV compared with placebo in both XELOX and FOLFOX-4 treatment subgroups. Based on the results of the statistical and clinical assessments of treatment interaction, the overall comparison for superiority in terms of PFS, XELOX+BV/FOLFOX+BV versus XELOX+P/FOLFOX+P, was justifiable as the primary analysis of superiority according to the protocol.

2/3.3 Regulators agree to extended data pooling

This approach to the pooling of data has been reviewed by medicines regulators throughout the world, including the EMEA in Europe which have all deemed it acceptable.

During early discussions with, the German Health Authority (BfArM) in their capacity as reapporteur to the EMEA on the relevant regulatory submission, an exploratory analysis based on all patients from Part I (2-arm) and Part II (2x2 factorial) of the study was included in the analysis plan, to be used in case of a borderline result for PFS in the primary analysis of superiority of bevacizumab versus placebo in combination with XELOX or FOLFOX.

It became clear during data analysis (see answer to question A4) that the patients receiving FOLFOX plus placebo did unexpectedly well in terms of PFS and OS with exploratory analysis of baseline risk factors indicating that this was the result of an imbalance in baseline risk factors favouring this group. Considering the positive trend but not significant result for OS, this exploratory analysis was performed for OS. The aim of this exploratory analysis was to assess OS when the impact of the outlier cohort is reduced by including a larger population in the OS analysis. The exploratory analysis showed a statistically significant benefit of bevacizumab over placebo for OS (HR=0.83 97.5% CI [0.73;0.95], p= 0.0019.

An alternative approach to the problem of the imbalance of baseline risk factors in the 2 x 2 part of the study through omitting from the analysis patients receiving adjuvant chemotherapy prior to study entry (rather trying to dilute the imbalance by including patients from the initial 2-arm part of the study is also included in response to Question A4.

A4. **Priority question: Section 6.8.1.2. Please provide tabulated results (ITT analysis) for each of the six treatment groups separately for 1) progression free survival, 2) overall survival and 3) tumour response (including Kaplan-Meier curves with numbers at risk and failures). Ideally data should be reported as follows: median follow up, event rates (number of events/total number) for each arm separately. In addition, provide hazard ratios, confidence intervals and p-values for all (i.e. 15) pairs of treatment groups.**

4.1 Information provided

In the time available for responding to NICE's request for clarification it has not been possible to carry out all of the additional statistical analysis required to provide all of the extra information requested. For each parameter the currently available data will be presented.

4.2 Response rate by study arm

In addition to the pooled results already provided this is available for the following individual study arms: P-FOLFOX, B-XELOX, B-FOLFOX as presented in Table 4.1

Table 4.1 Response rate by study arm in NO16966 study (ITT)

	Regimen		
	P-FOLFOX N=351	**B-FOLFOX (N=349)**	**B-XELOX (N=350)**
Overall Response % (95% CI)	50.4 (45.1; 55.8)	47.3 (41.9; 52.7)	46.3 (41.0; 51.7)
Complete Response % (95% CI)	2.0 (0.8; 4.1)	1.1 (0.3; 2.9)	1.1 (0.3; 2.9)
Partial Response % (95% CI)	48.4 (43.1; 53.8)	46.1 (40.8; 51.5)	45.1 (39.8; 50.5)
Stable Disease % (95% CI)	31.1 (26.2; 36.2)	35.8 (30.8; 41.1)	33.1 (28.2; 38.3)
Progressive Disease % (95% CI)	10.8 (7.8; 14.6)	4.3 (2.4; 7.0)	5.7 (3.5; 8.7)
Missing (no response assessment) %	7.7	12.6	14.9

The response rates shown in Table A4.1 are compared with each other in Table 4.2

Table 4.2 Differences in response rates between study arms shown in Table 4.1

Regimen A (response rate %)	**Regimen B (response rate %)**	**Difference in response rates (A-B%) (95% CI)**	**Odds ratio (97.5% CI) p-Value Chi-squared test**
B-FOLFOX (47.3)	P-FOLFOX (50.4)	-3.15 (-11.8; 5.5)	0.88 (0.63; 1.24) p=0.4048
B-XELOX (46.3)	B-FOLFOX (47.3)	-0.99 (-9.6; 7.6)	0.96 (0.68; 1.35)

In addition response rates for the B-XELOX and P-XELOX arms are available for the eligible patient population (EPP) as shown in Table 4.3

Table 4.3 Response rate by study arm in NO16966 study (EPP)

	Regimen	
	B-XELOX n=337	**P-XELOX n=327**
Overall Response % (95% CI)	46.0 (40.6; 51.5)	48.6 (43.1; 54.2)
Complete Response % (95% CI)	0.9 (0.2; 2.6)	2.4 (1.1; 4.8)
Partial Response % (95% CI)	45.1 (39.7; 50.6)	46.2 (40.7; 51.7)
Stable Disease % (95% CI)	33.2 (28.2; 38.5)	30 (25.1; 35.3)
Progressive Disease % (95% CI)	5.6 (3.4; 8.7)	11.3 (8.1; 15.3)
Missing (no response assessment) %	15.1	10.1
Difference in response rate B-XELOX-P-XELOX % (95% CI)	-2.63 (-11.5; 6.2)	
Odds ratio (95% CI) p-Value (Chi-squared Test)	0.90 (0.64; 1.28) p=0.4975	

4.3 Progression-free survival (PFS) by study arm

Table 4.4 shows which comparisons of PFS are currently available and in which Table the relevant pairwise comparison of PFS can be found.

Table 4.4 Comparisons of PFS for single study arms currently available for Study NO16966 (all ITT)

	FOLFOX	**XELOX**	**P-FOLFOX**	**P-XELOX**	**B-FOLFOX**	**B-XELOX**
FOLFOX	Not applicable	Yes- Table 4.5	No	No	No	No
XELOX	Yes- Table 4.5	Not applicable	No	No	No	No
P-FOLFOX	No	No	Not Applicable	No	Yes-Table 4.6	Yes- Table 4.7
P-XELOX	No	No	No	Not Applicable	Yes-Table 4.8	Yes-Table 4.9
B-FOLFOX	No	No	Yes-Table 4.9	Yes-Table 4.8	Not Applicable	Yes-Table 4.10
B-XELOX	No	No	Yes- Table 4.7	Yes-Table 4.6	Yes- Table 4.10	Not Applicable

Table 4.5 Comparison of PFS in the FOLFOX and XELOX arms of study NO16966 (ITT)

	FOLFOX-4 (N=317)	XELOX (N=317)

Patients with event	299 (94.3 %)		290 (91.5 %)
Patients without events*	18 (5.7 %)		27 (8.5 %)
Time to event (days)			
Median#	234.0		217.0
95% CI for Median#	[211;251]		[197;241]
25% and 75%-ile	139;332		136;326
Range##	1 to 1205		1 to 1164
Hazard Ratio		0.95	
97.5% CI		[0.79;1.15]	

* censored
# Kaplan-Meier estimate
including censored observations

Table 4.6 Comparison of PFS in the P-FOLFOX and B-FOLFOX arms of study NO16966 (ITT)

	P-FOLFOX (N=351)		B-FOLFOX (N=349)
Patients with event	321 (91.5 %)		299 (85.7 %)
Patients without events*	30 (8.5 %)		50 (14.3 %)
Time to event (days)			
Median#	261.0		285.0
95% CI for Median#	[241;279]		[264;302]
25% and 75%-ile	170;384		185;423
Range##	1 to 876		1 to 987
p-Value (Log-Rank Test)		0.1312	
Hazard Ratio		0.89	
97.5% CI		[0.74;1.06]	

* censored
# Kaplan-Meier estimate
including censored observations

Table 4.7 Comparison of PFS in the P-FOLFOX and B-XELOX arms of study NO16966 (ITT)

	P-FOLFOX (N=351)		B-XELOX (N=350)
Patients with event	321 (91.5 %)		295 (84.3 %)
Patients without events*	30 (8.5 %)		55 (15.7 %)
Time to event (days)			
Median#	261.0		284.0
95% CI for Median#	[241;279]		[267;302]
25% and 75%-ile	170;384		186;400
Range##	1 to 876		1 to 894
p-Value (Log-Rank Test)		0.0965	
Hazard Ratio		0.87	
97.5% CI		[0.73;1.05]	

* censored
\# Kaplan-Meier estimate
\## including censored observations

Table 4.8 Comparison of PFS in the P-XELOX and B-FOLFOX arms of study NO16966 (ITT)

	P-XELOX (N=350)		B-FOLFOX (N=349)
Patients with event	301 (86.0 %)		299 (85.7 %)
Patients without events*	49 (14.0 %)		50 (14.3 %)
Time to event (days)			
Median#	225.0		285.0
95% CI for Median#	[203;248]		[264;302]
25% and 75%-ile	136;353		185;423
Range##	1 to 910		1 to 987
p-Value (Log-Rank Test)		0.0108	
Hazard Ratio		0.81	
97.5% CI		[0.68;0.98]	

* censored
\# Kaplan-Meier estimate
\## including censored observations

Table 4.9 Comparison of PFS in the P-XELOX and B-XELOX arms of study NO16966 (ITT)

	P-XELOX (N=350)		B-XELOX (N=350)
Patients with event	301 (86.0 %)		295 (84.3 %)
Patients without events*	49 (14.0 %)		55 (15.7 %)
Time to event (days)			
Median#	225.0		284.0
95% CI for Median#	[203;248]		[267;302]
25% and 75%-ile	136;353		186;400
Range##	1 to 910		1 to 894
p-Value (Log-Rank Test)		0.0059	
Hazard Ratio		0.80	
97.5% CI		[0.66;0.96]	

* censored
\# Kaplan-Meier estimate
\## including censored observations

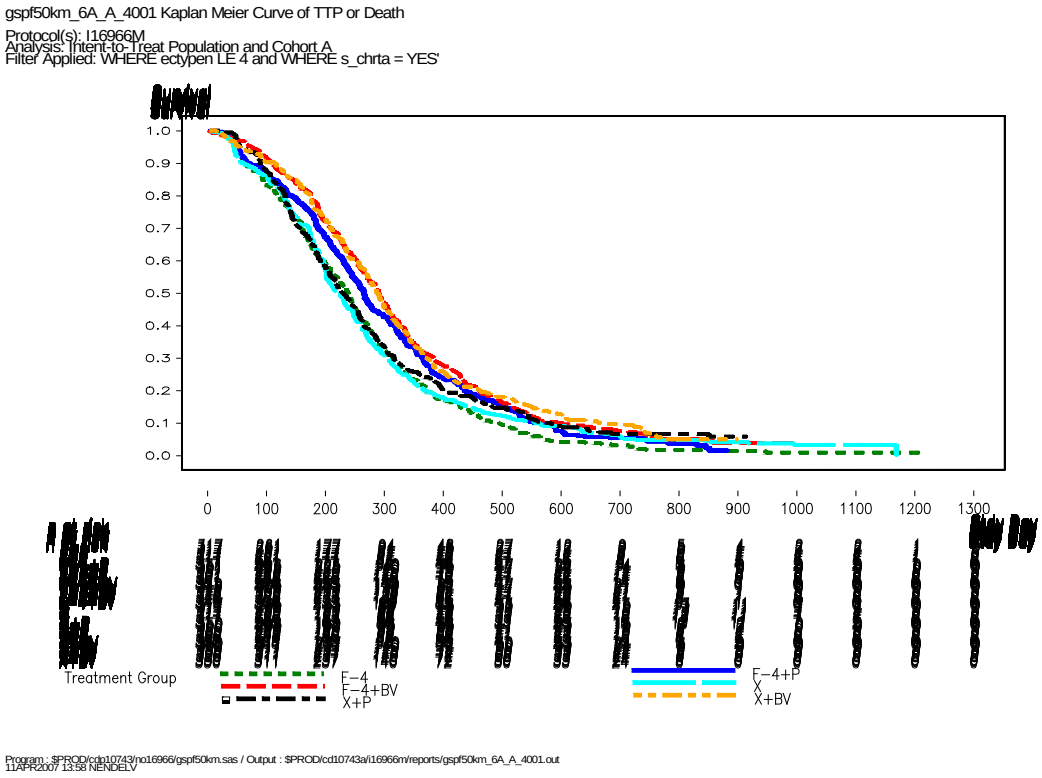
Table 4.10 Comparison of PFS in the B-FOLFOX and B-XELOX arms of study NO16966 (ITT)

	B-FOLFOX (N=349)		B-XELOX (N=350)
Patients with event	299 (85.7 %)		295 (84.3 %)
Patients without events*	50 (14.3 %)		55 (15.7 %)
Time to event (days)			
Median#	285.0		284.0
95% CI for Median#	[264;302]		[267;302]
25% and 75%-ile	185;423		186;400
Range##	1 to 987		1 to 894
Hazard Ratio		0.99	
97.5% CI		[0.82;1.19]	

* censored
\# Kaplan-Meier estimate
\## including censored observations

Kaplan-Meier curves for all 6 treatment arms with numbers at risk are shown in Figure 4.1

Figure 4.1 Kaplan-Meier PFS curves for individual study arms in Study NO16966



Paired Kaplan-Meier PFS curves for individual study arms are contained in Appendix 1. The pairs of curves available and location are shown in Table 4.11

Table 4.11 Pairs of Kaplan-Meier ITT OS curves presented in Appendix 1 and location within the Appendix

	FOLFOX	**XELOX**	**P-FOLFOX**	**P-XELOX**	**B-FOLFOX**	**B-XELOX**
FOLFOX	Not applicable	Yes- Figure 9	No	No	No	No
XELOX	Yes- Figure 9	Not applicable	No	No	No	No
P-FOLFOX	No	No	Not Applicable	No	Yes-Figure 2	Yes-Figure 4
P-XELOX	No	No	No	Not Applicable	Yes-Figure 3	Yes-Figure 10
B-FOLFOX	No	No	Yes-Figure 2	Yes-Figure 3	Not Applicable	Yes-Figure 5
B-XELOX	No	No	Yes- Figure 4	Yes- Figure 10	Yes-Figure 5	Not Applicable

4.4 Overall survival (OS) by study arm

Table 4.12 shows which comparisons of PFS are currently available

Table 4.12 Comparisons of OS for single study arms currently available for Study NO16966 (all ITT)

	FOLFOX	XELOX	P-FOLFOX	P-XELOX	B-FOLFOX	B-XELOX
FOLFOX	Not applicable	Yes- Table 4.13	No	No	No	No
XELOX	Yes- Table 4.13	Not applicable	No	No	No	No
P-FOLFOX	No	No	Not Applicable	No	Yes-Table 4.14	No
P-XELOX	No	No	No	Not Applicable	No	Yes-Table 4.15
B-FOLFOX	No	No	Yes-Table 4.14	No	Not Applicable	Yes-Table 4.16
B-XELOX	No	No	No	Yes-Table 4.15	Yes- Table 4.16	Not Applicable

Table 4.13 Comparison of OS in the FOLFOX and XELOX arms of study NO16966 (ITT)

	FOLFOX (N=317)	XELOX (N=317)
Patients with event	262 (82.6 %)	250 (78.9 %)
Patients without events*	55 (17.4 %)	67 (21.1 %)
Time to event (days)		
Median#	539.0	572.0
95% CI for Median#	[488;567]	[481;618]
25% and 75%-ile	294;837	295;944
Range##	1 to 1252	5 to 1254
Hazard Ratio	0.90	
97.5% CI	[0.74;1.10]	

* censored
\# Kaplan-Meier estimate
\## including censored observations

Table 4.14 Comparison of OS in the P-FOLFOX and B-FOLFOX arms of study NO16966 (ITT)

	P-FOLFOX (N=351)		B-FOLFOX (N=349)
Patients with event	224 (63.8 %)		209 (59.9 %)
Patients without events*	127 (36.2 %)		140 (40.1 %)
Time to event (days)			
Median#	619.0		644.0
95% CI for Median#	[576;710]		[583;708]
25% and 75%-ile	356;889		379;967
Range##	11 to 1081		1 to 992
p-Value (Log-Rank Test)		0.4937	
Hazard Ratio		0.94	
97.5% CI		[0.75;1.16]	

* censored
\# Kaplan-Meier estimate
including censored observations

Table 4.15 Comparison of OS in the P-XELOX and B-XELOX arms of study NO16966 (ITT)

	P-XELOX (N=350)		B-XELOX (N=350)
Patients with event	231 (66.0 %)		211 (60.3 %)
Patients without events*	119 (34.0 %)		139 (39.7 %)
Time to event (days)			
Median#	584.0		650.0
95% CI for Median#	[526;636]		[602;712]
25% and 75%-ile	334;913		405;.
Range##	1 to 1078		3 to 982
p-Value (Log-Rank Test)		0.0698	
Hazard Ratio		0.84	
97.5% CI		[0.68;1.04]	

* censored
\# Kaplan-Meier estimate
including censored observations

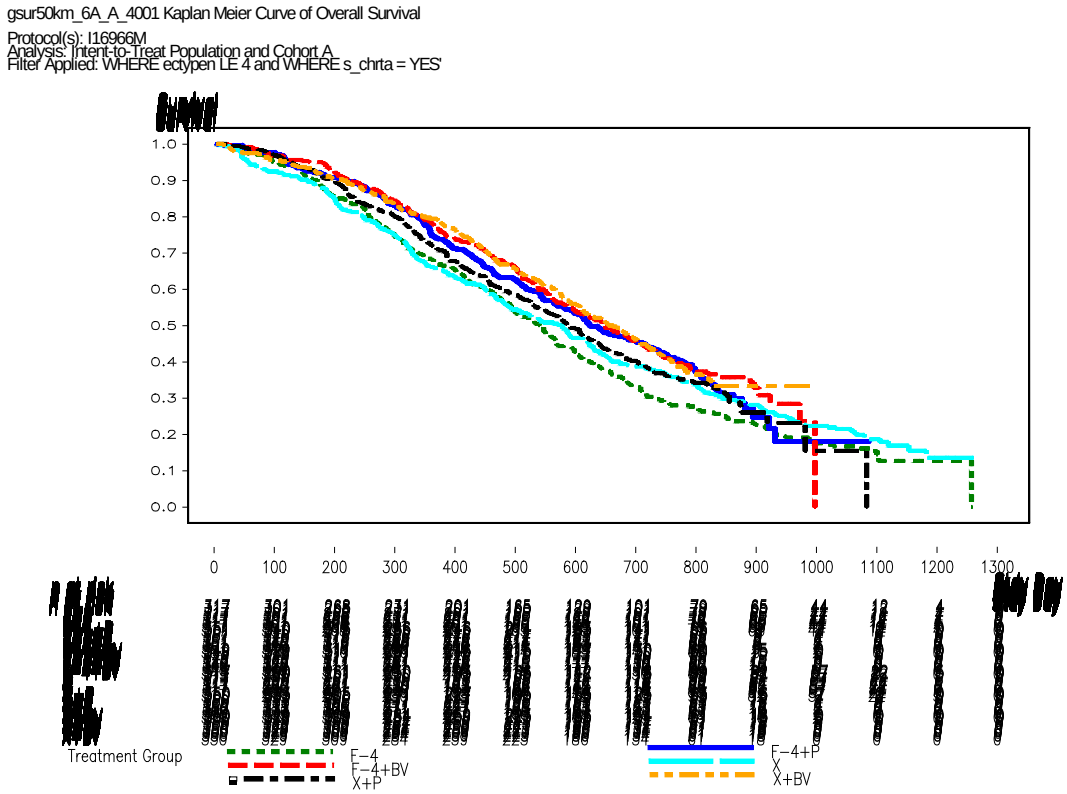
Table 4.16 Comparison of OS in the B-FOLFOX and B-XELOX arms of study NO16966 (ITT)

	B-FOLFOX (N=349)		B-XELOX (N=350)
Patients with event	209 (59.9 %)		211 (60.3 %)
Patients without events*	140 (40.1 %)		139 (39.7 %)
Time to event (days)			
Median#	644.0		650.0
95% CI for Median#	[583;708]		[602;712]
25% and 75%-ile	379;967		405;.
Range##	1 to 992		3 to 982
Hazard Ratio		0.99	
97.5% CI		[0.80;1.23]	

* censored
\# Kaplan-Meier estimate
\## including censored observations

Kaplan-Meier curves for all 6 treatment arms with numbers at risk are shown in Figure 4.2

Figure 4.2 Kaplan-Meier OS curves for individual study arms in Study NO16966



The paired Kaplan-Meier OS curves for individual study arms listed in Table 4.17 are are contained in Appendix 1

Table 4.17 Pairs of Kaplan-Meier ITT OS curves presented in Appendix XXXX and location within the Appendix

	FOLFOX	XELOX	P-FOLFOX	P-XELOX	B-FOLFOX	B-XELOX
FOLFOX	Not applicable	Yes- Figure 1	No	No	No	No
XELOX	Yes- Figure 1	Not applicable	No	No	No	No
P-FOLFOX	No	No	Not Applicable	No	Yes- Figure 6	No
P-XELOX	No	No	No	Not Applicable	No	Yes-Figure 7
B-FOLFOX	No	No	Yes-Figure 6	No	Not Applicable	Yes-Figure 8
B-XELOX	No	No	No	Yes-Figure 7	Yes-Figure 8	Not Applicable

4.5 Analysis and commentary on outcomes in individual study arms of NO16966

It is clear from the presentation of results by study arm that the P-FOLFOX arm is an outlier with regard to survival outcomes compared to all other non-bevacizumab groups (see Figures 4.1 and 4.2). The good outcomes in this group will have had the effect of diminishing the benefit from bevacizumab. It seemed likely that the good outcome of the P-FOLFOX group might have been due to an imbalance of baseline prognostic characteristics and this was investigated.

4.5.1 P-FOLFOX patients with prior adjuvant chemotherapy perform unexpectedly well.

Pre-defined subgroup analyses of PFS in part II of the NO16966 study showed a consistent benefit of bevacizumab vs placebo across all subgroups, with the marked exception of patients with prior adjuvant treatment in the FOLFOX arms (Table 4.18).

Table 4.18 PFS, Treatment Subgroup Comparison for Superiority: Previous Adjuvant Chemotherapy versus No Previous Adjuvant Chemotherapy

		No of patients		
Treatment group	Adjuvant chemotherapy	Placebo	BV	Hazard ratio (97.5% CI)
FOLFOX	No	266	261	0.72 (0.58, 0.90)
	Yes	85	88	**1.75 (1.15, 2.65)**
XELOX	No	259	274	0.77 (0.61, 0.96)
	Yes	91	76	0.75 (0.50, 1.12)

Source: espf13bl_AP_I_4001.out, espf13bl_AP_J_4001.out

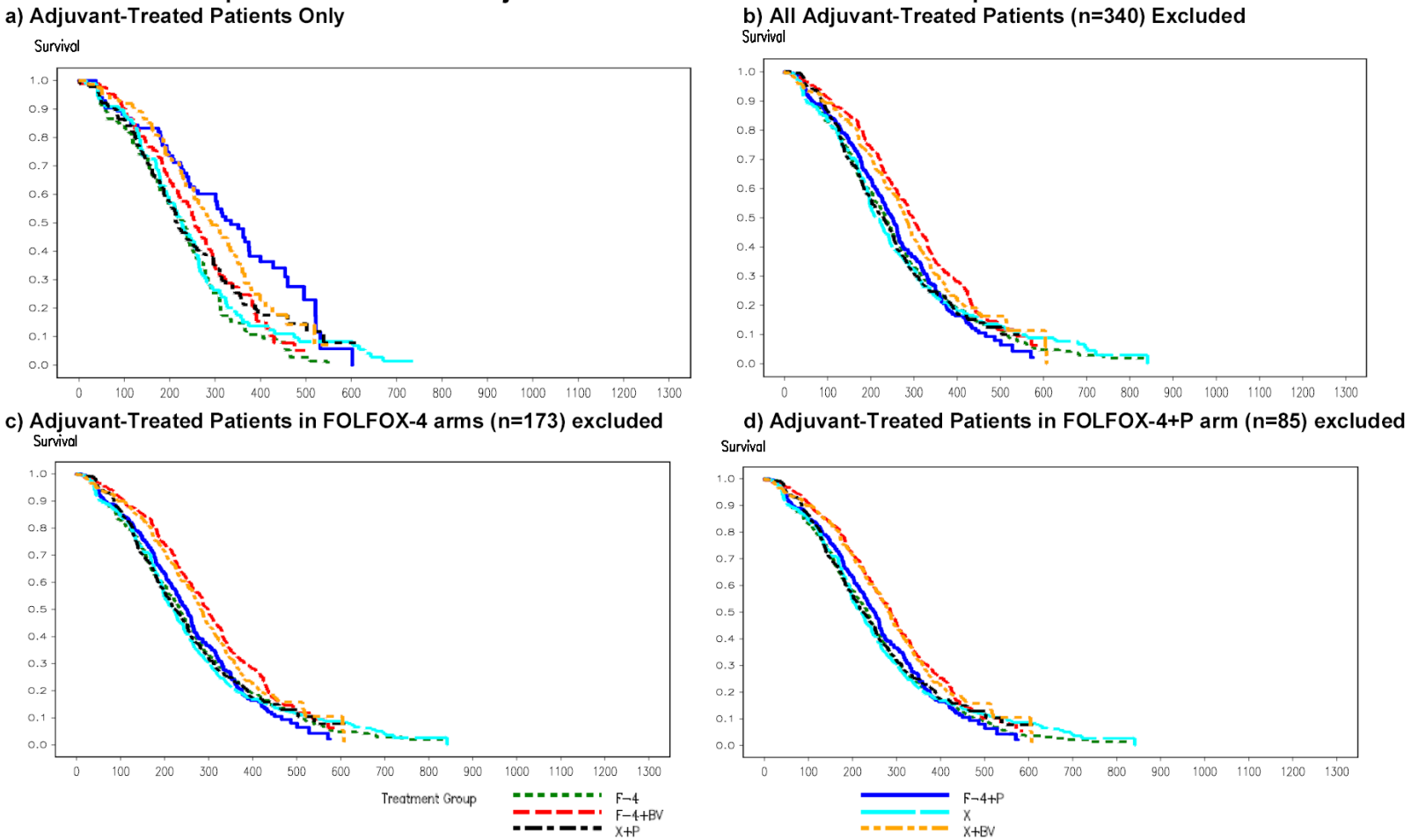
Additional exploratory analyses were, therefore, performed on the subgroup of patients with previous adjuvant treatment to evaluate whether this subgroup of patients was driving the unexpected results in the overall analysis.

Comparison of PFS across the 6 arms in the adjuvant-treated patient subgroup shows a markedly better outcome for the P-FOLFOX patients compared to the other three similar performing chemotherapy arms (i.e., FOLFOX, XELOX and P-XELOX) (Figure 4.3a). In contrast, all four chemotherapy PFS curves (XELOX, P-XELOX, FOLFOX and P-FOLFOX) are seen to be similar in outcomes in the following situations:

i.) all adjuvant-treated patients are excluded from the ITT population (Figure 4.3b), or

ii.) the adjuvant-treated patients are excluded from the FOLFOX arms only (Figure 4.3c), or the outlying adjuvant-treated patients (i.e. those with a better performance) are excluded from the FOLFOX-P arm only (Figure 4.3d).

Figure 4.3 **Study NO16966: KM Plots of PFS – Six-arm Comparison in Adjuvant-treated Patients and After Step-wise Exclusion of Adjuvant-treated Patients from the ITT Population**



source outputs gspf50km_6A_A_4006, gspf50km_6A_A_4007, gspf50km_6A_A_4159, gspf50km_6A_A_4017

The better performance of patients treated with adjuvant chemotherapy in the P-FOLFOX arm could thus explain the unexpected HR of 1.75 seen for the P-FOLFOX vs B-FOLFOX comparison in adjuvant-treated patients as well as the lower magnitude of benefit seen in the overall population.

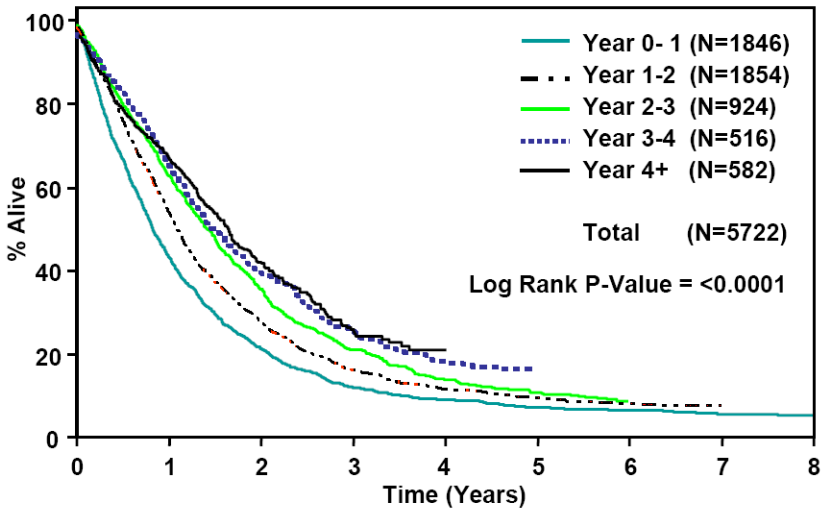
4.5.2 Why P-FOLFOX patients with prior adjuvant treatment perform anomalously

Time to recurrence after surgery is a significant prognostic factor recently identified by the ACCENT group (O'Connell *et al* 2008). A similar parameter (time from start of adjuvant treatment to randomization in study NO16966) was found to be associated with survival outcome in the NO16966 study.

To explore potential explanations for the unexpectedly good outcome in the P-FOLFOX patients with previous adjuvant treatment, baseline characteristics were compared in the adjuvant subgroup of patients.

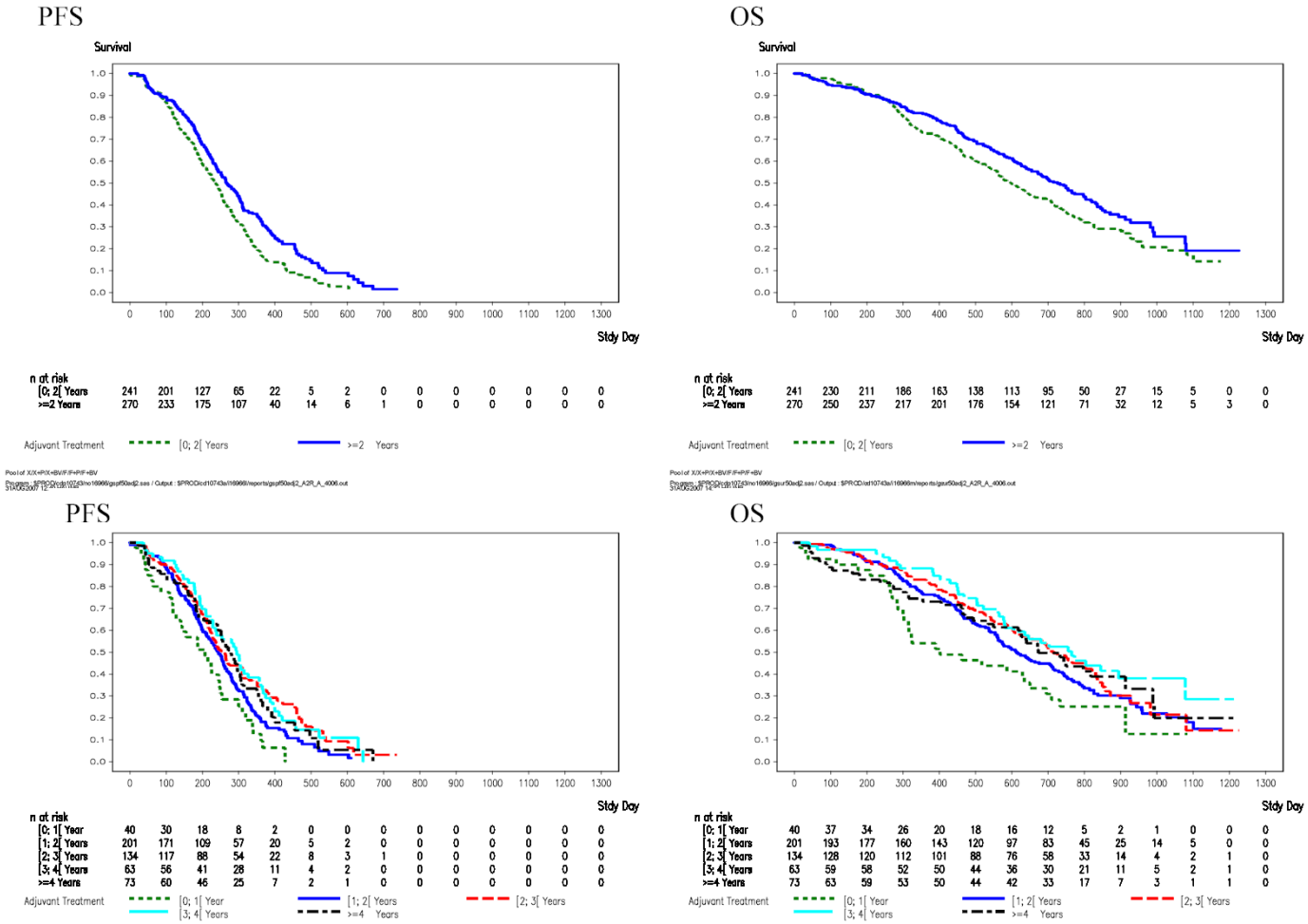
Recently, the Adjuvant Colon Cancer Endpoint (ACCENT) group showed in a pooled analysis of 5722 patients whose disease recurred after surgery and adjuvant treatment (O'Connell *et al* 2008) that there is a direct correlation between the time to recurrence after surgery and survival after recurrence (Figure 4.4). These data suggest that patients with a slower tumour growth leading to later recurrence after surgery have an improved survival due to slow growth of the recurrent tumour.

Figure 4.4 **ACCENT Group Data: Duration of Survival after Recurrence by Time to Recurrence after Surgery/Start of Adjuvant Therapy (O'Connell *et al* 2008)**



Using a similar parameter, time from start of adjuvant treatment to randomisation (the start of adjuvant treatment being close to surgery and randomization in NO16966 close to recurrence), a similar correlation between survival outcome and time from start of adjuvant therapy until randomization is apparent in the NO16966 dataset. Of particular note in the NO16966 group of adjuvant-treated patients, is the very poor outcome in patients with a time from start of adjuvant treatment to randomization of less than one year (Figure 1.5)

Figure 1.5 Study NO16966: Survival Endpoints by Time from Start of Adjuvant Therapy to Randomization



Source: gspf50adj2_A2R_A_4006gsur50adj2_A2R_A_4006, gspf50adj5_A5R_A_4006gsur50adj5_A5R_A_4006

Longer time from start adjuvant therapy to randomization in NO16966 could explain the better outcome in adjuvant- treated patients in the P-FOLFOX arm.

Consistent with the better than expected outcome in the P-FOLFOX arm, median time from start/end of adjuvant therapy to randomization (close to recurrence) was longer in the P-FOLFOX than in the other five treatment arms (Table 4.19).

Table 4.19 Study NO16966: Median Time to Recurrence - Patients with Prior Adjuvant Therapy

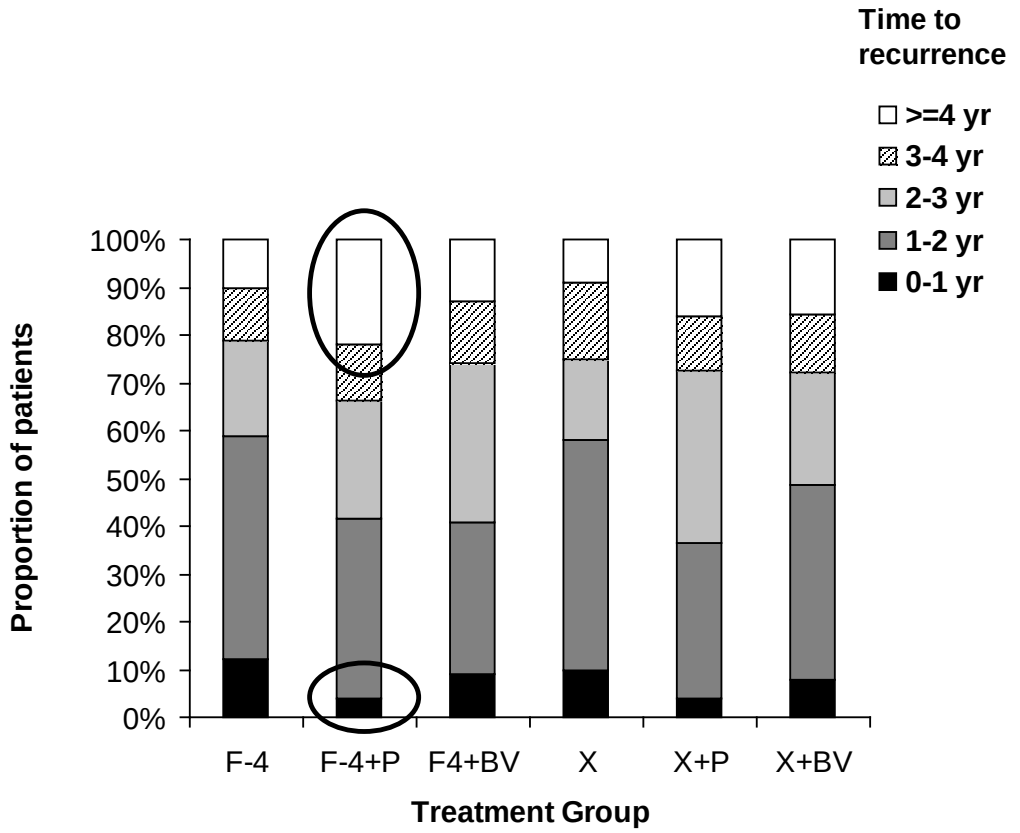
	FOLFOX N=83	**P-FOLFOX N=85**	**B-FOLFOX N=88**	**XELOX N=88**	**P-XELOX N=91**	**B-XELOX N=76**
Median time from start of adjuvant treatment to randomization in days (years)	613 (1.7)	**913 (2.5)**	813 (2.2)	687 (1.9)	843 (2.3)	725.5 (2.0)
Median time from end of adjuvant treatment to randomization in days (years)	517 (1.4)	**769 (2.1)**	623 (1.7)	511 (1.4)	660 (1.8)	597 (1.6)

Source: tr12ac_6aa4001

Furthermore, the P-FOLFOX group had the lowest proportion of patients with a time from start of adjuvant therapy to randomization of less than one year, and the highest proportion of patients with a time of ≥ 4 years, explaining, at least in part, the favourable outcome for this treatment group (Figure 4.6 **and**

Appendix 2).

Figure 4.6 Study NO16966: Distribution of Patients According to Time from Adjuvant treatment to Randomization by Treatment Arm



Source dm16adj_6aa4006 (

Appendix 2)

Abbreviations: F-4, FOLFOX; F-4+P, P-FOLFOX; F4+BV, B-FOLFOX; X, XELOX; X+P, P-XELOX; X+BV, B-XELOX

The ACCENT data (O'Connell *et al* 2008) showing that there is a significant direct correlation between the time to recurrence and overall survival in patients with mCRC were not available at the time of initiating the NO16966 trial. In light of these data as well as the NO16966 data, stratification for this factor would have been appropriate in the NO16966 trial and would have prevented the imbalance of this significant factor between P-FOLFOX and B-FOLFOX arm.

Three exploratory analyses, aimed at reducing the impact of the P-FOLFOX cohort, show a significant PFS benefit of bevacizumab vs placebo in the overall as well as both the treatment subgroup comparisons

Three exploratory analyses reducing the impact of the outlier patient cohort on PFS, show a more significant PFS benefit of bevacizumab vs Placebo in the overall comparison (Table 4.20) as well as in the FOLFOX comparison (Table 2) in part II of the study. This

translated into a significant improvement in the pooled OS comparison in favour of bevacizumab-treated patients as seen below.

Table 4.20 Study NO16966: PFS - HR after Step-wise Exclusion of Subgroups of Patients with Previous Adjuvant Chemotherapy

Population	No. of pts excluded from analysis	No. of pts included in analysis	HR (97.5%CI)	P-Value
All patients included (ITT)	0	1400	0.83 (0.72, 0.95)	0.0023
Exclusion of patients with adjuvant chemotherapy from all four treatment arms	85+91+88+76	1060 (1400-340)	0.74 (0.64, 0.87)	<0.0001
Exclusion of patients with adjuvant chemotherapy from FOLFOX arms only	85+88	1227 (1400-173)	0.75 (0.65, 0.87)	<0.0001
Exclusion of patients with adjuvant chemotherapy from P-FOLFOX arm only	85	1315 (1400-85)	0.77 (0.67;0.89)	<0.0001

Source data: espf40su, espf46su, espf73su, espf41su

Table 2.21 Study NO16966: PFS - HR after Step-wise Exclusion of Subgroups of Patients with Previous Adjuvant Chemotherapy: FOLFOX treatment subgroup

Population	No. of pts excluded from analysis	No. of pts included in analysis	HR (97.5%CI)	P-Value
All FOLFOX patients included (ITT)	0	700	0.89 (0.73, 1.08)	0.1871
Exclusion of patients with adjuvant chemotherapy from FOLFOX arms	85+88	527 (700 – 173)	0.72 (0.58, 0.90)	0.0009
Exclusion of patients with adjuvant chemotherapy from P-FOLFOX arm only	85	615 (700-85)	0.77 (0.63;0.95)	0.0051

Source data: espf40su, espf46su, espf73su, espf41su

A Cox regression model confirmed that time from start of adjuvant chemotherapy to randomization (recurrence) has an influence on OS.

The impact of time from start of adjuvant chemotherapy to randomization on OS was assessed using a Cox model including the time from start of adjuvant treatment to randomization as a variable (<900 days, >=900 days). The cut-off value 900 days was chosen because it is close to the median time from start of adjuvant treatment to

randomization in the P-FOLFOX group (913 days). When using this model, the HR for the pooled superiority comparison shifts from 0.89 (97.5% CI 0.76-1.03, p=0.0769) to 0.87 (97.5% CI [0.75;1.02], p=0.0437) showing that time from start of adjuvant chemotherapy to randomization (recurrence) has an influence on OS (**Appendix 1 Kaplan Meier Curves of OS and PFS for paired study arms in Study NO16966 (all ITT)**

Abbreviations: F-4, FOLFOX; F+BV, B-FOLFOX; F+P, P-FOLFOX; X, XELOX; X+BV, B-FOLFOX; X+P, P-XELOX.

Figure 1

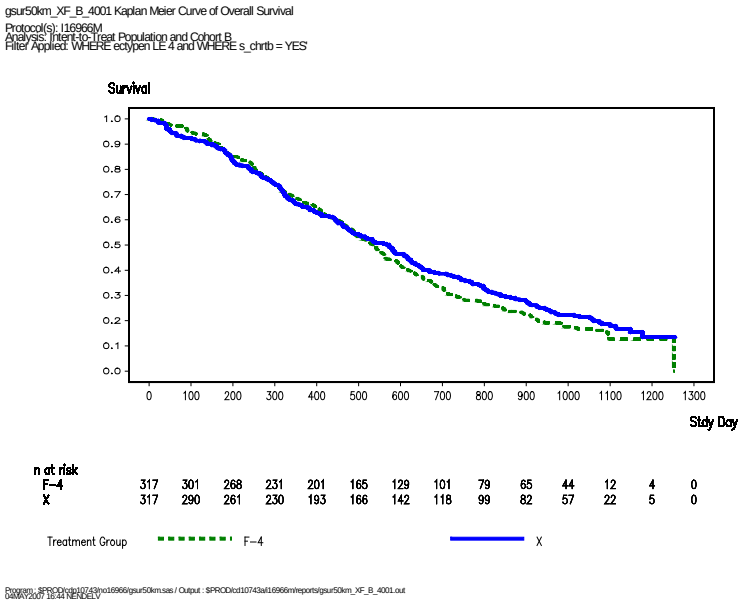
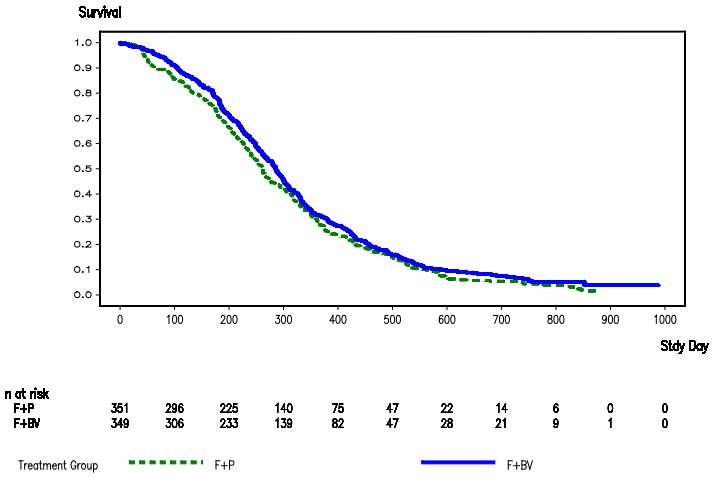


Figure 2

gspf50km_AP_I_4001 Kaplan Meier Curve of TTP or Death

Protocol(s): I16966M
Analysis: Intent-to-Treat Population and Cohort I
Filter Applied: WHERE ectypen LE 4 and WHERE s_chrti = YES'



n at risk											
F+P	351	296	225	140	75	47	22	14	6	0	0
F+BV	349	306	233	139	82	47	28	21	9	1	0

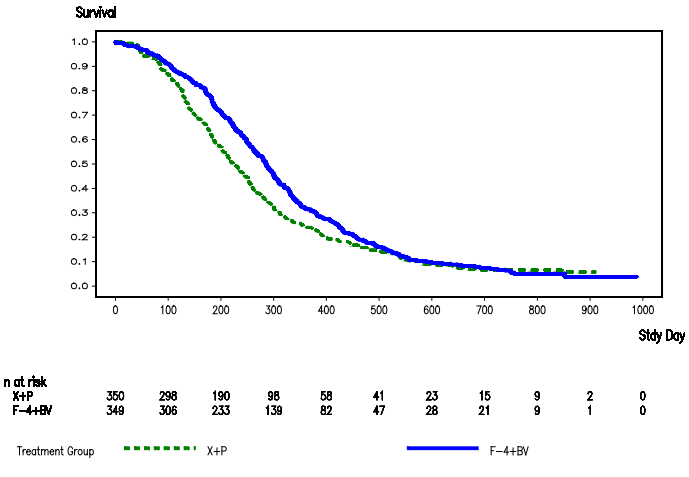
Treatment Group F+P F+BV

Program: $PROD/cdp10743/no16966/gspf50km.sas / Output : $PROD/cd10743a/i16966m/reports/gspf50km_AP_I_4001.out
11APR2d07 14:29 NENDELV

Figure 3

gspf50km_FAXP_L_4001 Kaplan Meier Curve of TTP or Death

Protocol(s): I16966M
Analysis: Intent-to-Treat Population and Cohort I
Filter Applied: WHERE ectypen LE 4 and WHERE s_chrtl = YES'



n at risk											
X+P	350	298	190	98	58	41	23	15	9	2	0
F-4+BV	349	306	233	139	82	47	28	21	9	1	0

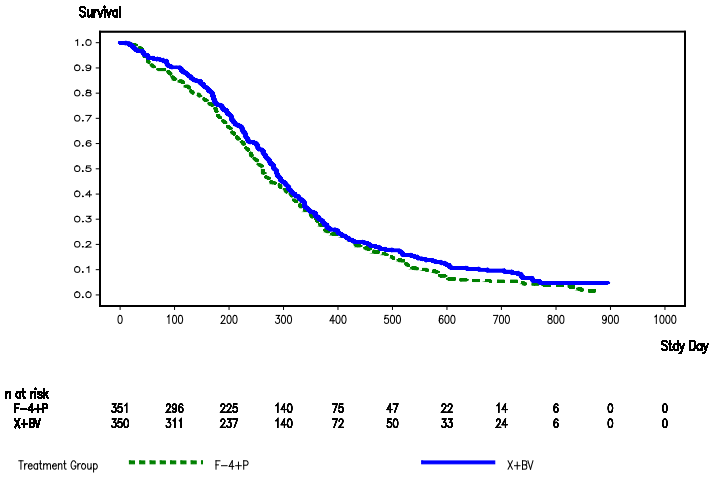
Treatment Group X+P F-4+BV

Program: $PROD/cdp10743/no16966/gspf50km.sas / Output : $PROD/cd10743a/i16966m/reports/gspf50km_FAXP_L_4001.out
11APR2d07 14:45 NENDELV

Figure 4

gspf50km_XAFP_K_4001 Kaplan Meier Curve of TTP or Death

Protocol(s): I16966M
Analysis: Intent-to-Treat Population and Cohort K
Filter Applied: WHERE ectypen LE 4 and WHERE s_chrtk = 'YES'



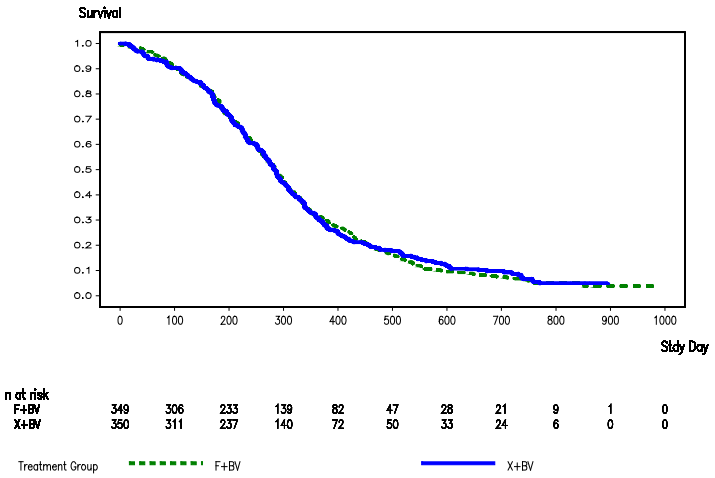
n at risk											
F-4+P	351	296	225	140	75	47	22	14	6	0	0
X+BV	350	311	237	140	72	50	33	24	6	0	0

Program: $PROD/cdp10743/no16966/gspf50km.sas / Output : $PROD/cd10743a/i16966m/reports/gspf50km_XAFP_K_4001.out
11APR2007 14:50 NIENDELV

Figure 5

gspf50km_XF_F_4001 Kaplan Meier Curve of TTP or Death

Protocol(s): I16966M
Analysis: Intent-to-Treat Population and Cohort F
Filter Applied: WHERE ectypen LE 4 and WHERE s_chrtf = 'YES'



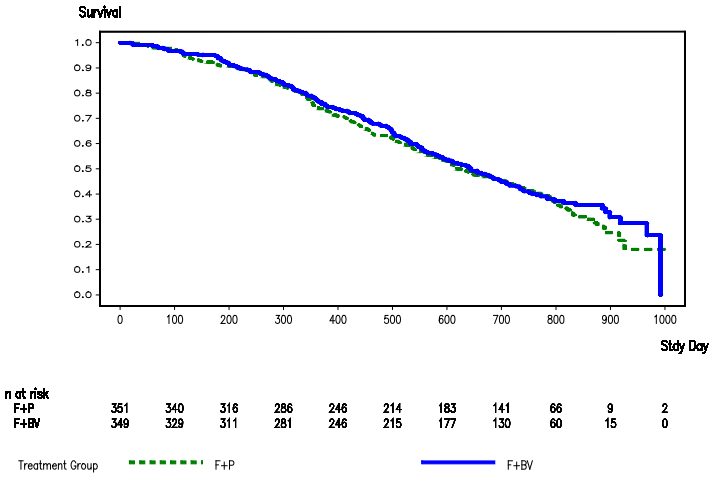
n at risk											
F+BV	349	306	233	139	82	47	28	21	9	1	0
X+BV	350	311	237	140	72	50	33	24	6	0	0

Program: $PROD/cdp10743/no16966/gspf50km.sas / Output : $PROD/cd10743a/i16966m/reports/gspf50km_XF_F_4001.out
11APR2007 15:17 NIENDELV

Figure 6

gsur50km_AP_I_4001 Kaplan Meier Curve of Overall Survival

Protocol(s): I16966M
Analysis: Intent-to-Treat Population and Cohort I
Filter Applied: WHERE ectypen LE 4 and WHERE s_chrti = 'YES'



n at risk											
F+P	351	340	316	286	246	214	183	141	66	9	2
F+BV	349	329	311	281	246	215	177	130	60	15	0

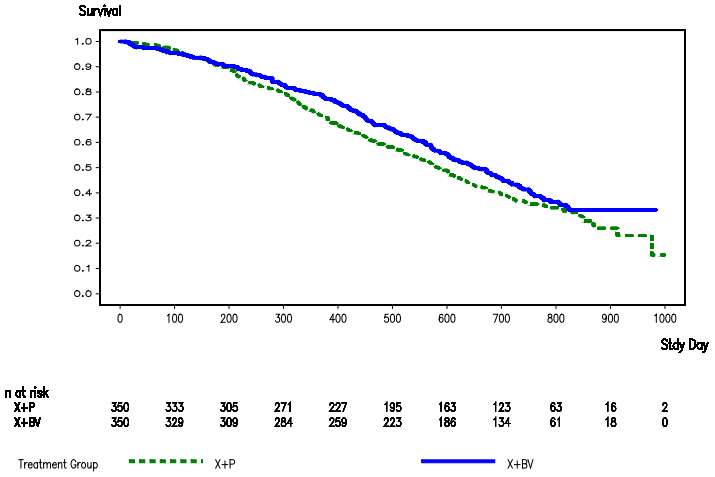
Treatment Group F+P F+BV

Program: $PROD/cdp10743/no16966/gsur50km.sas / Output : $PROD/cd10743a/i16966m/reports/gsur50km_AP_I_4001.out
11APR2007 17:47 NIENDELV

Figure 7

gsur50km_AP_J_4001 Kaplan Meier Curve of Overall Survival

Protocol(s): I16966M
Analysis: Intent-to-Treat Population and Cohort J
Filter Applied: WHERE ectypen LE 4 and WHERE s_chrtj = 'YES'



n at risk											
X+P	350	333	305	271	227	195	163	123	63	16	2
X+BV	350	329	309	284	259	223	186	134	61	18	0

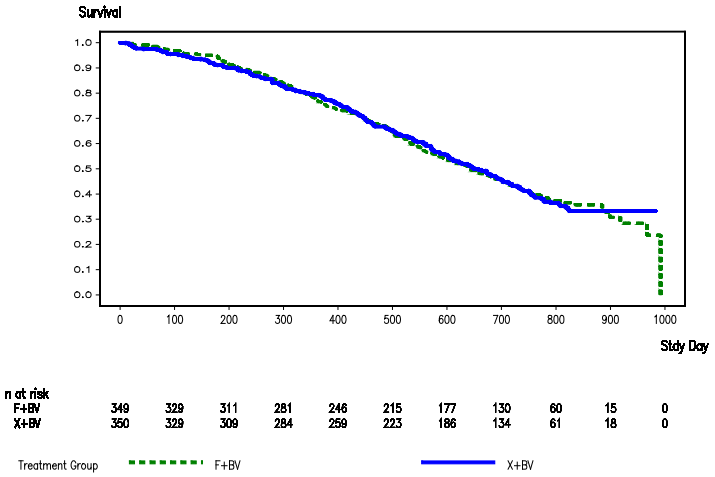
Treatment Group X+P X+BV

Program: $PROD/cdp10743/no16966/gsur50km.sas / Output : $PROD/cd10743a/i16966m/reports/gsur50km_AP_J_4001.out
11APR2007 17:51 NIENDELV

Figure 8

gsur50km_XF_F_4001 Kaplan Meier Curve of Overall Survival

Protocol(s): I16966M
Analysis: Intent-to-Treat Population and Cohort F
Filter Applied: WHERE ectypen LE 4 and WHERE s_chrtf = 'YES'



n at risk											
F+BV	349	329	311	281	246	215	177	130	60	15	0
X+BV	350	329	309	284	259	223	186	134	61	18	0

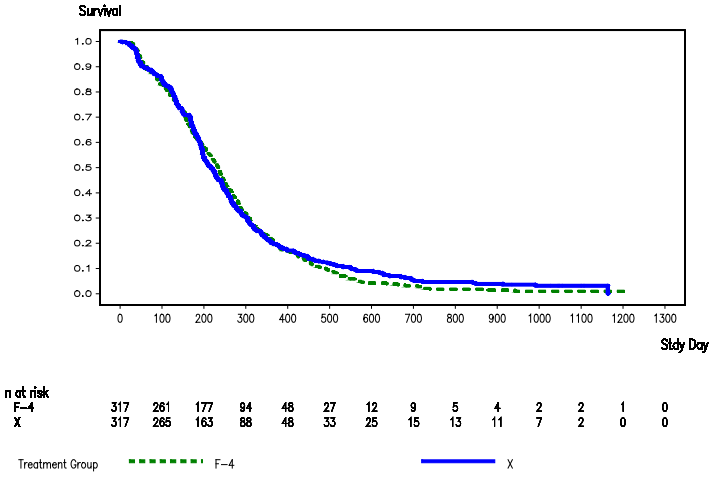
Treatment Group F+BV X+BV

Program: $PROD/cdp10743/no16966/gsur50km.sas / Output : $PROD/cd10743a/i16966m/reports/gsur50km_XF_F_4001.out
11APR2007 18:03 NBINDELV

Figure 9

gspf50km_XF_B_4001 Kaplan Meier Curve of TTP or Death

Protocol(s): I16966M
Analysis: Intent-to-Treat Population and Cohort B
Filter Applied: WHERE ectypen LE 4 and WHERE s_chrtb = 'YES'



n at risk														
F−4	317	261	177	94	46	27	12	9	5	4	2	2	1	0
X	317	265	163	88	48	33	25	15	13	11	7	2	0	0

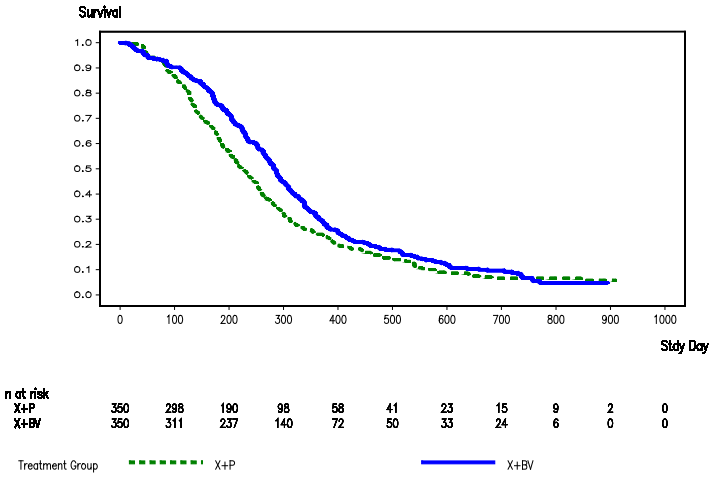
Treatment Group F−4 X

Program: $PROD/cdp10743/no16966/gspf50km.sas / Output : $PROD/cd10743a/i16966m/reports/gspf50km_XF_B_4001.out
04MAY2007 11:28 HAUNR

Figure 10

gspf50km_AP_J_4001 Kaplan Meier Curve of TTP or Death

Protocol(s): I16966M
Analysis: Intent-to-Treat Population and Cohort J
Filter Applied: WHERE ectypen LE 4 and WHERE s_chrtj = 'YES'



Program: $PRODdp10743/ro16966/gspf50km.sas / Output : $PRODdct10743a/i16966/mlreports/gspf50km_AP_J_4001.out
11APR2007 14:38 NBINDELV

Appendix 2 Summary of Time from Start of Adjuvant Treatment to Randomisation by Trial Treatment

dm16adj_6aa4006 Summary of Time from Start of Previous Adjuvant Chemo. to RND by Trial Treatment
Use of Adjuvant chemotherapy YES
Protocol(s): I16966L
Analysis: INTENT-TO-TREAT POPULATION Center: ALL CENTERS
Cohort A and comparison 6A

	XELOX	FOLFOX-4 XELOX+P	FOLFOX-4+P XELOX+BV	FOLFOX-
4+BV	N = 91	N = 83	N = 85	N = 88
88		N = 76		
Time from Start of Prior Adj. Chemo to RND				
[0; 1[Year	10 (12%)	3 (4%)	8 (9%)	9 (
10%)	4 (4%)	6 (8%)		
[1; 2[Years	39 (47%)	32 (38%)	28 (32%)	42 (
48%)	29 (32%)	31 (41%)		
[2; 3[Years	17 (20%)	21 (25%)	30 (34%)	15 (
17%)	33 (36%)	18 (24%)		
[3; 4[Years	9 (11%)	10 (12%)	11 (13%)	14 (
16%)	10 (11%)	9 (12%)		
[4; max] Years	8 (10%)	19 (22%)	11 (13%)	8
(9%)	15 (16%)	12 (16%)		
n	83	85	88	88
	91	76		

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
DM16 06SEP2007:19:26:11

Appendix).

Three exploratory analyses, aimed at reducing the impact of this cohort on OS, show a significant OS benefit of bevacizumab vs placebo.

In order to show the impact on overall survival of the outlying result in adjuvant-treated patients in the P-FOLFOX arm, the following patient cohorts were excluded in a step-wise manner from the analysis of OS

- Adjuvant treated patients in all treatment arms (n=340) (Figure 4.7b, Appendix 4)
- Adjuvant treated patients in the FOLFOX arms (n=173) (Figure 4.7c, Appendix 5)
- Adjuvant treated patients in the P-FOLFOX arm only (n=85) (Figure 4.7d, Appendix

These analyses resulted in a significantly improved OS benefit for bevacizumab versus placebo with similar HRs in the range of 0.83 to 0.85 (p=0.0116 to 0.0242) (see Table 4.22 for overview).

Table 4.22 Study NO16966: Overall Survival - HR after Step-wise Exclusion of Subgroups of Patients with Previous Adjuvant Chemotherapy (4MSU)

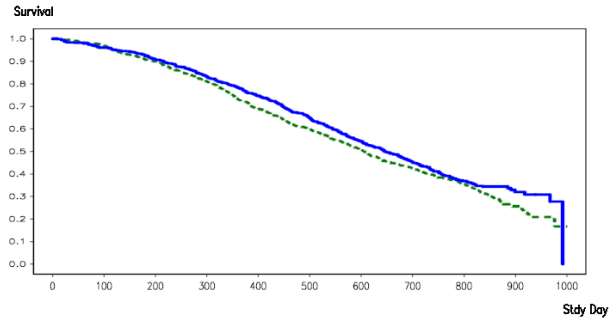
Population	No. of pts excluded from analysis	No. of pts included in analysis	HR (97.5%CI)	P-Value
All patients included (ITT)	0	1400	0.89 (0.76, 1.03)	0.0769
Exclusion of patients with adjuvant chemotherapy from all four treatment arms	85+91+88+76	1060 (1400-340)	0.83 (0.70, 0.99)	0.0183
Exclusion of patients with adjuvant chemotherapy from FOLFOX arms only	85+88	1227 (1400-173)	0.85 (0.72, 1.00)	0.0242
Exclusion of patients with adjuvant chemotherapy from P-FOLFOX arm only	85	1315 (1400-85)	0.84 (0.72;0.98)	0.0116

Source: esur40su, esur46su, esur73su, esur41su

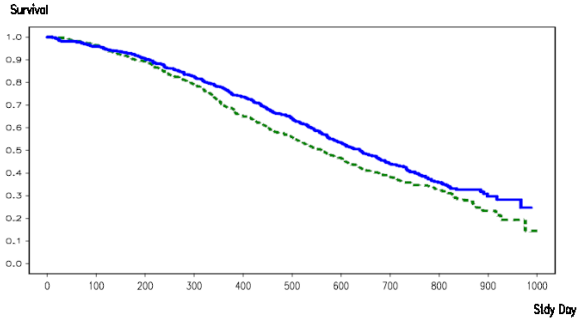
The hazard ratios (chemotherapy+bevacizumab vs. chemotherapy) were similar after exclusion of patients who received adjuvant chemotherapy from all treatment groups, from the FOLFOX treatment groups, or the P-FOLFOX group only. This indicates that the small subset of patients treated with prior adjuvant chemotherapy in the P-FOLFOX treatment group but not the whole adjuvant-treated patient group is driving the lower than expected survival benefit of BV.

Figure 4.7 Study NO16966: Overall Survival After Step-wise Exclusion of Adjuvant-Treated Patients (ITT)

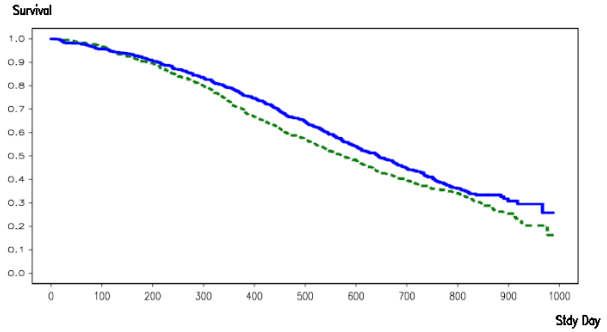
a) All Patients



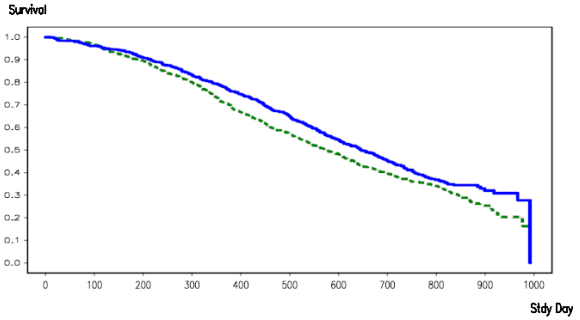
b) Adjuvant-treated patients (n=340) excluded



c) Adjuvant treated patients in FOLFOX-4 arms (n=173) excluded



d) Adjuvant-treated patients in FOLFOX-P arm (n=85) excluded



Source outputs: gsur50km_AP_C_4001, gsur50km_AP_C_4007, gsur50km_AP_C_4159, gsur50km_AP_C_4017

Abbreviations: FOLFOX-4, FOLFOX; FOLFOX-P, p,FOLFOX

4.5.3 Concluding comments on outcomes in individual study arms an impact of outlier results in P-FOLFOX group

In summary, an imbalance of baseline characeteristics of known prognostic significance appears to have favoured the P-FOLFOX group reducing the benefit seen when comparing B-FOLFOX to P-FOLFOX in the 2 x 2 factorial part of the study and to a lesser extent when when comparing B-chemo with P-chemo. In Roche's original submission the approach taken to minimise this problem was to include "chemotherapy alone" patients from the first part of the study to dilute the imbalance. As has been shown in this answer alternative approaches to dealing with the imbalance also show that the benefits of bevacizumab added to FOLFOX or oxaliplatin-based chemotherapy in general are greater than would appear from reference to the results of the 2 X 2 portion of the NO16966 study.

A5. <u>Priority question: Section 6.11. Please provide adverse event (tabulated results) data for each of the six treatment groups separately for 1) all grade adverse events 2) serious adverse events (grade 3/4). Also provide details (tabulated, if applicable) on the following 1) compliance to study treatment 2) rates/reasons of treatment discontinuation (including adverse events leading to discontinuation of trial treatments) and 3) number of patients treated until progressive disease, for each of the six treatment groups separately. In addition what was the mean/median duration of treatment with bevacizumab and how does this compare with other trials?</u>

5.1 Adverse events and study withdrawals by treatment arm in study NO16966

Tables A5.1 and A5.2 (based on the same data set as used for Roche's original submission) show the frequency of adverse events reported by study arm in study NO16966. Table A5.3 shows the reasons for stopping treatment by study arm in the ITT population, with insufficient therapeutic response being a reasonable surrogate for progression, given that the protocol for study NO16966 specified treatment until progression (or death, unacceptable toxicity or withdrawal of consent). It is hoped that this will satisfy the ERGs requirements for further information on rates/reasons for treatment discontinuation and number of patients treated until progression.

Table A5.1 All-grade Adverse Events in Study NO16966 (Safety population)

	Treatment Allocation					
Event (all grades unless otherwise stated)	**FOLFOX (N=313) n (%)**	**XELOX (N=316) n (%)**	**P-FOLFOX (N=335) n (%)**	**P-XELOX (N=339) N (%)**	**B-FOLFOX (N=342) n(%)**	**B-XELOX (N=353) n (%)**
Any Adverse Event	310 (99.0)	313 (99.1)	334 (99.7)	336 (99.1)	340 (99.4)	351 (99.4)
Any Related Adverse Event	308 (98.4)	309 (97.8)	332 (99.1)	333 (98.2)	336 (98.2)	349 (98.9)
Gastrointestinal Disorders	292 (93.3)	295 (93.4)	311 (92.8)	311 (91.7)	320 (93.6)	325 (92.1)
Blood and Lymphatic Disorders	216 (69.0)	163 (51.6)	232 (69.3)	149 (44.0)	229 (67.0)	125 (35.4)
Diarrhoea	194 (62.0)	217 (68.7)	200 (59.7)	212 (62.5)	219 (64.0)	224 (63.5)

Nausea/vomiting	228 (69.8)	225 (71.2)	224 (66.9)	239 (70.5)	235 (68.7)	252 (71.4)
Stomatitis	111 (35.5)	64 (20.3)	131 (39.1)	76 (22.4)	142 (41.5)	102 (28.9)
Neutropenia/granulocytopenia	176 (56.2)	89 (28.2)	203 (60.6)	91 (26.8)	189 (55.3)	70 (19.8)
Febrile Neutropenia	15 (4.8)	5 (1.6)	16 (4.8)	1 (0.3)	15 (4.4)	4 (1.1)
Hand/foot syndrome	34 (10.9)	98 (31.0)	36 (10.7)	103 (30.4)	47 (13.7)	141 (39.9)
Neurotoxicity	233 (74.4)	244 (77.2)	282 (84.2)	290 (85.5)	281 (82.2)	296 (83.9)
Gastrointestinal perforation	1 (0.2)	1 (0.3)	-	2 (0.6)	1 (0.3)	3 (0.8)
Bleeding problems	71 (22.7)	61 (19.3)	100 (29.9)	75 (22.1)	130 (38.0)	82 (23.2)
Venous thromboembolic events	41 (13.1)	32 (10.1)	43 (12.8)	21 (6.2)	58 (17.0)	34 (9.6)
Arterial thromboembolic events	5 (1.5)	2 (0.6)	6 (1.8)	4 (1.2)	8 (2.3)	9 (2.5)
Hypertension	10 (3.2)	4 (1.2)	27 (8.1)	16 (4.7)	70 (20.5)	62 (17.6)
Proteinuria	-	1 (0.3)	19 (5.7)	11 (3.2)	21 (6.1)	14 (4)
Wound healing complications	5 (1.6)	2 (0.6)	4 (1.2)	3 (0.9)	9 (2.6)	3 (0.8)
Fistula or intra-abdominal abscess	6 (1.9)	1 (0.3)	-	3 (0.9)	10 (2.9)	4 (1.1)
Cardiac disorders	20 (6.4)	12 (3.8)	20 (6.0)	15 (4.4)	23 (6.7)	31 (8.8)
Infections/infestations	134 (42.8)	99 (31.3)	158 (47.2)	110 (32.4)	163 (47.7)	137 (38.8)

In addition Figure 5.1 and 5.22 shows withdrawals by reason from NO16966 by week of treatment

Figure 5.1 Withdrawals due to PD and AEs over time from study NO16966 (ITT population)

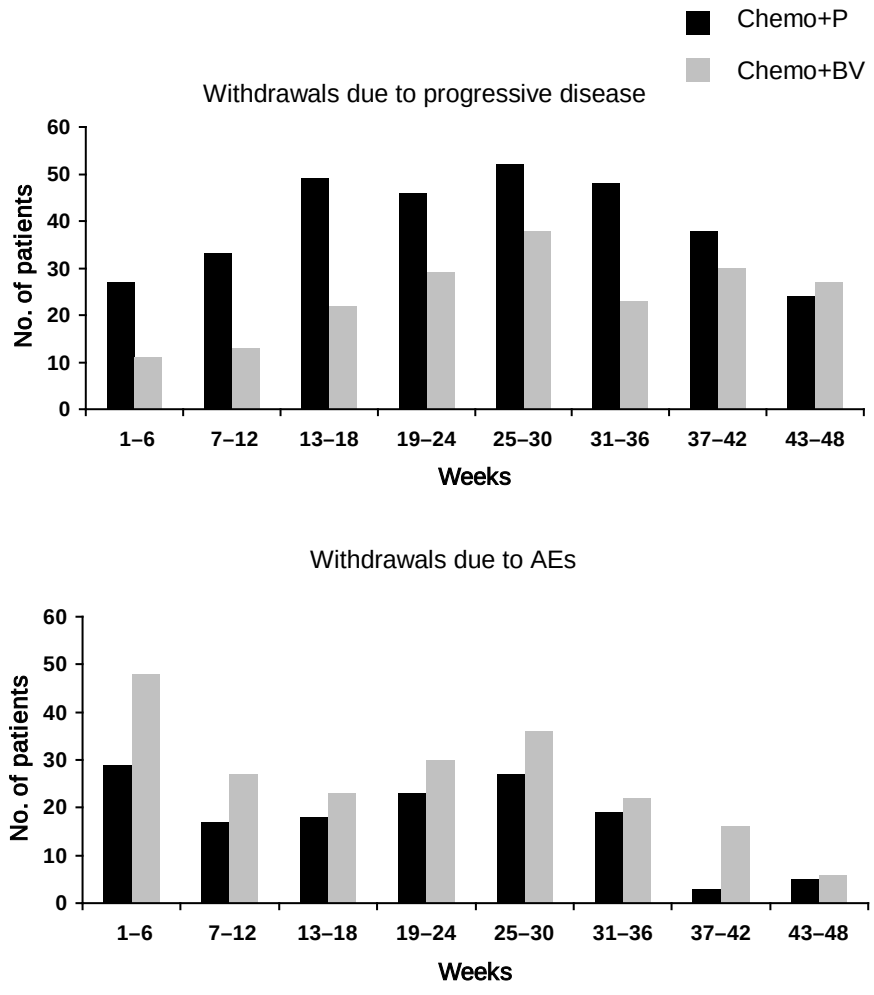


Fig 5.2 Withdrawals for reasons other than PD over time from study NO16966 (ITT population)

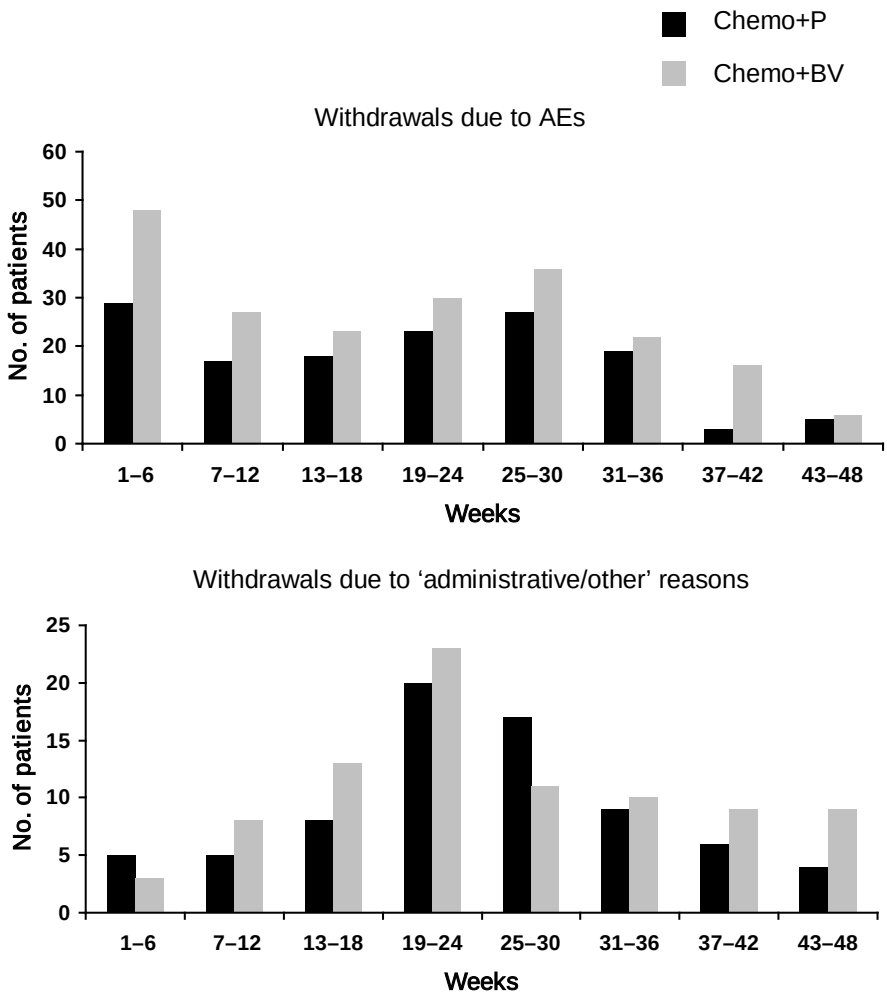


Table A5.2 Grade 3/4 Adverse Events in study NO16966 (Safety population).

	Treatment Allocation					
Event (grades 3 and 4 unless otherwise stated)	**FOLFOX (N=313) n (%)**	**XELOX (N=316) n (%)**	**P-FOLFOX (N=335) n (%)**	**P-XELOX (N=339) n (%)**	**B-FOLFOX (N=342) n(%)**	**B-XELOX (N=353) n (%)**
Serious Adverse Event	118 (37.7)	115 (36.4)	126 (37.6)	121 (35.7)	144 (42.1)	132 (37.4)
Related Serious Adverse Event	75 (24.0)	64 (20.2)	70 (20.9)	79 (23.3)	87 (25.4)	95 (26.9)
Grade ¾ adverse event	240 (76.7)	231 (73.1)	266 (79.4)	237 (69.9)	289 (84.5)	266 (75.4)
Grade 4 (life-threatening adverse events)	79 (25.2)	45 (14.2)	82 (24.5)	36 (10.6)	104 (30.4)	60 (17.0)
Discontinued treatment due to adverse event	91 (29.1)	99 (31.3)	68 (20.3)	72 (21.2)	105 (30.7)	109 (30.9)
Treatment-related deaths	7 (2..2)	10 (3.1)	7 (2.1)	6 (1.8)	7 (2.0)	8 (2.3)
Gastrointestinal disorders						

Grade 3/4	95 (30.4)	102 (32.3)	72 (21.5)	114 (33.6)	87 (25.4)	132 (37.4)
Grade 4	6 (1.9)	12 (3.8)	4 (1.2)	12 (3.5)	7 (2.0)	11 (3.1)
Blood and lymphatic disorders						
Grade 3/4	152 (48.6)	56 (18.0)	166 (69.3)	48 (14.2)	159 (46.5)	125 (35.4)
Grade 4	58 (17.3)	6 (1.9)	66 (19.7)	8 (2.4)	73 (21.3)	44 (12.5)
Diarrhoea	40 (11.9)	63 (19.9)	34 (10.1)	70 (20.6)	44 (12.9)	77 (21.8)
Nausea/vomiting	33 (10.5)	24 (7.6)	14 (4.2)	28 (8.3)	25 (7.3)	38 (10.8)
Stomatitis	7 (2.2)	2 (0.6)	6 (1.8)	6 (1.8)	12 (3.5)	7 (2.0)
Neutropenia/granulocytopenia	130 (41.5)	20 (6.3)	152 (45.4)	26 (7.7)	138 (40.4)	25 (7.1)
Febrile neutropenia	15 (4.8)	5 (1.6)	16 (4.8)	1 (0.3)	15 (4.4)	4 (1.1)
Hand/foot syndrome grade 3	4 (1.3)	21 (6.6)	4 (1.2)	19 (5.6)	6 (1.8)	42 (11.9)
Neurotoxicity	40 (12.8)	51 (16.1)	67 (20.0)	63 (18.6)	61 (17.8)	64 (18.1)
Gastrointestinal perforation	1 (0.3)	1 (0.3)	-	2 (0.6)	1 (0.3)	3 (0.8)
Bleeding problems	5 (16.0)	7 (2.2)	2 (0.6)	6 (1.8)	7 (2.0)	6 (1.7)
Venous thromboembolic events	17 (5.4)	16 (5.0)	24 (7.2)	9 (2.7)	32 (9.4)	22 (6.2)
Arterial thromboembolic events	4 (1.3)	1 (0.3)	4 (1.2)	3 (0.9)	5 (1.5)	7 (2.0)
Hypertension	1 (0.3)	1 (0.3)	4 (1.2)	4 (1.2)	12 (3.5)	16 (4.5)
Proteinuria	-	12 (4.7)	-	-	3 (0.9)	21 (5.9)
Wound healing complications	2 (0.6)	-	2 (0.6)	-	-	3 (0.8)
Fistula/intrabdominal abscess	5 (1.6)	3 (9.5)	-	1 (0.3)	4 (1.2)	2 (0.6)
Cardiac disorders	8 (2.5)	4 (1.3)	1 (0.3)	2 (0.6)	23 (6.7)	14 (4.0)
Infections/infestations	35 (11.2)	26 (8.2)	31 (9.3)	19 (5.6)	30 (8.8)	21 (5.9)
Laboratory abnormalities						
Low neutrophils	129 (41.2)	30 (9.5)	154 (46.0)	28 (8.3)	145 (42.4)	25 (7.1)
Low haemoglobin	11 (3.5)	11 (3.5)	5 (1.5)	8 (2.4)	10 (2.9)	7 (2.0)
Low platelets	14 (4.4)	30 (9.5)	14 (4.2)	24 (7.1)	12 (3.5)	15 (4.2)

Table 5.3 Reasons for stopping treatment during primary treatment phase of study NO16966 (ITT population).

Reason for withdrawal	**FOLFOX N=317 No. (%)**	**P-FOLFOX N=351 No. (%)**	**B-FOLFOX N=349 No. (%)**	**XELOX N=317 No. (%)**	**P-XELOX N=350 No. (%)**	**B-XELOX N=350 No. (%)**
Safety	99 (31)	77 (22)	109 (31)	113 (36)	74 (21)	117 (33)
Abnormality of lab test	0	0	0	0	0	0
Adverse event (a)	91	72	101	99	72	109
Death	8	5	8	14	2	8
Non-safety	203 (64)	237 (68)	188 (54)	182 (57)	235 (67)	179 (51)
Insufficient therapeutic response	127	155	102	131	174	101
Early improvement	0	0	0	0	0	0
Violation of selection criteria at entry	2	3	5	0	4	1
Other protocol violation	1	1	1	0	1	0
Refused treatment (b)	30	33	36	17	25	29
Failure to return	5	0	2	5	0	0
Other	38	45	42	29	31	48
Total	302 (95)	314 (89)	297 (85)	295 (93)	309 (88)	296 (85)
(a) includes intercurrent illness (b) Including “did not co-operate”, “withdrew consent”						

5.2 Adverse events leading to study withdrwal in Study NO16966

A more detailed analysis of patients withdrawing from study NO16966 as a result of Adverse Events is presented in Table 5.4.

In study NO16966, 30% of patients in the bevacizumab arms and 21% of patients in the placebo arms withdrew from all protocol therapy because of AEs. Reasons for the 9% difference are discussed in detail below.

5.2.1 Analysis of toxicity by grade

Withdrawal due to grade 1 and 2 toxicity: Of the patients who stopped therapy for AEs in NO16966 (N=348), nearly a third (102, 29%) were withdrawn due to only grade 1 or 2 toxicity, this may reflect investigator lack of familiarity with bevacizumab side-effects and their management prompting a cautious approach to managing patients experiencing them even at low grade.

Withdrawal due to grade 3 and 4 toxicity: In total, 21% percent of the patients in the chemotherapy+bevacizumab arm and 15% in the chemotherapy+placebo arm withdrew for grade 3 or 4 AEs (a 6% absolute difference between arms) (Table 5.4).

Bevacizumab-associated targeted events account for some but not all of the difference in all-grade toxicity between the treatment arms (3% absolute difference between groups) (Table 5.4).

Table 5.4 Proportion of Patient Withdrawing for AEs in Study NO16966 (Safety population)

	P-FOLFOX/P-XELOX N=675 n (%)	**B-FOLFOX/B-XELOX N=694 n (%)**
Proportion of patients with AEs leading to withdrawal		
All grade	141 (21)	207 (30)
G1/2 only	40 (6)	62 (9)
G3/4	101 (15)	145 (21)
Bevacizumab targeted	16 (2)	36 (5)

5.2.2 Influence of withdrawal due to progressive disease on reporting of AEs

A possible explanation for the higher rate of withdrawal for non-bevacizumab associated toxicity in the bevacizumab arms than in the placebo arms is that patients progressed earlier in the placebo arms. Over each six-weekly time interval up to week 42, more patients in the placebo arms withdrew for PD. Conversely, fewer patients were progressing and the number of patients in whom an AE could occurr and who could be withdrawn for it was higher in the bevacizumab arms over most of these time intervals – see **Error! Reference source not found.**.

5.3 Non-bevacizumab adverse events may have curtailed bevacizmab treatment and limited efficacy compared with other situations.

Several observations can be made based on the above. Firstly, that withdrawal from study treatment for those toxicities thought to be bevacizumab-related were low with only a 3% absolute excess in the bevacizumab arms over the non-bevacizumab arms (Table 5.4). Secondly, that there was a large withdrawal of patients at around 6 months for reasons

other than toxicity or progression, suggesting that clinicians followed there usual practice of time-limiting treatment, despite a protocol specification that patients should continue on treatment until disease progression (Figure 5.2). Thirdly, that a significant proportion of patients were withdrawn from *all* study treatment, including bevacizumab, in response to adverse events that were probably not bevacizumab-related, limiting the therapeutic benefit of bevacizumab (see Table 5.5).

These last two factors may explain the somewhat reduced overall survival benefit in the NO16966 study compared with that reported by Hurwitz *et al* in the AVF2107g (where median OS was improved by 4.7s by the addition of bevacizumab to IFL; HR for death 0.66; P<0.001). The backbone chemotherapy in AV2107g utilised irinotecan rather oxaliplatin. Since irinotecan, unlike oxaliplatin, does not have cumulative toxicity there is less tendency to stop treatment (including bevacizumab) once patients are established on a regimen that they find tolerable.

The impact of cumulative oxaliplatin toxicity can be seen in Appendix 7 which describes dose intensity (dose delivered versus full protocol dose) for the drugs used in the NO16966 study by treatment cycle. The most significant change with increasing cycle number is a reduction in dose-intensity for oxaliplatin - there is a weaker trend for both fluoropyrimidines and virtually no reduction in dose intensity for bevacizumab and bevacizumab placebo.

The other factor driving shorter treatment duration in Study NO16966 compared to AVF2107g is the geographic area in which the studies were conducted.AVF2107g was conducted in North America where treatment until progression is a more widespread practice than in certain other countries participating in the global NO16966 study.

Table 5.5 Bevacizumab treatment duration in studies NO16966 and AVF2107g *

Study	Treatment	Median treatment duration	Mean treatment duration[2]
NO16966	Bevacizumab +XELOX Bevacizumab +FOLFOX	6.5 months[3] 6.5 months[3]	6.8 months[3] 7.3 months[3]
AVF2107g	Bevacizumab +IFL	10.1 months[1]	10.9 months[2]

* *Treatment durations applied in the Cost Effectiveness analysis are slightly different to those reported in the study report and/or publications due to necessary survival analysis method.. See appendix A of the cost effectiveness response and original submission for treatment duration methods and assumptions.*

1. Hurwitz *et al* (2004), converted from 40.4 weeks assuming 1 month=4weeks
2. Roche Data on File, 93% dose intensity observed in Hurwitz study applied to mean PFS reported by SCHARR Bevacizumab economic model (11.7 months)
3. N016966 study report (see Appendix 8), converted from days assuming 1 month=28 days.

5.4 Concluding comments on safety

In summary, the arm by arm analysis confirms the safety results included in Roche's original submission. The addition of bevacizumab results in an increase in those toxicities previously associated with bevacizumab: bleeding problems, hypertension and proteinuria. The impact on all-grade thromboembolic events is unclear. Looking at more serious adverse events there is an approximate 6 or 7% increase in absolute terms in grade 3 and 4 adverse events on adding bevacizumab to oxaliplatin-based chemotherapy. However, as Table 5.4 shows, the excess of adverse events leading to patient withdrawal in bevacizumab recipients are not, generally, those events particularly associated with bevacizumab where the absolute excess is only 3% - the remainder are likely to consist largely of those resulting from a longer duration of cytotoxic treatment in patients who disease progression has been halted by bevacizumab.

A6. **We request further details on the systematic review as follows:**

- **Section 6.6. Please could you clarify if data selection (provide kappa agreement scores, if applicable) and abstraction was taken independently by two reviewers and how any disagreements were resolved. Section 6.6.2. Please could you clarify the inclusion/exclusion criteria in terms of the population, interventions, comparators, outcomes and study design?**

- **Section 6.6.3. As stated in section 6.2.3 of the STA specification for Manufacturer Submission of Evidence '…a flow diagram of the number of studies included and excluded at each stage should be provided…as per the QUORUM statement flow diagram." Can you provide a QUORUM flow diagram?**

- **Section 6.7. As stated in section 6.3 of the STA specification for Manufacturer Submission of Evidence '… items 2 to 14 of the CONSORT checklist should be provided… where there is more than one RCT, the information should be tabulated'. Can you provide a tabulated summary of the included RCTs according to items 2 to 14 of the CONSORT checklist?**

- **Section 6.14.3. Please provide further details on whether a systematic review of non-RCTs was undertaken by the manufacturer? if so, how was this done (including details of identification and selection, critical appraisal [relevant checklist] and data synthesis)?**

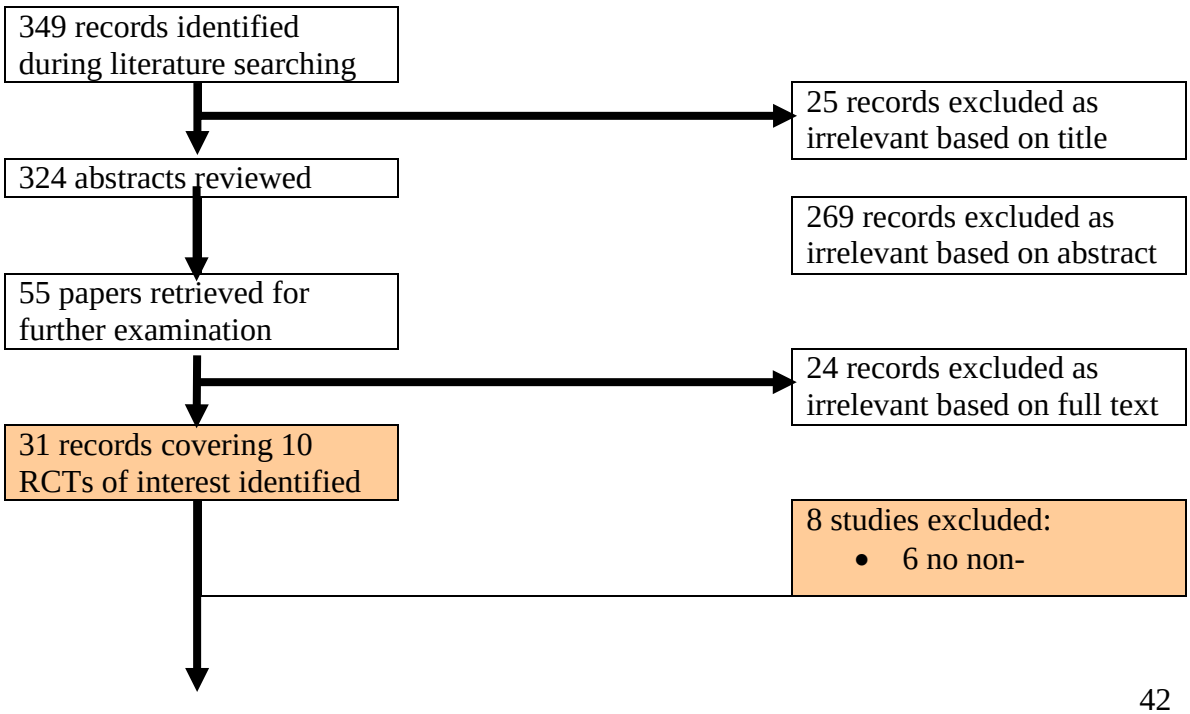
- Data selection and abstraction was undertaken by one individual.

- As specified in Section 6.5 of Roche's original submission, our literature searching was designed to retrieve citations covering clinical trials conducted in colorectal cancer utilising oxaliplatin and bevacizumab. These citations were then

reviewed as requested in the instructions at the start of Section 6.6.1 of the Manufacturer's template to produce a list of all RCTs that compare the intervention of interest (in this case "oxaliplatin-based chemotherapy plus bevacizumab" as defined in the appraisal Scope) in the relevant patient group (in this case "patients with mCRC" as defined in the appraisal Scope). This provided the "complete list of RCTs" in Table 5 of Roche's original submission. Some of these were uninformative with regard to the current appraisal and were removed from the "complete list of RCTs" to give the list of list "relevant RCTs" presented in Table 6 of our original submission. The rules used to exclude studies are given in Section 6.6.2 and how they impacted on the "complete list of RCTs" is given in Table 6 of our original submission. If the process for study selection is still unclear Roche would be happy to answer a more specific clarification question.

- The QUORUM flow chart as shown on the website referenced in the NICE STA template is designed to explain inclusion and exclusion of clinical trials in a meta-analysis and uses "number of RCTs" included and rejected at each stage. This does not lend itself particularly well to the literature search strategy used in a NICE submission, where many literature references are removed before the search is narrowed down to RCTs. This is reflected in the following flow chart. Our interpretation is that the portion shaded in pink represents the closest approximation to the QUORUM diagram published by CONSORT but this is less informative than the totality of what is presented. We hope this is acceptable.

Figure 6.1 QUORUM flow diagram of study selection process used in Roche's original submission



- Summary data from the RCTs included in the original Roche submission presented according to items 2 to 14 of the CONSORT checklist follows:-

	Trial	
	N016966	**E3200**
1. Scientific background and explanation of rationale	Cytotoxic chemotherapy with the FOLFOX regimen of the intravenously (IV) infused fluoropyrimidine 5-FU potentiated by folinic acid (FA) combined with oxaliplatin is a global standard for the first-line treatment of mCRC. The orally administered fluoropyrimidine capecitabine has been shown to be as effective as IV 5-FU in other settings is but more convenient and cost-effective. The first objective of this study is to determine whether the 5-FU and FA element of the FOLFOX regimen can be replaced by capecitabine without loss of antitumour efficacy. Vascular endothelial growth factor (VEGF) is a critical mediator of angiogenesis, whose dysregulation appear to have a pivotal role in malignancy. Bevacizumab	Vascular endothelial growth factor (VEGF) is a critical mediator of angiogenesis, whose dysregulation appears to have a pivotal role in malignancy. Bevacizumab is a monoclonal antibody which binds with high specificity to VEGF preventing its receptor interactions and abrogating its biological activities. Phase I studies have shown it to have good tolerability when administered alone or in combination with cytotoxic chemotherapy. This study is designed to examine its impact on survival in relapsed mCRC when used alone or in conjunction with the FOLFOX-4 chemotherapy regimen of 5–FU, folinic acid and oxaliplatin

	is a monoclonal antibody which binds with high specificity to VEGF preventing its receptor interactions and abrogating its biological activities. It has been shown to improve outcomes when added to chemotherapy regimens including 5-FU and irinotecan as the cytotoxic agents. The second objective of this study is to determine whether bevacizumab also improves antitumour outcomes when added to first-line chemotherapy for mCRC with an oxaliplatin-fluoropyrimidine combination.	
3 Study participants	Participants were >/= 18 years of age with a histologically confirmed diagnosis of adenocarcinoma of the colon or rectum with metastatic disease without previous systemic treatment for advanced disease.	Participants were 18 years of age or over with measurable, histologically confirmed, relapsed, previously treated, advanced or metastatic adenocarcinoma of the colon or rectum.
4. The intervention	Between Feb 2004 and Feb 2005, the first 634 patients were randomly assigned to chemotherapy with either FOLFOX-4 or XELOX chemotherapy. Following protocol amendment the remaining 1401 patients were randomly assigned to either FOLFOX-4 plus bevacizumab (B-FOLFOX), FOLFOX-4 plus bevacizumab placebo (P-FOLFOX), XELOX plus bevacizumab (B-XELOX) or placebo plus bevacizumab (P-XELOX).	There were three study arms to which patients were randomly allocated. Patients received FOLFOX-4 chemotherapy alone administered every 2 weeks, FOLFOX-4 chemotherapy plus bevacizumab 10mg/kg bodyweight every 2 weeks or bevacizumab 10 mg/kg bodyweight as a single agent. Recruitment to the bevacizumab alone arm closed early because of limited efficacy. All treatments were administered until disease

	Details of the regimens are as follows:- **B-FOLFOX**(14 day cycle) *Day 1* Oxaliplatin 85 mg/mg^2 IV infusion over 2 hours plus FA, 200 mg/m^2 IV infusion over 2 hours, followed by 5-FU 400 mg/m^2 as IV bolus injection followed by 5-FU 600 mg/m^2 IV infusion over 22 hours, plus bevacizumab 5 mg/kg as IV infusion over 30-90 minutes prior to oxaliplatin on Day 1. *Day 2* FA 200 mg/m^2 IV infusion over 2 hours, followed by 5-FU 400 mg/m^2 as IV bolus injection followed by 5-FU 600 mg/m^2 IV infusion over 22 hours **P-FOLFOX** (14 day cycle) As B-FOLFOX but with placebo identical in appearance to bevacizumab 5mg/kg administered on Day 1 in place of bevacizumab **FOLFOX** (14 day cycle) As B-FOLFOX but without bevacizumab or placebo on Day 1 **B- XELOX** (21 day cycle) *Day 1* Bevacizumab 7.5 mg/kg IV over 30-90 minutes plus oxaliplatin 130 mg/mg^2 IV infusion over 2 hours *Days 1-14* Capecitabine 1000 mg/m^2 by mouth, twice daily, within 30 minutes of the end of breakfast and dinner. **P- XELOX** (21 day cycle)	progression. FOLFOX chemotherapy consisted of : *Day 1* Oxaliplatin 85 mg/mg^2 IV infusion over 2 hours plus FA, 200 mg/m^2 IV infusion over 2 hours, followed by 5-FU 400 mg/m^2 as IV bolus injection followed by 5-FU 600 mg/m^2 IV infusion over 22 hours, plus bevacizumab 5 mg/kg as IV infusion over 30-90 minutes prior to oxaliplatin on Day 1. *Day 2* FA 200 mg/m^2 IV infusion over 2 hours, followed by 5-FU 400 mg/m^2 as IV bolus injection followed by 5-FU 600 mg/m^2 IV infusion over 22 hours All treatment regimens were continued until disease progression or unacceptable toxicity.

	As B-XELOX but with placebo identical in appearance to bevacizumab 7.5 mg/kg IV over 30-90 minutes on Day 1 in place of bevacizumab **XELOX** As B-XELOX but with neither bevacizumab or placebo on Day 1 All treatment regimens were continued until disease progression or unacceptable toxicity.	
5. Objectives	This study tested two hypotheses:- 1. That in the FOLFOX-4 chemotherapy regimen for the first-line therapy of mCRC, IV 5-FU and FA can be replaced with oral capecitabine without loss of efficacy 2. The addition of bevacizumab to first-line chemotherapy of mCRC using a combination of a fluoropyrimidine and oxaliplatin improves efficacy.	The objective of this study was to determine the impact of bevacizumab on survival in patients with relapsed advanced or mCRC when used alone or added to standard FOLFOX-4 chemotherapy, compared with FOLFOX-4 chemotherapy alone.
6. Study outcomes	**Primary** PFS (superiority of bevacizumab plus chemotherapy over chemotherapy and non-inferiority of XELOX+/-B *versus* FOLFOX+/-B). PFS was defined as the time from the date of randomisation to the first day of documented disease progression or death due to any cause. **Secondary**: These included:	**Primary.** The primary efficacy end-point was a comparison of overall survival (time from randomisation to death from any cause) in the principal arms defined in the Study Statistical Analysis Plan as FOLFOX and B-FOLFOX. **Secondary.** These included: • Response Rate (using RECIST

	Efficacy • PFS for superiority of XELOX over FOLFOX • Overall Survival • Overall Rate of Best Response (using RECIST criteria) • Time to Response • Duration of Response • Duration of Complete Response • Time to Treatment Failure **Safety** • Adverse events • Serious adverse events • Dose modifications • Premature withdrawal from treatment etc	Criteria) • PFS, defined as the time from randomisation to disease progression or death from any cause within 30 days following discontinuation of protocol therapy • Duration of response, defined as time from the first tumour assessment that met the criteria for objective response, as assessed by the ECOG Coordinating Center, to the time of disease progression or death from any cause within 30 days of following discontinuation of protocol therapy. • Safety
7. Sample Size	It was calculated that 1200 events in the eligible patient population of all randomized patients would be required to ensure 90% power for PFS non-inferiority testing. However, in case of interaction, 900 events in the eligible patient population of patients randomised either to the initial 2-arm part or the placebo containing arms of the 4-arm factorial part of the study will still ensure 80% power for the non-inferiority testing. To	The original design had a greater than 90% power to detect a 50% improvement in median survival (from 7.5 to 10 months); however, with faster than anticipated accrual, the study was modified to maintain its power to detect a 50% difference in overall survival with 13 months of follow-up before the final analysis.

	achieve this number of events, it was decided to recruit an additional 300 patients to the initial 2-arm part of the study and so increase the planned sample size of 1620 patients to 1920 (600 patients to initial 2-arm part and 1320 patients to the factorial 4-arm part). The required number of 900 events in the non-bevacizumab treatment groups will occur later than the 1200 events among all patients. The time-point of the final analysis will therefore be determined by the 900 events in the eligible patient population of arms XELOX, P-XELOX, FOLFOX and P-FOLFOX (expected to occur approximately 26 months after start of enrolment into the factorial 4-arm part). The following assumptions have been made for the power calculations of the final analysis: • 600 patients are recruited to the initial 2-arm part of the study over 8 months and followed for another 23 months • 1320 patients are recruited to the factorial 4-arm part of the study in total, starting 5 months after the overall study start − 164 patients over the first 3 months, followed for another 23 months − 1160 patients during the	

	subsequent 10 months, followed for another 13 months • 15% of all randomized patients are excluded from the eligible patient population	
8. Randomization generation	A list of patient randomisation numbers and associated treatment(s) was generated by Roche	Details are unclear from published report but this was done centrally
9. Allocation concealment	Randomisation was carried our centrally by interactive voice recognition system (IVRS)	Randomisation was carried out centrally by the ECOG Co-ordinating Center no further details are available
10. Randomisation implementation	The randomisation number, the treatment group allocation/medication numbers were provided to the investigator via IVRS at the time of enrollment. In addition, a confirmation fax containing the randomisation number and medication kits assigned to a patient was sent from the IVRS to the investigator	Randomisation was carried out centrally by the ECOG Co-ordinating Center
11. Blinding/masking	In the assessment of bevacizumab efficacy, a matched placebo was used to which patients and investigators were blind. For the comparison of oral capecitabine and IV 5-FU, placebo control was impractical and unethical (widespread use of IV placebo). Therefore, patients and clinicians were unblinded to treatment allocation. However, the primary study end-point was objective (tumour shrinkage on a scan) and the investigator assessment of response was checked using	This was an open label study. However, the primary study end-point of OS is not liable to investigator bias

	radiologists blind to treatment allocation	
12. Statistical methodology	An interaction test was performed on the primary endpoint of PFS to detect any kind of interaction between the different regimens (FOLFOX, XELOX, placebo or bevacizumab) and to justify pooling of data for comparison of the primary study end-points as described above. The interaction test was repeated for the two secondary parameters of overall survival (based on Cox proportional hazards regression) and overall rate of best response (based on logistic regression). PFS was the primary endpoint of the study and was used to assess non-inferiority of XELOX+/-B to FOLFOX +/-B and superiority of bevacizumab in combination with chemotherapy over chemotherapy alone. For testing non-inferiority for the primary endpoint of PFS, the hazard ratio (HR) and associated 97.5% confidence interval (CI) were calculated based on a proportional hazards model. Non-inferiority was concluded if the upper limit of the two-sided 97.5% CI for the HR did not exceed 1.23. Non-inferiority hypotheses were also tested for the secondary endpoints. Superiority of bevacizumab in combination with	Duration of survival was formally compared between B-FOLFOX and FOLFOX arms using the two-sided stratified log-rank test. Kaplan-Meier methodology was used to estimate median duration of survival for each treatment arm. The HR for death on the B-FOLFOX arm relative to the FOLFOX arm was estimated using a stratified Cox regression model. The stratification factors were baseline ECOG performance status (0, >/=1) and prior radiation therapy (yes, no). Stratification factors were determined from data collected on the Case Report Form. The Type 1 error rate for the comparison of the principal arms for the primary endpoint of duration of survival was alpha=0.0167 (two-sided). To control the Type 1 error rate for the primary end-point of duration of survival, accounting for two formal interim analyses of efficacy, the Lan and DeMets implementation of the O'Brien-Fleming alpha-spending function was used.

	chemotherapy (B-XELOX, B-FOLFOX) to chemotherapy alone (P-XELOX, P-FOLFOX) was based on the stratified log-rank test and used a two-sided significance level of 2.5%.	
13a PT disposition 13b Protocol deviations	13 a Refer to Fig 7 of Roche's original submission for flow-chart showing disposition of trial subjects 13b Apart from the double randomized patient referred to in Fig. 7 of Roche's original submission, we are unaware of protocol deviations likely to have impacted the outcomes of this study. 50 (2.4%) patients were lost-to follow-up	13a Refer to Fig 8 of Roche's original submission for flow-chart showing disposition of trial subjects 13b Roche is unaware of protocol deviations likely to have impacted the outcomes of this study
14 Dates of recruitment	2035 patients were recruited between July 2003 and February 2004 were recruited to the XELOX versus FOLFOX comparison between July 2003 and Feb 2004, with 1401 recruited to the 2 x 2 amended study between February 2004 and February 2005	829 patients were recruited between November 2001 and April 2003.

- As indicated in our original text Roche did not carry out a systematic review of non-RCTs as part of our submission. Those included were identified either as part of the systematic review done to identify relevant RCTs or because they were already known to Roche and were considered to be of interest in the context of the current appraisal

A7. **Section 6.7.6. As stated in the Summary of Product Characteristics, the recommended dose of bevacizumab, administered as intravenous infusion, is either 5 or 10 mg/kg of body weight given once every two weeks or 7.5 or 15 mg/kg of body weight given once every 3 weeks. In the NO16966 trial the doses of bevacizumab studied were 7.5mg/kg every 3 weeks (XELOX) and 5mg/kg every 2 weeks (FOLFOX-4). In the ECOG E3200 trial the dose of bevacizumab was 10mg/kg every 2 weeks. Please provide evidence on the efficacy of the higher dose in first line use and the lower dose in second line use.**

The Summary of product Characteristics for Avastin does indeed reflect the fact that in the N016966 and E3200 studies of oxaliplatin-based chemotherapy doses equivalent to 5 mg/kg and 10 mg/kg bevacizumab every 2 weeks have been shown to improve outcomes. It should be noted that the E3200 study was planned before the publication of the results of the AVF0780g study – a randomized phase II dose finding study conducted by Genentech (the original developers of bevacizumab). In AVF0780g patients with advanced colorectal cancer which had not been treated with systemic chemotherapy were randomized to receive one of three treatment regimens – the Roswell Park regimen of 5-FU and folinic acid alone, Roswell Park plus bevacizumab 5 mg/kg every 2 weeks or Roswell Park plus bevacizumab 10 mg/kg every 2 weeks. The results of this study which have been published by Kabinavar *et al* (2003, 2005) are presented in Table7.1.

Table 7.1. Efficacy results from randomized phase II dose-finding study AVF0780g – the addition of 5 mg/kg or 10 mg/kg bevacizumab to the Rosswell Park regimen of 5-FU/FA in chemotherapy-naïve patients with metastic colorectal cancer

Endpoint	**Control (N=36)**	**Bevacizumab 5 mg/kg (N=35)**	**10 mg/kg (N=33)**
Time to disease progression (IRF)			
Number of progressions	26 (72%)	22 (63%)	23 (70%)
Median (months)	5.2	9.0	7.2
Hazard ratio	-	0.440	0.692
p-value (log-rank)	-	0.005	0.217
Objective response rate (IRF)			
Objective response	6 (17%)	14 (40%)	8 (24%)
p-value (chi-squared)	-	0.029	0.434
Complete response	0	2 (6%)	0
Duration of survival			
Number of deaths	19 (53%)	12 (34%)	19 (58%)
Median (months)	13.6	17.7	15.2
Hazard ratio	-	0.521	1.009
p-value (log-rank)	-	0.073	0.078

Abbreviations: IRF, determined by independent review facility.

Both of the primary end-points (response rate and time to disease progression) as assessed by an independent review facility were significantly improved by the addition of fortnightly bevacizumab (5 mg/kg) to 5-FU/FA. These parameters also showed a clear trend towards

improvement in the 10 mg/kg group, although the magnitude of the improvements was less than in the 5mg/kg group and they did not reach statistical significance.

Once the results of AVF0780g were available it was concluded that the balance of benefit and risk in mCRC favoured the 5 mg/kg dose of bevacizumab over the 10 mg/kg dose and future developmental studies utilized the lower dose. These studies included not only the NO16966 study but also the AVF0780g of IFL (irinotecan, 5-FU and folinic acid) chemotherapy +/- bevacizumab that resulted in the original regulatory approval for bevacizumab.

Unless a new and plausible hypothesis is proposed explaining why a higher dose of bevacizumab would be useful in particular situations it is unlikely that the higher dose will be explored in future trials in mCRC.

Roche is currently conducting/supporting 3 ongoing trials that will provide information from approximately 750 patients with mCRC treated with bevacizumab at a dose of 2.5 mg/kg/wk equivalent in second line.

- **BRITE US registry tria**l:
  In this sudy patients are treated with bevacizumab as part of first-line therapy and the use of bevacizumab in second-line after progression is given at the investigator's discretion: 642 patients out of the 1445 observed received continuous treatment with bevacizumab into second-line. In the second-line, the majority of patients (70%) received a dose of 5mg/2wk (equivalent to the dose of 2.5 mg/kg/week) (Roche submission to New Zealand Medicines Advisory Committee, 2008).

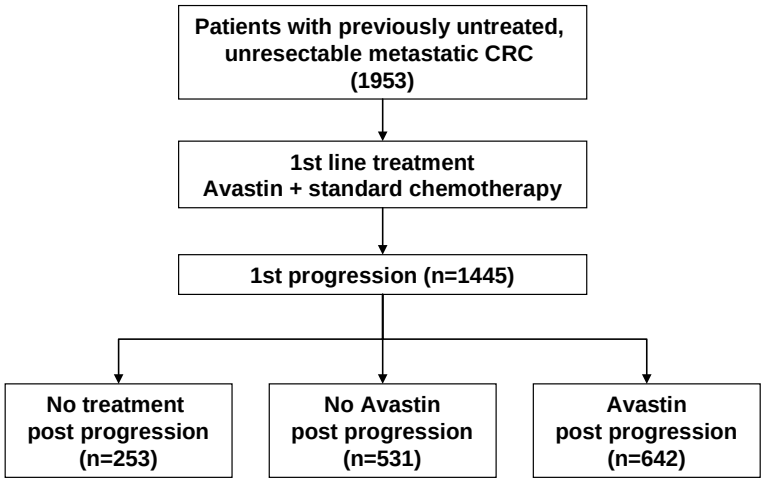
- **Phase II BEVACOLOR trial** (single centre study in France):
  The aim of this study is to assess the efficacy and safety of adding bevacizumab at the dose of 2.5 mg/kg/wk equivalent to the most common chemotherapy regimens used in second-line therapy in mCRC.

- **Study ML 18147** (multicentre study):
  572 patients with mCRC and first progression will be randomized to receive 5-FU-based chemotherapy with irinotecan or 5-FU-based chemotherapy with oxaliplatin. Half of the patients in both arms will receive bevacizumab at the dose of 2.5 mg/kg/wk equivalent which will be compared to no bevacizumab in second-line treatment.

Of these three studies only BRITE has yet yielded results (Grothey *et al* 2007, 2008). As stated above BRITE was a registry study in which US clinicians were allowed to treat any patient with previously untreated mCRC with any chemotherapy regimen they deemed appropriate combined with bevacizumab. Patients were followed up according to the usual clinical practice of the clinicians concerned. The objective was to gain an impression of the efficacy and tolerability of bevacizumab outside of the more strictly regulated environment of a Phase III trial. BRITE and its findings with regard to the first-line use of bevacizumab are described in Section 6.14 of Roche's original submission. BRITE did not specify what treatment should be provided to patients when their disease progressed after first-line bevacizumab plus chemotherapy. However, patients were permitted to receive bevacizumab as part of second-line therapy and an analysis has

been presented of survival beyond first progression according to treatment received. Figure 7.1 shows the treatments received by patients in BRITE after first progression.

Figure 7.1 Disposition of patients in the BRITE study

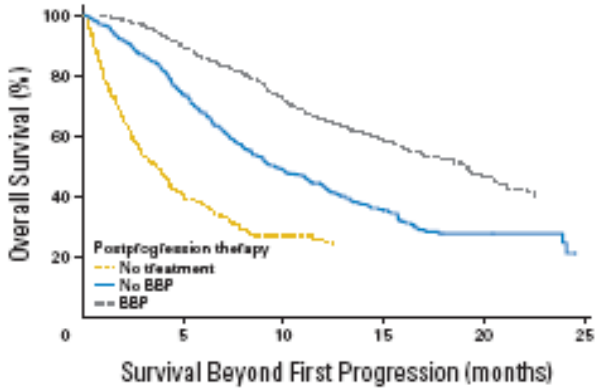


Data cutoff January 21, 2007:
- **1445 pts with 1st Progression**
- **932 death events**
- **Median follow-up time 19.6 months**

Grothey et al. ASCO 2007

As shown in Figure 7.2, patients receiving bevacizumab beyond disease progression showed a significantly longer overall survival than those receiving no treatment after first-progression or treatment without bevacizumab. Although there are obvious limitations to the non randomised design of the BRITE study, the survival of bevacizumab administered in the second-line setting, predominantly at a dose equivalent to 5 mg/kg fortnightly, in a group of patients who might be expected to be relatively resistant to the drug suggests that the lower dose of bevacizumab used in NO16966 study is active in the second-line setting too.

Figure 7.2 Overall survival from first progression according to second-line treatment administered in the BRITE study (Grothey *et al.* 2008)



	All patients (N = 1,053)	No post-progression treatment (n = 253)	No BBP (n = 531)	BBP (n = 642)
Number of deaths	932	168	305	260
Percent	47.7	66.4	57.8	40.5
1-year survival rate, %	74.7	52.5	77.3	87.7
95% CI	72.7 to 76.7	46.2 to 58.8	73.7 to 80.9	85.2 to 90.3
Median survival beyond first progression, months	12.0	3.6	9.5	19.2
95% CI	11.1 to 13.3	2.7 to 4.3	8.4 to 11.2	18.8 to 20.7

A8. **<u>Section 6.8.2. Please provide further details (including tabulated results by each treatment group; reference sources; was it a priori or post hoc analysis), on the subgroup analyses in patients with liver metastases in the NO16966 trial and any other supportive evidence.</u>**

The analysis reported by Cassidy *et al* and reproduced in Section 6.8.2 of our original submission was conducted on a *post-hoc* basis in response to the growing interest in liver resection in recent years. No further data from this *post-hoc* analysis of liver resection is available within the time-scale of responding to the current request for clarification.

Because the presence or absence of liver metastases at baseline was a stratification factor for the NO16966 study, the DRAM pre-specified that exploratory analysis should be carried out to determine degree of benefit from the addition of bevacizumab in patients with and without liver metastases. This is, however, uninformative with regard to any impact of bevacizumab on resection rate or outcomes in resected patients.

Significant further data on the use of bevacizumab plus chemotherapy as an adjunct to the resection of isolated liver metastases in the treatment of potentially resectable liver metastases is anticipated at the ESMO meeting in September 2009 with the presentation of results from the BOXER study by Wong *et al.* BOXER is a multicentre phase II trial of capecitabine and oxaliplatin plus bevacizumab as neoadjuvant treatment for patients with liver-only metastases from colorectal cancer unsuitable for upfront resection. Roche will be happy to provide information from this study when it becomes available.

A9. **Can you provide supportive evidence for your assumption of equivalence for the following regimens**

- **FOLFOX and FOLFIRI**
- **FOLFOX and XELOX**
- **FOLFOX-6 and FOLFOX-4**

See question A1 for evidence of the equivalence of FOLFOX-6 and FOLFOX-4.

With regard to the equivalence of FOLFOX and XELOX, the main part of our original submission deals with the NO16966 study which examined the equivalence of FOLFOX-4 and XELOX. We would refer you to our original submission which reported on the non-inferiority of XELOX compared to FOLFOX-4 with regard to progression-free survival and overall survival and which discusses the tolerability profile of FOLFOX and XELOX.

The best evidence for the equivalence of FOLFOX and FOLFIRI comes from Tournigand *et al* (2004), who compared FOLFIRI with FOLFOX-6 with cross-over at disease progression (reflecting current UK clinical practice as enshrined in the current NICE clinical guideline on treating mCRC). They report median PFS of 8.5 months (95% CI, 7.0 to 9.5) for first-line FOLFIRI and 8.0 months (95% CI 6.2 to 9.4) for first-line FOLFOX-6 (p=0.64).They reported median OS of 21.5 months (range, 16.9 to 25.2 months) for patients receiving FOLFIRI first and 20.6 months (range, 17.7 to 24.6 months) for those treated with FOLFOX first (p=0.99).

As we noted in Section 2, Note 2 of our original submission NICE itself was unable to distinguish between oxaliplatin-based and irinotecan-based first-line chemotherapy for mCRC. We do not believe that any data that has become available in the intervening years has changed this.

It should be reiterated that the scope for this Appraisal concerns the clinical and cost effectiveness of adding bevacizumab to oxaliplatin-based chemotherapy. As such the equivalence of FOLFIRI and FOLFOX is of limited relevance. Its importance is restricted to the group of patients currently receiving FOLFIRI who might be switched to bevacizumab plus FOLFOX/XELOX should it become available. As explained Note 2 of Section 2 of our original submission, this is a small patient group - FOLFIRI is used for a minority of patients requiring first-line treatment for mCRC in the UK many of whom are likely to have contraindications to oxaliplatin and, as such, are not candidates for switching.

C1. **Priority question: The statement "the comprehensive safety data collected in study NO16966 and elsewhere, and meta-analysed by Cao et al (2009), demonstrated that B-XELOX and B-FOLFOX has similar tolerability to FOLFOX and XELOX" appears to be selectively reported and misleading.**

The meta-analysis by Cao et al (2009) also highlighted that a higher incidence of grade 3/4 adverse events, hypertension, thromboembolic /thrombotic events; bleeding and gastrointestinal perforation was associated with chemotherapy plus bevacizumab compared with chemotherapy alone. The Evidence Review Group also notes that more recent meta-analyses have also found an increased risk of gastrointestinal perforation (Hapani et al. Risk of gastrointestinal perforation in patients with cancer treated with bevacizumab: a meta-analysis. Lancet Oncol 2009; 10: 559-568) and venous thromboembolism (Nalluri et al. Risk of Venous Thromboembolism with the Angiogenesis Inhibitor Bevacizumab in Cancer Patients - A Meta-analysis JAMA. 2008; 300(19):2277-2285) associated with bevacizumab therapy. Please clarify.

The statement to which the ERG appear to have taken exception is from the Executive Summary of Roche's original submission. It was intended to convey that for most patients bevacizumab is a well tolerated addition to standard treatment and that the burden it imposes does not outweigh the benefits it confers – the majority of adverse events in patients receiving bevacizumab plus chemotherapy are chemotherapy related and, as reported above in response to Question A5 the absolute excess of patients withdrawing from study N016966 for adverse events clearly linked to bevacizumab was only 3%. The EMEA and medicines regulators in many other countries have concluded that the risk:benefit ratio for bevacizumab added to first-line chemotherapy for mCRC is favourable.

The contentious statement was not intended to replace the detailed consideration of safety included in Section 6.11 of Roche's original submission. There can be no dispute that the use of bevacizumab is associated with characteristic adverse events. The most common ones are proteinuria (usually clinically silent and not requiring intervention – note the increase in frequency of proteinuria between chemotherapy alone arms and placebo plus chemotherapy arms of the NO16966 study where clinically irrelevant proteinuria is identified once it becomes a matter of interest in the trial) and hypertension (usually asymptomatic and readily managed).

There are also uncommon but more serious complications of bevacizumab treatment – namely GI perforation, high-grade throboembolic problems and bleeding problems. The frequency of these is such that they can be hard to identify from individual clinical trials, even large ones, but meta-analyses such as that by Cao *et al.* cited by Roche and those identified by the ERG are helping to give greater precision to estimates of the risk of these unusual events.

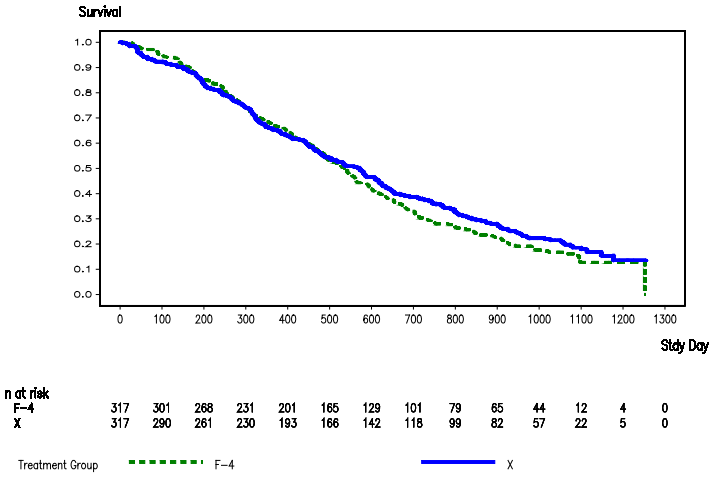
Appendix 1 Kaplan Meier Curves of OS and PFS for paired study arms in Study NO16966 (all ITT)

Abbreviations: F-4, FOLFOX; F+BV, B-FOLFOX; F+P, P-FOLFOX; X, XELOX; X+BV, B-FOLFOX; X+P, P-XELOX.

Figure 1

gsur50km_XF_B_4001 Kaplan Meier Curve of Overall Survival

Protocol(s): I16966M
Analysis: Intent-to-Treat Population and Cohort B
Filter Applied: WHERE ectypen LE 4 and WHERE s_chrtb = 'YES'



n at risk													
F--4	317	301	268	231	201	165	129	101	79	65	44	12	4	0
X	317	290	261	230	193	166	142	118	99	82	57	22	5	0

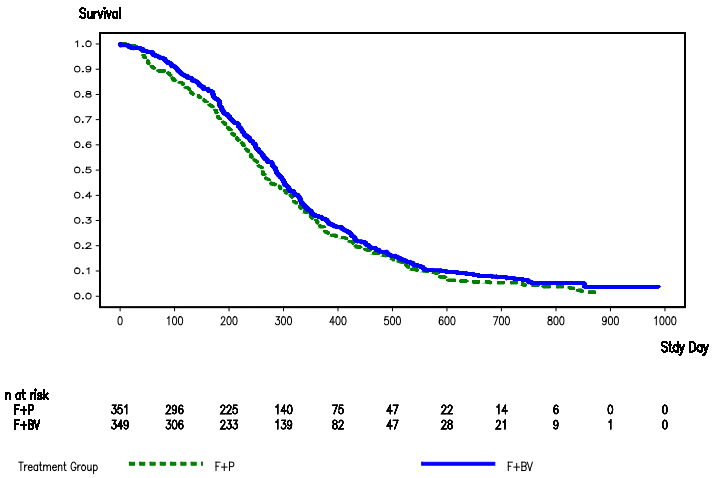
Treatment Group F--4 X

Program: $PROD/cdi10743/no16966/gsur50km.sas / Output : $PROD/cdi10743a/i16966m/reports/gsur50km_XF_B_4001.out
04MAY2007 16:44 NEHDELV

Figure 2

gspf50km_AP_I_4001 Kaplan Meier Curve of TTP or Death

Protocol(s): I16966M
Analysis: Intent-to-Treat Population and Cohort I
Filter Applied: WHERE ectypen LE 4 and WHERE s_chrti = 'YES'



n at risk											
F+P	351	296	225	140	75	47	22	14	6	0	0
F+BV	349	306	233	139	82	47	28	21	9	1	0

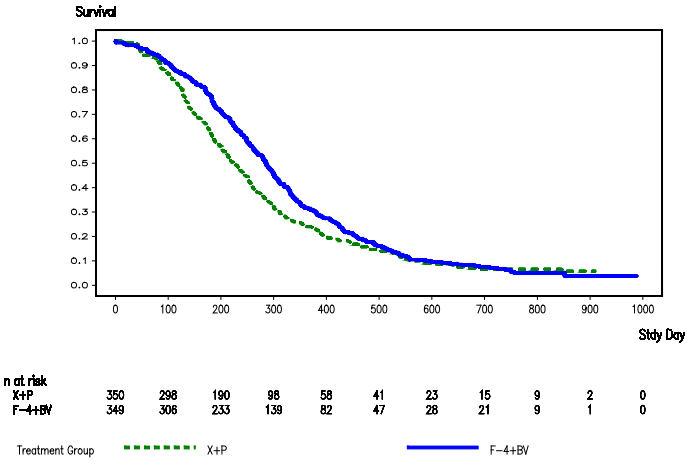
Treatment Group F+P F+BV

Program: $PROD/cdi10743/no16966/gspf50km.sas / Output : $PROD/cdi10743a/i16966m/reports/gspf50km_AP_I_4001.out
11APR2007 14:29 NEHDELV

Figure 3

gspf50km_FAXP_L_4001 Kaplan Meier Curve of TTP or Death

Protocol(s): I16966M
Analysis: Intent-to-Treat Population and Cohort L
Filter Applied: WHERE ectypen LE 4 and WHERE s_chrtl = 'YES'



n at risk											
X+P	350	298	190	98	58	41	23	15	9	2	0
F-4+BV	349	306	233	139	82	47	28	21	9	1	0

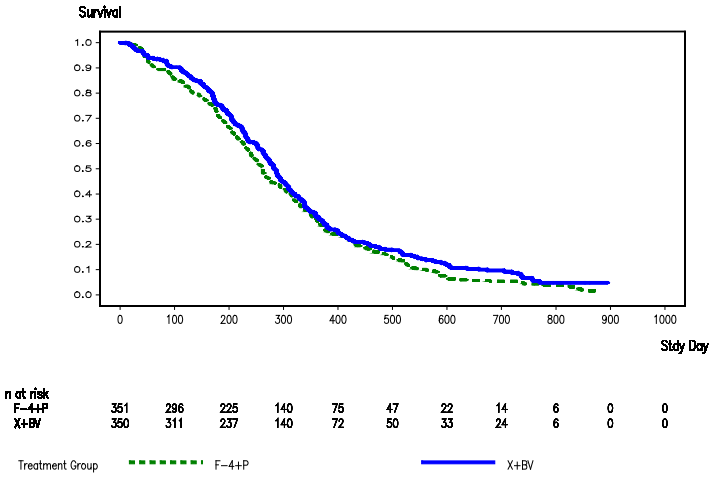
Treatment Group X+P F-4+BV

Program: $PROD/cdp10743/no16966/gspf50km.sas / Output : $PROD/cd10743a/i16966m/reports/gspf50km_FAXP_L_4001.out
11APR2007 14:45 NENDELV

Figure 4

gspf50km_XAFP_K_4001 Kaplan Meier Curve of TTP or Death

Protocol(s): I16966M
Analysis: Intent-to-Treat Population and Cohort K
Filter Applied: WHERE ectypen LE 4 and WHERE s_chrtk = 'YES'



n at risk											
F-4+P	351	296	225	140	75	47	22	14	6	0	0
X+BV	350	311	237	140	72	50	33	24	6	0	0

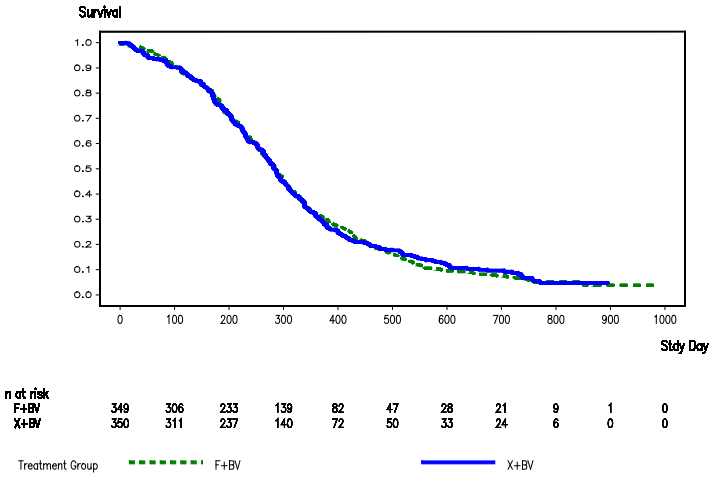
Treatment Group F-4+P X+BV

Program: $PROD/cdp10743/no16966/gspf50km.sas / Output : $PROD/cd10743a/i16966m/reports/gspf50km_XAFP_K_4001.out
11APR2007 14:50 NENDELV

Figure 5

gspf50km_XF_F_4001 Kaplan Meier Curve of TTP or Death

Protocol(s): I16966M
Analysis: Intent-to-Treat Population and Cohort F
Filter Applied: WHERE ectypen LE 4 and WHERE s_chrtf = 'YES'



n at risk											
F+BV	349	306	233	139	82	47	28	21	9	1	0
X+BV	350	311	237	140	72	50	33	24	6	0	0

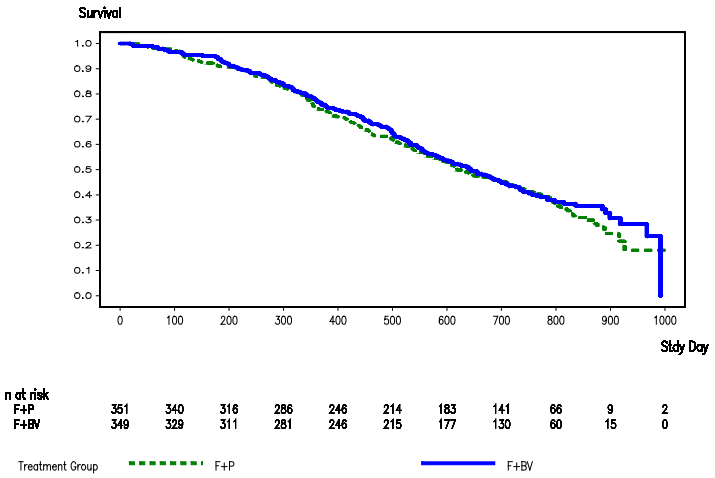
Treatment Group F+BV X+BV

Program: $PROD/cdp10743/no16966/gspf50km.sas / Output : $PROD/cd10743a/i16966m/reports/gspf50km_XF_F_4001.out
11APR2007 15:17 NIENDELV

Figure 6

gsur50km_AP_I_4001 Kaplan Meier Curve of Overall Survival

Protocol(s): I16966M
Analysis: Intent-to-Treat Population and Cohort I
Filter Applied: WHERE ectypen LE 4 and WHERE s_chrti = 'YES'



n at risk											
F+P	351	340	316	286	246	214	183	141	66	9	2
F+BV	349	329	311	281	246	215	177	130	60	15	0

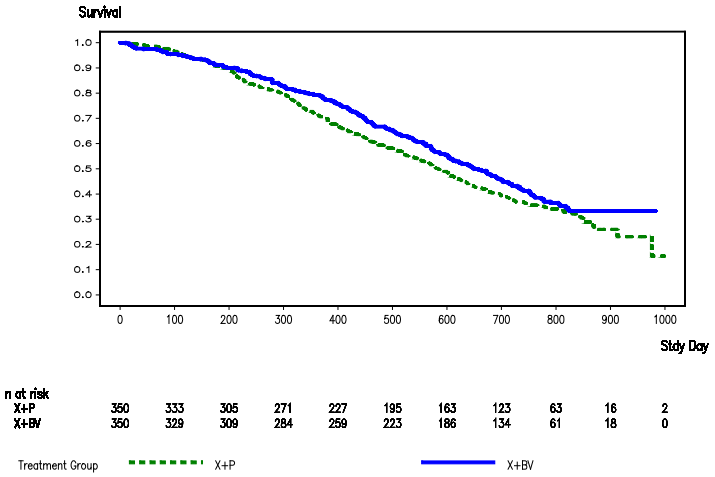
Treatment Group F+P F+BV

Program: $PROD/cdp10743/no16966/gsur50km.sas / Output : $PROD/cd10743a/i16966m/reports/gsur50km_AP_I_4001.out
11APR2007 17:47 NIENDELV

Figure 7

gsur50km_AP_J_4001 Kaplan Meier Curve of Overall Survival

Protocol(s): I16966M
Analysis: Intent-to-Treat Population and Cohort J
Filter Applied: WHERE ectypen LE 4 and WHERE s_chrtj = 'YES'



n at risk											
X+P	350	333	305	271	227	195	163	123	63	16	2
X+BV	350	329	309	284	259	223	186	134	61	18	0

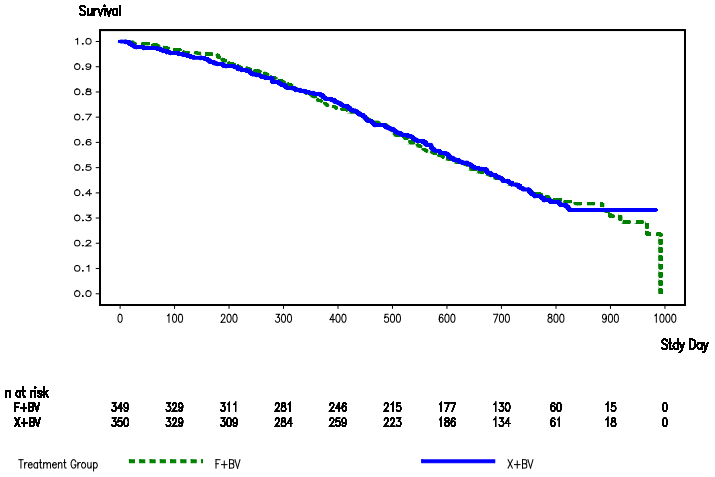
Treatment Group X+P X+BV

Program: $PROD/cdp10743/no16966/gsur50km.sas / Output : $PROD/cd10743a/i16966m/reports/gsur50km_AP_J_4001.out
11APR2d07 17:51 NIENDELV

Figure 8

gsur50km_XF_F_4001 Kaplan Meier Curve of Overall Survival

Protocol(s): I16966M
Analysis: Intent-to-Treat Population and Cohort F
Filter Applied: WHERE ectypen LE 4 and WHERE s_chrtf = 'YES'



n at risk											
F+BV	349	329	311	281	246	215	177	130	60	15	0
X+BV	350	329	309	284	259	223	186	134	61	18	0

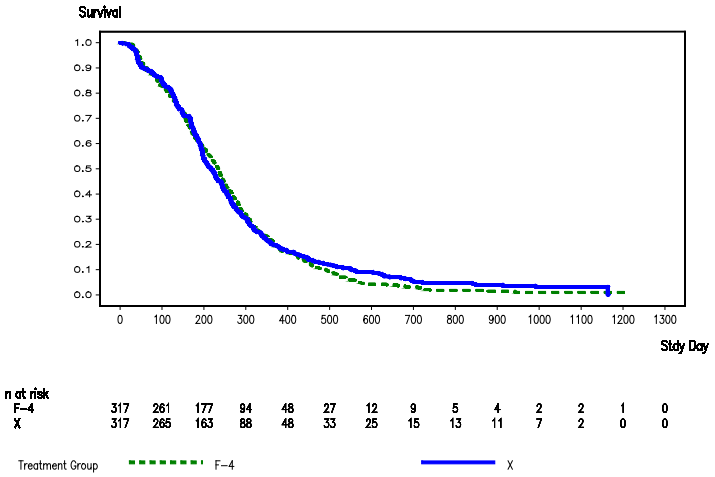
Treatment Group F+BV X+BV

Program: $PROD/cdp10743/no16966/gsur50km.sas / Output : $PROD/cd10743a/i16966m/reports/gsur50km_XF_F_4001.out
11APR2d07 18:03 NIENDELV

Figure 9

gspf50km_XF_B_4001 Kaplan Meier Curve of TTP or Death

Protocol(s): I16966M
Analysis: Intent-to-Treat Population and Cohort B
Filter Applied: WHERE ectypen LE 4 and WHERE s_chrtb = 'YES'



n at risk													
F–4	317	261	177	94	48	27	12	9	5	4	2	2	1	0
X	317	265	163	88	48	33	25	15	13	11	7	2	0	0

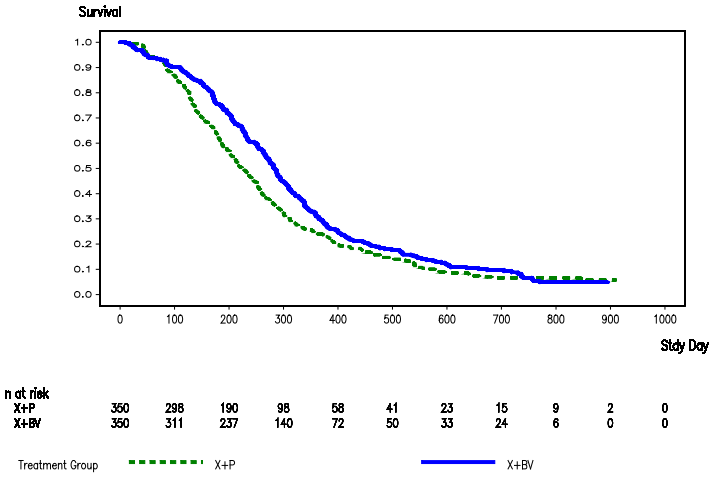
Treatment Group F–4 X

Program: $PRODdp10743/no16966/gspf50km.sas / Output : $PRODdct10743a/l16966/mreports/gspf50km_XF_B_4001.out
04MAY2d07 11:28 HAUNR

Figure 10

gspf50km_AP_J_4001 Kaplan Meier Curve of TTP or Death

Protocol(s): I16966M
Analysis: Intent-to-Treat Population and Cohort J
Filter Applied: WHERE ectypen LE 4 and WHERE s_chrtj = 'YES'



n at risk											
X+P	350	298	190	98	58	41	23	15	9	2	0
X+BV	350	311	237	140	72	50	33	24	6	0	0

Treatment Group X+P X+BV

Program: $PRODdp10743/no16966/gspf50km.sas / Output : $PRODdct10743a/l16966/mreports/gspf50km_AP_J_4001.out
11APR2d07 14:38 NEWDELV

Appendix 2 Summary of Time from Start of Adjuvant Treatment to Randomisation by Trial Treatment

dm16adj_6aa4006 Summary of Time from Start of Previous Adjuvant Chemo. to RND by Trial Treatment
Use of Adjuvant chemotherapy YES
Protocol(s): I16966L
Analysis: INTENT-TO-TREAT POPULATION Center: ALL CENTERS
Cohort A and comparison 6A

	FOLFOX-4	FOLFOX-4+P	FOLFOX-4+BV	XELOX	XELOX+P	XELOX+BV
	N = 83	N = 85	N = 88	N = 91	N = 76	N = 88

Time from Start of Prior Adj. Chemo to RND					
[0; 1[Year	10 (12%)	3 (4%)	8 (9%)	9 (10%)	4 (4%)
[1; 2[Years	39 (47%)	32 (38%)	28 (32%)	42 (48%)	29 (32%)
[2; 3[Years	17 (20%)	21 (25%)	30 (34%)	15 (17%)	33 (36%)
[3; 4[Years	9 (11%)	10 (12%)	11 (13%)	14 (16%)	10 (11%)
[4; max] Years	8 (10%)	19 (22%)	11 (13%)	8 (9%)	15 (16%)
n	83	85	88	88	91

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
DM16 06SEP2007:19:26:11

Appendix 3 Study NO16966: Summary of Multiple Cox Regression for Overall Survival – Model Including Time from Start of Adjuvant Chemotherapy to Randomization

esur18m11_AP_C_4001 Summary of Multiple Cox Regression for Overall Survival

Protocol(s): I16966M
Analysis: Intent-to-Treat Population and Cohort C Filter Applied: WHERE ectypen LE 4 and WHERE s_chrtc = 'YES'

Effect/ Covariate included in the Model	Hazard Ratio	97.5% CI for Hazard Ratio	p-Value
Randomization treatment	0.87	[0.75;1.02]	0.0437
Time from Start of Adj. Chemoth. to RND (<= 900 vs. > 900 days or no adj. chemo.)	0.82	[0.65;1.03]	0.0522
Time from Start of Adj. Chemoth. to RND (> 900 vs. <= 900 days or no adj. chemo.)	0.68	[0.52;0.89]	0.0015

Comparison: F-4+BV/X+BV vs. F-4+P/X+P
Stratified by F+P/F+BV vs. X+P/X+BV

Program : $PROD/cdp10743/no16966/esur18m11.sas
Output : $PROD/cd10743a/i16966m/reports/esur18m11_AP_C_4001.out
19SEP2007 14:56 NENDELV

Appendix 4 Study NO16966: Overall Survival – All Adjuvant-treated Patients Excluded (Data cut-off 31 January 2007)

esur46su_AP Main Efficacy Results for Superiority on Overall Survival

Protocol(s): I16966M

Pop.	Treatment Regimens				Hazard Ratio	97.5% CI	p-Value (Log-Rank)
OVERALL COMPARISON:							
	FOLFOX-4+P/XELOX+P		FOLFOX-4+BV/XELOX+BV				
	Number of Patients with Event	Median Time to Event [Days]	Number of Patients with Event	Median Time to Event [Days]			
ITT	355	560.0	331	639.0	0.83	[0.70;0.99]	0.0183
EPP	336	560.0	316	637.0	0.84	[0.71;1.00]	0.0293
PP	290	602.0	265	674.0	0.83	[0.68;1.00]	0.0246
TREATMENT SUBGROUP COMPARISONS:							
	FOLFOX-4+P		FOLFOX-4+BV				
	Number of Patients with Event	Median Time to Event [Days]	Number of Patients with Event	Median Time to Event [Days]			
ITT	178	558.0	163	639.0	0.86	[0.68;1.10]	0.1762
EPP	166	560.0	154	625.0	0.89	[0.69;1.14]	0.2876
PP	143	619.0	135	656.0	0.88	[0.67;1.15]	0.2719
	XELOX+P		XELOX+BV				
	Number of Patients with Event	Median Time to Event [Days]	Number of Patients with Event	Median Time to Event [Days]			
ITT	177	562.0	168	638.0	0.81	[0.63;1.03]	0.0470
EPP	170	562.0	162	637.0	0.80	[0.63;1.03]	0.0440
PP	147	587.0	130	689.0	0.78	[0.59;1.02]	0.0373

Patients without Prior Adjuvant Chemotherapy

Program : $PROD/cdp10743/no16966/esur46su.sas / Output : $PROD/cd10743a/i16966m/reports/esur46su_AP.out
18APR2007 12:42 NENDELV
Page 1 of 1

Appendix 5 Study NO16966: Overall Survival – Adjuvant-treated Patient in FOLFOX-4 arms excluded (Data cut-off 31 January 2007)

esur73su_AP Main Efficacy Results for Superiority on Overall Survival

Protocol(s): I16966M

OVERALL COMPARISON:

Pop.	FOLFOX-4+P/XELOX+P: Number of Patients with Event	FOLFOX-4+P/XELOX+P: Median Time to Event [Days]	FOLFOX-4+BV/XELOX+BV: Number of Patients with Event	FOLFOX-4+BV/XELOX+BV: Median Time to Event [Days]	Hazard Ratio 97.5% CI	p-Value (Log-Rank)
ITT	409	574.0	374	644.0	0.85 [0.72;1.00]	0.0242
EPP	385	574.0	355	642.0	0.85 [0.72;1.01]	0.0302
PP	330	617.0	298	682.0	0.84 [0.70;1.00]	0.0264

TREATMENT SUBGROUP COMPARISONS:

Pop.	FOLFOX-4+P: Number of Patients with Event	FOLFOX-4+P: Median Time to Event [Days]	FOLFOX-4+BV: Number of Patients with Event	FOLFOX-4+BV: Median Time to Event [Days]	Hazard Ratio 97.5% CI	p-Value (Log-Rank)
ITT	178	558.0	163	639.0	0.86 [0.68;1.10]	0.1762
EPP	166	560.0	154	625.0	0.89 [0.69;1.14]	0.2876
PP	143	619.0	135	656.0	0.88 [0.67;1.15]	0.2719

Pop.	XELOX+P: Number of Patients with Event	XELOX+P: Median Time to Event [Days]	XELOX+BV: Number of Patients with Event	XELOX+BV: Median Time to Event [Days]	Hazard Ratio 97.5% CI	p-Value (Log-Rank)
ITT	231	584.0	211	650.0	0.84 [0.68;1.04]	0.0698
EPP	219	579.0	201	658.0	0.83 [0.66;1.03]	0.0511
PP	187	613.0	163	697.0	0.81 [0.63;1.03]	0.0460

Patients with Prior Adjuvant Chemotherapy Randomized to FOLFOX Arms Excluded

Program : $PROD/cdp10743/no16966/esur73su.sas / Output : $PROD/cd10743a/i16966m/reports/esur73su_AP.out
25JUN2007 15:04 NENDELV
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Appendix 6 Study NO16966: Overall Survival – Adjuvant-treated Patients in FOLFOX-4+P arm excluded (Data cut-off 31 January 2007)

esur41su_AP Main Efficacy Results for Superiority on Overall Survival

Protocol(s): I16966M

Pop.	Treatment Regimens				Hazard Ratio	97.5% CI	p-Value (Log-Rank)
OVERALL COMPARISON:							
	FOLFOX-4+P/XELOX+P		FOLFOX-4+BV/XELOX+BV				
	Number of Patients with Event	Median Time to Event [Days]	Number of Patients with Event	Median Time to Event [Days]			
ITT	409	574.0	420	646.0	0.84	[0.72;0.98]	0.0116
EPP	385	574.0	396	644.0	0.84	[0.72;0.99]	0.0170
PP	330	617.0	335	685.0	0.83	[0.70;0.99]	0.0179
TREATMENT SUBGROUP COMPARISONS:							
	FOLFOX-4+P		FOLFOX-4+BV				
	Number of Patients with Event	Median Time to Event [Days]	Number of Patients with Event	Median Time to Event [Days]			
ITT	178	558.0	209	644.0	0.84	[0.66;1.05]	0.0786
EPP	166	560.0	195	644.0	0.86	[0.68;1.09]	0.1594
PP	143	619.0	172	673.0	0.86	[0.67;1.11]	0.1824
	XELOX+P		XELOX+BV				
	Number of Patients with Event	Median Time to Event [Days]	Number of Patients with Event	Median Time to Event [Days]			
ITT	231	584.0	211	650.0	0.84	[0.68;1.04]	0.0698
EPP	219	579.0	201	658.0	0.83	[0.66;1.03]	0.0511
PP	187	613.0	163	697.0	0.81	[0.63;1.03]	0.0460

Patients with Prior Adjuvant Chemotherapy Randomized to FOLFOX-4 + P Excluded

Program : $PROD/cdp10743/no16966/esur41su.sas / Output : $PROD/cd10743a/i16966m/reports/esur41su_AP.out
13AUG2007 16:18 NENDELV
Page 1 of 1

Appendix 7 Dose intensity planned versus delivered by drug by treatment cycle for all arms of Study NO16966

ed16_4A_C_3001 Summary of Dose Intensity per Cycle by Trial Treatment

Protocol(s): I16966M
Analysis: Safety Population - Cohort C
Filter applied: WHERE ectypen LE 3 AND s_chrtc = 'YES'

Treatment Group: FOLFOX-4+P

Treatment		N	Mean	Std	Minimum	Q1	Median	Q3	Maximum
5-FLUOROURACIL	Total	335	0.94	0.09	0.41	0.88	0.98	1.00	1.14
	Cycle 1	335	0.99	0.07	0.15	0.99	1.00	1.00	1.68
	Cycle 2	326	0.98	0.09	0.00	0.99	1.00	1.00	1.68
	Cycle 3	321	0.97	0.11	0.00	0.98	1.00	1.00	1.68
	Cycle 4	297	0.96	0.09	0.20	0.97	1.00	1.00	1.14
	Cycle 5	289	0.95	0.10	0.40	0.96	1.00	1.00	1.14
	Cycle 6	277	0.94	0.12	0.00	0.83	0.99	1.00	1.14
	Cycle 7	260	0.92	0.14	0.00	0.81	0.99	1.00	1.14
	Cycle 8	254	0.92	0.13	0.00	0.81	0.99	1.00	1.15
	Cycle 9	242	0.92	0.12	0.40	0.81	0.99	1.00	1.14
	Cycle 10	219	0.90	0.15	0.00	0.80	0.99	1.00	1.14
	Cycle 11	204	0.90	0.15	0.00	0.80	0.98	1.00	1.14
	Cycle 12	187	0.89	0.16	0.09	0.80	0.98	1.00	1.05
	Cycle 13	141	0.88	0.20	0.00	0.80	0.98	1.00	1.05
	Cycle 14	123	0.89	0.17	0.00	0.80	0.98	1.00	1.05
	Cycle 15	114	0.89	0.14	0.41	0.80	0.97	1.00	1.05
	Cycle 16	87	0.89	0.13	0.41	0.80	0.97	1.00	1.05
	Cycle 17	80	0.87	0.19	0.00	0.80	0.96	1.00	1.05

				Cycle 18	71	0.87	0.17	0.00	
0.79	0.92	1.00	1.05						
				Cycle 19	59	0.89	0.14	0.40	
0.80	0.92	1.00	1.05						
				Cycle 20	52	0.89	0.12	0.49	
0.80	0.91	1.00	1.05						
				Cycle 21	50	0.86	0.18	0.00	
0.79	0.90	1.00	1.05						
				Cycle 22	43	0.86	0.19	0.00	
0.79	0.90	1.00	1.03						
				Cycle 23	37	0.88	0.14	0.49	
0.80	0.90	1.00	1.03						
				Cycle 24	35	0.88	0.15	0.49	
0.79	0.98	1.00	1.03						
OXALIPLATIN				Total	335	0.89	0.13	0.30	
0.82	0.93	0.99	1.03						
				Cycle 1	335	0.99	0.02	0.86	
0.99	1.00	1.00	1.13						
				Cycle 2	326	0.98	0.09	0.00	
0.99	1.00	1.00	1.13						
				Cycle 3	320	0.97	0.07	0.67	
0.98	1.00	1.00	1.04						
				Cycle 4	297	0.95	0.12	0.00	
0.97	0.99	1.00	1.04						
				Cycle 5	289	0.93	0.14	0.00	
0.96	0.99	1.00	1.04						
				Cycle 6	277	0.92	0.16	0.00	
0.79	0.99	1.00	1.07						
				Cycle 7	260	0.90	0.17	0.00	
0.77	0.99	1.00	1.05						
				Cycle 8	252	0.89	0.20	0.00	
0.77	0.99	1.00	1.15						
				Cycle 9	238	0.88	0.20	0.00	
0.76	0.99	1.00	1.05						

ed16_4A_C_3001 Summary of Dose Intensity per Cycle by Trial Treatment

Protocol(s): I16966M
Analysis: Safety Population - Cohort C
Filter applied: WHERE ectypen LE 3 AND s_chrtc = 'YES'

Treatment Group: FOLFOX-4+P

Treatment		N	Mean	Std	Minimum	Q1	Median	Q3	Maximum
OXALIPLATIN	Cycle 10	214	0.86	0.24	0.00	0.76	0.98	1.00	1.04
	Cycle 11	199	0.81	0.28	0.00	0.76	0.92	1.00	1.05
	Cycle 12	175	0.77	0.31	0.00	0.75	0.78	1.00	1.10
	Cycle 13	125	0.70	0.36	0.00	0.74	0.77	0.99	1.03
	Cycle 14	102	0.71	0.34	0.00	0.74	0.77	0.99	1.04
	Cycle 15	93	0.70	0.35	0.00	0.74	0.77	0.99	1.04
	Cycle 16	69	0.69	0.35	0.00	0.73	0.77	0.98	1.04
	Cycle 17	63	0.59	0.41	0.00	0.00	0.76	0.98	1.04
	Cycle 18	55	0.58	0.40	0.00	0.00	0.76	0.89	1.04
	Cycle 19	44	0.53	0.42	0.00	0.00	0.75	0.79	1.04
	Cycle 20	40	0.49	0.42	0.00	0.00	0.74	0.77	1.01
	Cycle 21	34	0.54	0.39	0.00	0.00	0.75	0.77	1.00
	Cycle 22	29	0.47	0.41	0.00	0.00	0.74	0.77	1.00
	Cycle 23	23	0.53	0.41	0.00	0.00	0.75	0.77	1.00
	Cycle 24	23	0.50	0.42	0.00	0.00	0.74	0.77	1.00
PLACEBO	Total	335	1.00	0.03	0.88	0.99	1.00	1.00	1.17
	Cycle 1	335	1.00	0.06	0.03	1.00	1.00	1.00	1.51
	Cycle 2	325	1.00	0.05	0.25	1.00	1.00	1.00	1.21
	Cycle 3	320	1.00	0.02	0.83	1.00	1.00	1.00	1.12

			Cycle 4	295	0.99	0.06	0.00	
1.00	1.00	1.00	1.12					
			Cycle 5	287	1.00	0.02	0.87	
1.00	1.00	1.00	1.13					
			Cycle 6	276	1.00	0.03	0.87	
1.00	1.00	1.00	1.13					
			Cycle 7	257	0.99	0.07	0.00	
1.00	1.00	1.00	1.13					
			Cycle 8	251	1.00	0.07	0.00	
1.00	1.00	1.00	1.13					
			Cycle 9	239	1.00	0.04	0.87	
1.00	1.00	1.00	1.13					
			Cycle 10	217	1.00	0.04	0.87	
1.00	1.00	1.00	1.13					
			Cycle 11	203	1.00	0.08	0.00	
1.00	1.00	1.00	1.15					
			Cycle 12	186	1.01	0.04	0.90	
1.00	1.00	1.00	1.15					
			Cycle 13	139	1.01	0.04	0.88	
1.00	1.00	1.01	1.14					
			Cycle 14	122	1.01	0.04	0.88	
1.00	1.00	1.01	1.14					
			Cycle 15	115	1.00	0.11	0.00	
1.00	1.00	1.01	1.18					
			Cycle 16	89	1.02	0.05	0.86	
1.00	1.00	1.02	1.18					
			Cycle 17	79	1.02	0.06	0.86	
1.00	1.00	1.02	1.18					
			Cycle 18	73	1.02	0.06	0.86	
1.00	1.00	1.05	1.18					
			Cycle 19	60	1.03	0.05	0.94	
1.00	1.00	1.05	1.18					

ed16_4A_C_3001 Summary of Dose Intensity per Cycle by Trial Treatment

Protocol(s): I16966M
Analysis: Safety Population - Cohort C
Filter applied: WHERE ectypen LE 3 AND s_chrtc = 'YES'

Treatment Group: FOLFOX-4+P

Treatment		N	Mean	Std	Minimum	Q1	Median	Q3	Maximum
PLACEBO	Cycle 20	54	1.02	0.05	0.94	1.00	1.00	1.05	1.18
	Cycle 21	51	1.02	0.05	0.94	1.00	1.00	1.05	1.18
	Cycle 22	44	1.03	0.06	0.88	1.00	1.00	1.06	1.18
	Cycle 23	38	1.03	0.06	0.88	1.00	1.00	1.09	1.18
	Cycle 24	34	1.02	0.06	0.88	1.00	1.00	1.06	1.14

ed16_4A_C_3001 Summary of Dose Intensity per Cycle by Trial Treatment

Protocol(s): I16966M
Analysis: Safety Population - Cohort C
Filter applied: WHERE ectypen LE 3 AND s_chrtc = 'YES'

Treatment Group: FOLFOX-4+BV

Treatment		N	Mean	Std	Minimum	Q1	Median	Q3	Maximum
5-FLUOROURACIL	Total	342	0.92	0.11	0.20	0.86	0.98	1.00	1.08
	Cycle 1	342	0.99	0.07	0.20	0.99	1.00	1.00	1.11

			Cycle 2	332	0.98	0.06	0.23	
0.99	1.00	1.00	1.11					
			Cycle 3	323	0.96	0.09	0.00	
0.98	1.00	1.00	1.08					
			Cycle 4	309	0.94	0.12	0.00	
0.96	1.00	1.00	1.08					
			Cycle 5	299	0.94	0.13	0.00	
0.93	0.99	1.00	1.08					
			Cycle 6	290	0.92	0.13	0.00	
0.81	0.99	1.00	1.08					
			Cycle 7	271	0.93	0.13	0.00	
0.81	0.99	1.00	1.08					
			Cycle 8	260	0.92	0.13	0.39	
0.80	0.99	1.00	1.08					
			Cycle 9	250	0.91	0.15	0.00	
0.80	0.99	1.00	1.08					
			Cycle 10	227	0.90	0.16	0.00	
0.80	0.99	1.00	1.08					
			Cycle 11	213	0.91	0.14	0.20	
0.80	0.99	1.00	1.08					
			Cycle 12	201	0.89	0.17	0.00	
0.80	0.98	1.00	1.08					
			Cycle 13	159	0.90	0.14	0.17	
0.80	0.98	1.00	1.09					
			Cycle 14	148	0.90	0.13	0.50	
0.80	0.98	1.00	1.08					
			Cycle 15	136	0.88	0.16	0.28	
0.80	0.98	1.00	1.08					
			Cycle 16	127	0.88	0.16	0.40	
0.80	0.98	1.00	1.10					
			Cycle 17	119	0.87	0.19	0.00	
0.79	0.97	1.00	1.10					
			Cycle 18	113	0.86	0.19	0.00	
0.80	0.96	1.00	1.10					
			Cycle 19	95	0.84	0.23	0.00	
0.79	0.93	1.00	1.10					
			Cycle 20	85	0.83	0.23	0.00	
0.79	0.84	1.00	1.10					
			Cycle 21	80	0.84	0.21	0.00	
0.80	0.85	1.00	1.08					
			Cycle 22	61	0.84	0.20	0.00	
0.79	0.82	1.00	1.06					
			Cycle 23	57	0.83	0.20	0.00	
0.79	0.82	1.00	1.06					
			Cycle 24	51	0.82	0.22	0.00	
0.79	0.82	1.00	1.05					
			Cycle 25	1	1.00	.	1.00	
1.00	1.00	1.00	1.00					
OXALIPLATIN			Total	342	0.89	0.13	0.28	
0.82	0.95	0.99	1.17					
			Cycle 1	342	0.99	0.02	0.86	
0.99	1.00	1.00	1.17					
			Cycle 2	332	0.98	0.06	0.74	
0.99	1.00	1.00	1.17					
			Cycle 3	323	0.96	0.08	0.71	
0.98	1.00	1.00	1.17					

			Cycle 4	309	0.94	0.11	0.00	
0.96	0.99	1.00	1.17					
			Cycle 5	299	0.94	0.10	0.70	
0.94	0.99	1.00	1.18					
			Cycle 6	290	0.93	0.11	0.53	
0.77	0.99	1.00	1.17					
			Cycle 7	269	0.91	0.14	0.00	
0.77	0.99	1.00	1.06					
			Cycle 8	258	0.91	0.15	0.00	
0.77	0.99	1.00	1.10					

ed16_4A_C_3001 Summary of Dose Intensity per Cycle by Trial Treatment

Protocol(s): I16966M
Analysis: Safety Population - Cohort C
Filter applied: WHERE ectypen LE 3 AND s_chrtc = 'YES'

Treatment Group: FOLFOX-4+BV

Treatment				N	Mean	Std	Minimum	
Q1	Median	Q3	Maximum					
OXALIPLATIN			Cycle 9	248	0.88	0.21	0.00	
0.76	0.99	1.00	1.06					
			Cycle 10	224	0.86	0.23	0.00	
0.76	0.98	1.00	1.06					
			Cycle 11	209	0.84	0.26	0.00	
0.76	0.98	1.00	1.06					
			Cycle 12	193	0.82	0.26	0.00	
0.76	0.94	1.00	1.08					
			Cycle 13	147	0.76	0.32	0.00	
0.75	0.77	1.00	1.09					
			Cycle 14	135	0.74	0.34	0.00	
0.75	0.77	0.99	1.04					
			Cycle 15	122	0.72	0.35	0.00	
0.74	0.77	0.99	1.04					
			Cycle 16	109	0.66	0.37	0.00	
0.72	0.76	0.96	1.10					
			Cycle 17	102	0.62	0.38	0.00	
0.00	0.76	0.95	1.10					
			Cycle 18	89	0.63	0.38	0.00	
0.50	0.76	0.85	1.10					
			Cycle 19	74	0.57	0.40	0.00	
0.00	0.76	0.81	1.10					
			Cycle 20	62	0.63	0.38	0.00	
0.50	0.76	0.90	1.10					

			Cycle 21	57	0.59	0.39	0.00	0.00	0.76
0.81	1.01								
			Cycle 22	41	0.55	0.41	0.00	0.00	0.75
0.83	1.01								
			Cycle 23	36	0.55	0.41	0.00	0.00	0.75
0.80	1.01								
			Cycle 24	33	0.55	0.41	0.00	0.00	0.76
0.78	1.01								
			Cycle 25	1	0.76	.	0.76	0.76	0.76
0.76	0.76								
BEVACIZUMAB			Total	342	1.00	0.03	0.88	0.99	1.00
1.00	1.25								
			Cycle 1	334	1.00	0.04	0.84	1.00	1.00
1.00	1.50								
			Cycle 2	325	1.00	0.02	0.94	1.00	1.00
1.00	1.27								
			Cycle 3	313	1.00	0.02	0.88	1.00	1.00
1.00	1.27								
			Cycle 4	297	1.00	0.03	0.76	1.00	1.00
1.00	1.27								
			Cycle 5	286	0.99	0.05	0.34	1.00	1.00
1.00	1.16								
			Cycle 6	273	0.99	0.07	0.00	1.00	1.00
1.00	1.39								
			Cycle 7	248	1.00	0.06	0.50	1.00	1.00
1.00	1.39								
			Cycle 8	239	1.00	0.05	0.83	1.00	1.00
1.00	1.39								
			Cycle 9	231	1.00	0.05	0.83	0.99	1.00
1.00	1.39								
			Cycle 10	209	1.00	0.04	0.87	1.00	1.00
1.00	1.15								
			Cycle 11	199	1.00	0.04	0.87	1.00	1.00
1.00	1.15								
			Cycle 12	187	1.00	0.05	0.87	1.00	1.00
1.00	1.15								
			Cycle 13	147	1.00	0.05	0.87	1.00	1.00
1.00	1.15								
			Cycle 14	139	1.00	0.05	0.87	1.00	1.00
1.00	1.14								
			Cycle 15	129	1.01	0.05	0.80	1.00	1.00
1.00	1.14								
			Cycle 16	116	1.00	0.05	0.80	1.00	1.00
1.00	1.14								
			Cycle 17	112	1.00	0.06	0.80	1.00	1.00
1.00	1.14								

ed16_4A_C_3001 Summary of Dose Intensity per Cycle by Trial Treatment

Protocol(s): I16966M
Analysis: Safety Population - Cohort C
Filter applied: WHERE ectypen LE 3 AND s_chrtc = 'YES'

Treatment Group: FOLFOX-4+BV

Treatment		N	Mean	Std	Minimum	Q1	Median	Q3	Maximum
BEVACIZUMAB	Cycle 18	105	1.00	0.06	0.80	1.00	1.00	1.00	1.14
	Cycle 19	87	1.00	0.06	0.83	1.00	1.00	1.01	1.14
	Cycle 20	80	1.00	0.06	0.83	1.00	1.00	1.00	1.19
	Cycle 21	76	0.99	0.06	0.80	1.00	1.00	1.00	1.14
	Cycle 22	58	0.99	0.05	0.87	1.00	1.00	1.00	1.14
	Cycle 23	54	1.00	0.06	0.87	1.00	1.00	1.00	1.14
	Cycle 24	50	1.00	0.07	0.78	1.00	1.00	1.00	1.14
	Cycle 25	1	1.00	.	1.00	1.00	1.00	1.00	1.00
PLACEBO	Total	11	0.95	0.15	0.50	0.93	1.00	1.01	1.05
	Cycle 1	8	1.00	0.01	0.99	1.00	1.00	1.00	1.02
	Cycle 2	5	1.00	0.01	0.99	1.00	1.00	1.00	1.02
	Cycle 3	6	1.00	0.01	0.99	1.00	1.00	1.00	1.02
	Cycle 4	7	0.83	0.37	0.00	0.88	0.99	1.00	1.00
	Cycle 5	6	0.98	0.04	0.91	1.00	1.00	1.00	1.00
	Cycle 6	6	0.98	0.05	0.88	1.00	1.00	1.00	1.01
	Cycle 7	5	0.99	0.05	0.91	1.00	1.00	1.00	1.02
	Cycle 8	5	1.01	0.06	0.91	1.00	1.00	1.04	1.08
	Cycle 9	5	1.01	0.06	0.91	1.00	1.00	1.04	1.08
	Cycle 10	4	1.03	0.04	1.00	1.00	1.02	1.06	1.08

			Cycle 11	4	1.03	0.04	1.00
1.00	1.01	1.05	1.08				
			Cycle 12	3	1.01	0.01	1.00
1.00	1.01	1.02	1.02				
			Cycle 13	3	1.02	0.05	0.99
0.99	1.00	1.08	1.08				
			Cycle 14	3	1.03	0.04	1.00
1.00	1.01	1.08	1.08				
			Cycle 15	3	1.03	0.04	1.00
1.00	1.02	1.08	1.08				
			Cycle 16	3	1.03	0.04	1.00
1.00	1.02	1.08	1.08				
			Cycle 17	2	1.04	0.06	1.00
1.00	1.04	1.08	1.08				
			Cycle 18	3	1.04	0.04	1.00
1.00	1.05	1.08	1.08				
			Cycle 19	3	1.04	0.04	1.00
1.00	1.05	1.08	1.08				
			Cycle 20	2	1.02	0.03	1.00
1.00	1.02	1.05	1.05				
			Cycle 21	2	1.03	0.04	1.00
1.00	1.03	1.06	1.06				
			Cycle 22	2	1.03	0.04	1.00
1.00	1.03	1.06	1.06				
			Cycle 23	2	1.02	0.03	1.00
1.00	1.02	1.05	1.05				
			Cycle 24	2	1.02	0.03	1.00
1.00	1.02	1.05	1.05				

ed16_4A_C_3001 Summary of Dose Intensity per Cycle by Trial Treatment

Protocol(s): I16966M
Analysis: Safety Population - Cohort C
Filter applied: WHERE ectypen LE 3 AND s_chrtc = 'YES'

Treatment Group: XELOX+P

Treatment		N	Mean	Std	Minimum	Q1	Median	Q3	Maximum
CAPECITABINE	Total	338	0.87	0.17	0.04	0.79	0.93	1.00	1.10
	Cycle 1	338	0.95	0.16	0.04	0.96	1.00	1.00	1.37
	Cycle 2	321	0.93	0.18	0.00	0.93	1.00	1.00	1.15
	Cycle 3	297	0.91	0.17	0.11	0.92	1.00	1.00	1.11
	Cycle 4	289	0.88	0.19	0.00	0.77	1.00	1.00	1.11
	Cycle 5	254	0.87	0.19	0.11	0.75	1.00	1.00	1.11
	Cycle 6	236	0.86	0.18	0.06	0.75	0.96	1.00	1.10
	Cycle 7	196	0.85	0.18	0.00	0.73	0.93	1.00	1.11
	Cycle 8	168	0.86	0.17	0.21	0.75	0.90	1.00	1.14
	Cycle 9	125	0.85	0.19	0.00	0.75	0.92	1.00	1.11
	Cycle 10	113	0.84	0.21	0.00	0.72	0.92	1.00	1.11
	Cycle 11	84	0.83	0.20	0.00	0.75	0.87	1.00	1.11
	Cycle 12	71	0.85	0.20	0.00	0.75	0.92	1.00	1.11
	Cycle 13	57	0.83	0.19	0.31	0.74	0.83	1.00	1.11
	Cycle 14	51	0.84	0.18	0.41	0.74	0.91	1.00	1.11
	Cycle 15	41	0.82	0.22	0.00	0.75	0.90	1.00	1.11
	Cycle 16	38	0.84	0.18	0.44	0.75	0.90	1.00	1.11
OXALIPLATIN	Total	339	0.92	0.12	0.36	0.87	0.98	1.00	1.04
	Cycle 1	339	1.00	0.03	0.67	0.99	1.00	1.00	1.12

			Cycle 2	323	0.99	0.06	0.28	
0.99	1.00	1.00	1.12					
			Cycle 3	297	0.97	0.10	0.00	
0.99	1.00	1.00	1.04					
			Cycle 4	289	0.95	0.11	0.00	
0.98	1.00	1.00	1.04					
			Cycle 5	253	0.94	0.12	0.00	
0.91	0.99	1.00	1.19					
			Cycle 6	235	0.91	0.17	0.00	
0.77	0.99	1.00	1.09					
			Cycle 7	194	0.88	0.21	0.00	
0.77	0.99	1.00	1.09					
			Cycle 8	166	0.84	0.24	0.00	
0.76	0.96	1.00	1.08					
			Cycle 9	117	0.78	0.31	0.00	
0.75	0.79	1.00	1.08					
			Cycle 10	102	0.75	0.33	0.00	
0.75	0.77	1.00	1.08					
			Cycle 11	76	0.68	0.34	0.00	
0.65	0.77	0.98	1.06					
			Cycle 12	62	0.64	0.37	0.00	
0.60	0.77	0.97	1.06					
			Cycle 13	47	0.60	0.39	0.00	
0.00	0.76	0.97	1.06					
			Cycle 14	44	0.57	0.39	0.00	
0.00	0.76	0.78	1.02					
			Cycle 15	35	0.52	0.40	0.00	
0.00	0.70	0.78	1.01					
			Cycle 16	33	0.45	0.41	0.00	
0.00	0.65	0.77	1.01					

ed16_4A_C_3001 Summary of Dose Intensity per Cycle by Trial Treatment

Protocol(s): I16966M
Analysis: Safety Population - Cohort C
Filter applied: WHERE ectypen LE 3 AND s_chrtc = 'YES'

Treatment Group: XELOX+P

Treatment		N	Mean	Std	Minimum	Q1	Median	Q3	Maximum
PLACEBO	Total	339	1.00	0.04	0.49	0.99	1.00	1.00	1.20
	Cycle 1	339	1.00	0.06	0.03	1.00	1.00	1.00	1.26
	Cycle 2	319	1.00	0.02	0.88	1.00	1.00	1.00	1.17
	Cycle 3	292	0.99	0.07	0.00	1.00	1.00	1.00	1.17
	Cycle 4	286	0.99	0.07	0.00	1.00	1.00	1.00	1.17
	Cycle 5	250	1.00	0.04	0.79	0.99	1.00	1.00	1.22
	Cycle 6	231	1.00	0.04	0.79	0.99	1.00	1.00	1.24
	Cycle 7	193	1.00	0.05	0.79	0.99	1.00	1.00	1.24
	Cycle 8	166	1.00	0.05	0.79	1.00	1.00	1.00	1.35
	Cycle 9	123	1.00	0.05	0.81	1.00	1.00	1.00	1.21
	Cycle 10	112	1.01	0.06	0.81	1.00	1.00	1.00	1.24
	Cycle 11	83	1.00	0.05	0.81	0.99	1.00	1.00	1.15
	Cycle 12	70	0.99	0.13	0.00	0.99	1.00	1.00	1.15
	Cycle 13	56	1.00	0.07	0.81	0.99	1.00	1.00	1.22
	Cycle 14	51	1.01	0.07	0.81	0.99	1.00	1.00	1.22
	Cycle 15	41	1.01	0.08	0.81	1.00	1.00	1.00	1.23
	Cycle 16	39	1.00	0.08	0.79	1.00	1.00	1.00	1.23
	Cycle 17	1	1.00	.	1.00	1.00	1.00	1.00	1.00
	Cycle 18	1	1.00	.	1.00	1.00	1.00	1.00	1.00

ed16_4A_C_3001 Summary of Dose Intensity per Cycle by Trial Treatment

Protocol(s): I16966M
Analysis: Safety Population - Cohort C
Filter applied: WHERE ectypen LE 3 AND s_chrtc = 'YES'

Treatment Group: XELOX+BV

Treatment		N	Mean	Std	Minimum	Q1	Median	Q3	Maximum
CAPECITABINE	Total	352	0.84	0.18	0.07	0.74	0.89	0.99	1.18
	Cycle 1	352	0.93	0.17	0.07	0.95	1.00	1.00	1.18
	Cycle 2	324	0.93	0.15	0.11	0.93	1.00	1.00	1.14
	Cycle 3	303	0.89	0.19	0.00	0.77	1.00	1.00	1.16
	Cycle 4	293	0.86	0.21	0.00	0.75	1.00	1.00	1.11
	Cycle 5	265	0.85	0.20	0.14	0.72	0.96	1.00	1.39
	Cycle 6	254	0.84	0.20	0.16	0.72	0.93	1.00	1.11
	Cycle 7	222	0.83	0.21	0.23	0.72	0.93	1.00	1.39
	Cycle 8	208	0.81	0.24	0.00	0.70	0.88	1.00	1.93
	Cycle 9	169	0.79	0.24	0.00	0.68	0.83	1.00	1.39
	Cycle 10	148	0.80	0.22	0.00	0.70	0.79	1.00	1.52
	Cycle 11	119	0.80	0.21	0.00	0.70	0.79	1.00	1.11
	Cycle 12	108	0.80	0.25	0.00	0.68	0.77	1.00	1.52
	Cycle 13	84	0.78	0.23	0.00	0.66	0.77	1.00	1.08
	Cycle 14	76	0.77	0.24	0.00	0.58	0.76	1.00	1.08
	Cycle 15	67	0.77	0.22	0.00	0.59	0.75	1.00	1.11
	Cycle 16	55	0.75	0.23	0.00	0.56	0.75	1.00	1.08

			Cycle 17	2	0.74	0.36	0.48	0.48	0.74
1.00	1.00								
OXALIPLATIN			Total	353	0.90	0.14	0.12	0.84	0.96
1.00	1.05								
			Cycle 1	352	0.99	0.02	0.85	0.99	1.00
1.00	1.04								
			Cycle 2	325	0.97	0.09	0.00	0.98	1.00
1.00	1.04								
			Cycle 3	303	0.95	0.13	0.00	0.96	0.99
1.00	1.10								
			Cycle 4	292	0.93	0.15	0.00	0.95	0.99
1.00	1.10								
			Cycle 5	266	0.92	0.15	0.00	0.93	0.99
1.00	1.10								
			Cycle 6	252	0.92	0.13	0.00	0.78	0.99
1.00	1.10								
			Cycle 7	221	0.89	0.18	0.00	0.77	0.99
1.00	1.08								
			Cycle 8	205	0.84	0.26	0.00	0.76	0.97
1.00	1.08								
			Cycle 9	162	0.79	0.31	0.00	0.75	0.95
1.00	1.08								
			Cycle 10	141	0.71	0.36	0.00	0.69	0.77
1.00	1.13								
			Cycle 11	106	0.67	0.37	0.00	0.64	0.77
0.98	1.08								
			Cycle 12	92	0.64	0.40	0.00	0.00	0.77
0.98	1.06								
			Cycle 13	70	0.60	0.40	0.00	0.00	0.76
0.97	1.06								
			Cycle 14	63	0.61	0.39	0.00	0.00	0.75
0.97	1.06								
			Cycle 15	56	0.58	0.39	0.00	0.00	0.75
0.81	1.06								
			Cycle 16	46	0.61	0.37	0.00	0.49	0.75
0.83	1.01								

ed16_4A_C_3001 Summary of Dose Intensity per Cycle by Trial Treatment

Protocol(s): I16966M
Analysis: Safety Population - Cohort C
Filter applied: WHERE ectypen LE 3 AND s_chrtc = 'YES'

Treatment Group: XELOX+BV

Treatment		N	Mean	Std	Minimum	Q1	Median	Q3	Maximum
OXALIPLATIN	Cycle 17	2	0.97	0.04	0.95	0.95	0.97	1.00	1.00
BEVACIZUMAB	Total	353	1.00	0.04	0.80	0.99	1.00	1.00	1.22
	Cycle 1	349	1.00	0.03	0.68	1.00	1.00	1.00	1.22
	Cycle 2	318	0.99	0.04	0.68	1.00	1.00	1.00	1.22
	Cycle 3	291	1.00	0.03	0.86	1.00	1.00	1.00	1.22
	Cycle 4	282	0.99	0.04	0.83	1.00	1.00	1.00	1.22
	Cycle 5	254	1.00	0.05	0.80	1.00	1.00	1.00	1.22
	Cycle 6	237	1.00	0.05	0.83	1.00	1.00	1.00	1.22
	Cycle 7	210	1.00	0.07	0.39	0.99	1.00	1.00	1.22
	Cycle 8	194	1.00	0.06	0.83	1.00	1.00	1.00	1.22
	Cycle 9	160	1.00	0.06	0.83	1.00	1.00	1.00	1.22
	Cycle 10	140	1.00	0.11	0.00	1.00	1.00	1.01	1.31
	Cycle 11	111	0.99	0.09	0.40	0.99	1.00	1.00	1.22
	Cycle 12	100	1.02	0.14	0.83	0.99	1.00	1.01	2.00
	Cycle 13	79	1.01	0.12	0.50	0.99	1.00	1.01	1.71
	Cycle 14	71	0.98	0.20	0.00	0.99	1.00	1.00	1.71
	Cycle 15	63	1.01	0.11	0.77	0.99	1.00	1.00	1.71
	Cycle 16	55	1.00	0.17	0.07	0.99	1.00	1.01	1.71
	Cycle 17	2	1.00	0.17	0.88	0.88	1.00	1.12	1.12

PLACEBO			Total	6	1.03	0.04	1.00	
1.00	1.01	1.05	1.11					
			Cycle 1	4	1.00	0.00	1.00	
1.00	1.00	1.00	1.00					
			Cycle 2	4	1.00	0.00	0.99	
0.99	1.00	1.00	1.00					
			Cycle 3	4	1.01	0.02	0.99	
0.99	1.00	1.02	1.04					
			Cycle 4	3	1.05	0.06	1.00	
1.00	1.03	1.11	1.11					
			Cycle 5	2	1.05	0.08	1.00	
1.00	1.05	1.11	1.11					
			Cycle 6	4	1.03	0.08	0.97	
0.98	1.00	1.08	1.16					
			Cycle 7	3	1.07	0.08	1.00	
1.00	1.05	1.16	1.16					
			Cycle 8	4	1.05	0.08	0.97	
0.99	1.03	1.11	1.16					
			Cycle 9	5	1.05	0.06	1.00	
1.00	1.04	1.05	1.14					
			Cycle 10	4	1.07	0.06	1.00	
1.02	1.07	1.12	1.14					
			Cycle 11	4	1.07	0.06	1.00	
1.02	1.07	1.12	1.14					
			Cycle 12	4	1.07	0.06	1.00	
1.02	1.07	1.12	1.14					
			Cycle 13	4	1.07	0.06	1.00	
1.02	1.07	1.12	1.14					
			Cycle 14	3	1.08	0.07	1.00	
1.00	1.09	1.14	1.14					

ed16_4A_C_3001 Summary of Dose Intensity per Cycle by Trial Treatment

Protocol(s): I16966M
Analysis: Safety Population - Cohort C
Filter applied: WHERE ectypen LE 3 AND s_chrtc = 'YES'

Treatment Group: XELOX+BV

Treatment		N	Mean	Std	Minimum	Q1	Median	Q3	Maximum
PLACEBO	Cycle 15	3	1.08	0.07	1.00	1.00	1.09	1.14	1.14
	Cycle 16	2	1.05	0.07	1.00	1.00	1.05	1.09	1.09

Appendix 8 Days of bevacizumab/placebo treatment by study arm in Study NO16966

scom12_4A_C_3001 Summary of Number of Days Under Treatment by Treatment Components
and Trial Treatment

Protocol(s): I16966M
Analysis: Safety Population - Cohort C
Filter applied: WHERE ectypen LE 3 AND s_chrtc = 'YES'

	FOLFOX-4+P (N = 335)	FOLFOX-4+BV (N = 342)	XELOX+P (N = 339)	XELOX+BV (N = 353)
Number of Days with 5-FU Treatment				
Mean	203.9	215.1	185.0	199.3
SD	111.2	116.4	104.4	115.1
Median	192.0	203.0	170.0	191.0
Min-Max	10-508	14-511	18-483	9-483
n	335	342	338	352
Number of Days with Capecitabine Treatment				
Mean	182.8	192.9	172.5	182.2
SD	97.3	102.3	93.3	104.9
Median	182.0	183.0	168.0	177.0
Min-Max	10-504	14-511	18-483	9-483
n	335	342	339	353
Number of Days with Oxaliplatin Treatment				
Mean	203.9	215.1	185.0	199.3
SD	111.2	116.4	104.4	115.1
Median	192.0	203.0	170.0	191.0
Min-Max	10-508	14-511	18-483	9-483
n	335	342	338	352
Number of Days with Bevacizumab Treatment				

```
     Mean                                                  203.8á
190.2á
     SD                                                    118.5á
115.7á
     Median                                                183.5á
183.0á
     Min-Max                                          á 14á-á511ááá
á  9á-á471ááá
     n                                                       342á
353á


     Note: n is the number of patients with this treatment

Program : $PROD/cdp10743/com12.sas / Output :
$PROD/cd10743a/i16966m/reports/scom12_4A_C_3001.out
11APR2007  1:49 NENDELV
Page 1 of 2

scom12_4A_C_3001 Summary of Number of Days Under Treatment by Treatment
Components
and Trial Treatment

Protocol(s): I16966M
Analysis: Safety Population - Cohort C
Filter applied: WHERE ectypen LE 3 AND s_chrtc = 'YES'


_____________________________________________________________________
_____________________

                                    FOLFOX-4+P     FOLFOX-4+BV
XELOX+P         XELOX+BV
                                    (N = 335)       (N = 342)       (N =
339)       (N = 353)
  ---------------------------------------------------------------------
----------------------

  Number of Days with Placebo Treatment

     Mean                             203.7á          139.5á
183.1á          243.5á
     SD                               111.9á          152.0á
105.5á          183.6á
     Median                           192.0á           70.0á
168.0á          300.0á
     Min-Max                     á 10á-á508ááá   á 13á-á427ááá   á 18á-
á483ááá   á 21á-á462ááá
     n                                335á             11á
339á              6á
```

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Section B: Clarification on cost-effectiveness data

B1. **Priority question: Section 6.8.1, As noted earlier, the validity of combining the two parts of the NO16966 trial may be questioned (The NO16966 effectively consists of two separate trials: the first being XELOX vs. FOLFOX and the second having four arms XELOX+placebo/Bev and FOLFOX+placebo/Bev). As the base-case (i.e. please use this for all subsequent sensitivity analyses) please use the data from the 2x2 factorial part of the trial to calculate survival as presented in Saltz et al 2008. Please provide possible reasons why survival was better in the XELOX/FOLFOX+placebo arms compared to the XELOX/FOLFOX arms.**

The results of the requested analysis excluding the patients from the first part of the study (i.e. excluding XELOX and FOLFOX) are provided in appendix A. However Roche believe that pooling the chemotherapy arms with and without placebo provides a broader evidence base and a more robust estimate of the baseline risk and bevacizumab treatment effect for the reasons as detailed in the response to question A2 above.

B2. **Priority question: Section 6.8.1. The true relative risk of adding bevacizumab may differ when added to XELOX rather than FOLFOX, also the underlying efficacy of XELOX and FOLFOX may be different. Please perform a sensitivity analysis in which the XELOX and FOLFOX arms are not pooled.**

The results of the requested analysis are presented in Appendix A.

B3. **Priority question: Section 7.2.6.8. After the median follow-up time of 28 months for overall survival (OS) there were 14% (96) and 16% (211) remaining in the XELOX/FOLFOX and XELOX/FOLFOX+Bev arms respectively. Please clarify why the data after median follow-up was not included in the modelling even though the method of fitting the parametric curves to survival data should allow for the greater uncertainty present in the tail of the curve. Please use the whole data set to fit the curve in the base-case analysis and also present a graph comparing the entire Kaplan-Meier curve to the fitted parametric curve.**

The rational for truncating the data at 28 months was to further reduce the impact of the increased uncertainty ("noise") in the tail of the Kaplan-Meier curves and also to attempt to correct for the imbalance in follow-up duration between the chemotherapy+-Placebo and the Chemotherapy+Bevacizumab arms. Truncating the data, prior to the curve fitting, as we did in the submission seems to have very little effect on the resulting parameter estimates with the ICER changing by just £79 in the B-XELOX vs XELOX+-P comparison. All the additional analyses presented in appendix A utilise the untruncated data to estimate the Weibull parameter estimates as per the above request.

B4. **Priority question: Section 7.2.6.8. The three phases of the progression free survival (PFS) curve described on p119 may be somewhat subjective. In**

addition, it is not clear why an exponential function rather than a Weibull function is appropriate as this seems inconsistent with the approach taken for overall survival (OS). Please fit a Weibull curve to the PFS data from month 6 onwards and use this in the base-case analysis.

The additional analyses, presented in Appendix A, have been performed using the approach suggested above.

B5. **Priority question: Section 6.8.2. On p71 the impact of adding bevacizumab to oxaliplatin-based chemotherapy in patients with liver metastases in trial NO16966 is discussed. If possible, please evaluate the cost effectiveness of adding bevacizumab in this group as a subgroup analysis.**

Given the volume of new analyses required for answering the clarification questions, Roche has been unable to prioritise and prepare such analysis within the timescales available.

B6. Priority question: Section 7.2.1.2. On p105 of the manufacturer's submission it states that in the N016966 trial, treatment with bevacizumab was often stopped at the same time point as the base chemotherapy was stopped. Please provide data on the number of patients for whom treatment with bevacizumab continued after chemotherapy was stopped. Our clinical advisors suggest that in practice chemotherapy treatment would be likely to be stopped gradually rather than all at the same time. For example, oxaliplatin may be stopped initially and other drugs continued. Please clarify whether all treatment was stopped at the same time in the trial. Please provide details of the number of persons in the trial who continued receiving bevacizumab for over 1 year.

In the economic analysis it was assumed that all chemotherapy drugs in the regimen would be stopped at the same time-point and that bevacizumab would typically be stopped at the same time or after chemotherapy cessation. We used Kaplan-Meier analysis of the time to last dose of 5-FU / capecitabine for estimating treatment duration for the chemotherapy+-Placebo arms and time to last dose of bevacizumab for the bevacizumab arms.

Given the comments made by the clinical experts, additional Kaplan-Meier analysis was performed for each of the chemotherapy drugs in each arm in the study. The results of this analysis for chemotherapy +- Placebo and the bevacizumab containing arms are shown below. They suggest that the various component regimens of the chemotherapy treatment was typically stopped at slightly different time points as suggested by the clinical experts.

These analysis however confirm that bevacizumab was typically not continued beyond cessation of the chemotherapy treatment.

Figure 2: Treatment duration XELOX+-P

Figure 3: Treatment duration FOLFOX+-P

Figure 4: Treatment duration B-XELOX

Figure 5: Treatment duration B-FOLFOX

Given that there did appear to be a slight difference in the time-points that treatment with each drug in any one regimen were stopped, the additional analysis presented in Appendix A attempts to account for this as follows:

- Time to last dose of oxaliplatin has now been used to estimate the mean drug acquisition cost of oxaliplatin and also the associated administration, pharmacy and monitoring costs of combination therapy in the arms without bevacizumab.

- Time to last dose of capecitabine and 5-FU has been used to calculate the mean drug acquisition cost of capecitabine and 5-FU/LV for the XELOX and FOLFOX arms respectively.

- For the bevacizumab arms the acquisition, administration, pharmacy and monitoring costs of the combination regimen were applied for the duration of bevacizumab treatment. This was done to simplify the model design, however may very slightly over estimate the cost of the preparation and administering of Oxaliplatin in the FOLFOX+-P arm as bevacizumab treatment continued for slightly longer than Oxaliplatin in this arm.

- A monthly cost for administration, pharmacy, and monitoring during treatment on monotherapy post cessation of oxaliplatin was calculated (see table below) and multiplied by the time on monotherapy treatment (the difference between the estimated time on treatment for oxaliplatin, or bevacizumab, and capecitabine / 5-FU) to estimate the total cost of monotherapy per patient.

- The time in the PFS_T and PFS_{PT} health states has now been calculated using 5-FU and capecitabine for the FOLFOX and XELOX regimens with or without bevacizumab for the purpose of calculating utility and monitoring costs post cessation of treatment; as these were the drugs used for the longest in each arm of the study.

The monthly cost of monotherapy was calculated using the same assumptions as were used to calculate the combination therapy as described previously in the submission. The resulting per cycle and monthly costs are shown in the table below:

Table 1: Revised Per cycle and Monthly Costs

Unit cost		capecitabine mono therapy	5-FU / LV monotherapy mdG	5-FU / LV monotherapy dG
	Cycles per month	1.31	1.84	1.84
	Per cycle pharmacy preparation and dispensing			
42	Pharmacy complex	0	2	4
25	Pharmacy simple	1	1	2
	Pharmacy cost per cycle (£'s)	**25**	**109**	**218**
	Per cycle administration:			
29	patient transport	0.3	0.3	0.6
35	Ambulatory pump		1	1
37	District Nurse Visit		1	1
317	Administration outpatient 1st day of cycle		1	1
227	Administration Outpatient subsequent visits per cycle			1
1,052	Administration overnight visits			
	Administration cost per cycle (£'s)	**9**	**398**	**634**
	Total: admin and pharmacy cost / month (£'s)	**45**	**933**	**1567**
	Monthly Monitoring during treatment			
125	Consultation OP appointment in PFS	1.00	1.00	2.00
3	Bloods	1.31	1.84	1.84
135	CT scan once per 3 months in PFS	0.33	0.33	0.33
	Monthly monitoring cost (£'s)	**174**	**176**	**301**
	Total admin, pharmacy and monitoring cost / month (£'s)	**219**	**1108**	**1868**

The proportion of patients observed to be on treatment beyond one year was approximately [redacted] for both B-XELOX and B-FOLFOX arms, however this estimate does not account for missing data and therefore the Kaplan-Meier analysis represents a better estimate of the number of patients still on treatment after one year. Based on the Kaplan-Meier of time to last dose there were [redacted] of patients in the B-XELOX and B-FOLFOX arms respectively that were on treatment at the start of the second year.

B7. Priority question: Our clinical advisors suggest that in practice treatment may be stopped and then restarted a few months later if toxicity (e.g. oxaliplatin) became a problem. As an example, for a patient receiving treatment for 6 months, then having a 3 month break, then continuing on treatment, how would the APAS scheme be applied? Would the continuation of treatment still be regarded as first line?

If chemotherapy (eg. oxaliplatin) is stopped due to chemotherapy-related adverse events then there is no reason to discontinue Avastin at that time. The licence and the trial evidence for Avastin is based on continuous treatment with Avastin until disease progression. There is no clinical rationale for discontinuing Avastin for 3 months.

The scheme will only be applicable for *first-line mCRC patients* and so, if after 3 months in the stated example, at the point the patient resumed treatment they had progressed (by RECIST criteria), then the scheme would no longer apply as they would no longer be considered *first line*. However if they had not yet progressed at the point of their treatment resuming, then the scheme would apply.

B8. Priority question: Section 7.2.9.1. Our clinical advisors suggest that the addition of bevacizumab is unlikely to reduce the incidence of adverse events. The incidence of neutropenia/granulocytopenia is 44% with FOLFOX and 2% with FOLFOX+Bev. Similarly the incidence of diarrhoea, nausea/vomiting, and neurotoxicity were seen to be lower in the +bevacizumab arms. Please perform a sensitivity analysis in which the incidence of the non-bevacizumab related adverse events is the same with and without bevacizumab (To further clarify the Evidence Review Group recommends that adverse event incidence figures from the XELOX and XELOX+bev arms are pooled for the non-bevacizumab specific adverse events).

Whilst the figures in the model are correct they were misrepresented in table 35 of the submission in error for which we apologise. Please find below the corrected version of this table. It can be seen from the corrected table that the incidence of neutropenia is similar in the bevacizumab and the respective chemotherapy arms. Given these more comparable figures, it is assumed the requested sensitivity analysis is no longer required.

Table 2: Incidence (%) of adverse events costed in the model from NO16966

Adverse event	FOLFOX	XELOX	B-FOLFOX	B-XELOX
cardiac disorders	1.39	0.92	6.73	3.97

Diarrhoea	15.07	25.38	15.31	27.48
Febrile Neutropenia	4.98	0.92	5.00	1.13
hypertension	0.77	0.95	4.56	5.67
Infections (excl. Febrile neutropenia)	10.19	6.87	9.74	5.95
Neurotoxicity	16.51	17.10	17.84	18.13
Neutropenia / granulocytopenia	54.40	9.06	52.46	8.57
Palmar-plantar erythrodysaesthesia syndrome (Hand and Foot)	1.23	6.78	1.75	13.80
Stomatitis	2.01	1.47	3.51	1.98
Venous thromboembolism	6.33	3.82	9.36	6.23
Vomiting / Nausea	8.56	8.81	7.31	12.92

B9. Priority question: Section 7.2.8.3. Please clarify whether a systematic review was performed to obtain data on utility values. Please provide references for the original sources of the utility values used in the modelling and provide details of any assumptions made. Please include the source of the lower and upper values for the utility values used in the sensitivity analyses. On p115 Bidard et al 2008 is referenced, please clarify as there is no mention of quality of life in the abstract.

A systematic literature review was completed in April 2007 and the associated report is included as Appendix B. Despite a number of utility studies identified in colorectal cancer, they were considered of limited value because they did not conform to the NICE reference case for utility values (for instance, by utilizing alternative elicitation methods or instruments as described in Section 7.2.8.3 of the submission). It was therefore determined that the utility values used in the base case analysis would be based on those previously accepted by NICE within an mCRC technology appraisal. The utilities were therefore taken from the recent cetuximab NICE appraisal, as these best match the reference case requirement and offered consistency across the appraisals. The only reason to consider that these utilities would be suitable for the appraisal of cetuximab but not for the appraisal of bevacizumab would be if there was believed to be a difference in utility between the two treatments. Clinical experts indicated this was unlikely to be the case with the only potential difference being a slightly higher utility might be expected for bevacizumab at the beginning of 1st line treatment due to the different side effect profile for the drugs

The source of the utility values in the base case is taken directly from the manufacturer's submission for the cetuximab 1st line metastatic colorectal cancer submission. [1] This can be found in Table H24 on page 91. The sensitivity analyses simply utilised a lower and upper bound based on +/- 5% of the base case value so there is no official source for these figures, only an assumption.

[1] http://www.nice.org.uk/nicemedia/pdf/MerckSeronoCC.pdf Accessed 21 August 2009

The paper by de Gramont et al (*de Gramont A, Buyse M, Cortinas Abrahantes J, et al: Reintroduction of oxaliplatin is associated with improved survival in advanced colorectal cancer. J Clin Oncol 25:3224-3229, 2007*) discusses the motivation for the Optimox study, which was to see if an intermittent treatment schedule could be used to reduce treatment related toxicity without sacrificing efficacy with a view to improving quality of life, though quality of life was not actually recorded within the study.

B10. Priority question: Section 7.2.8.3. A review of utility values for CRC (Sharp et al 2009, www.hiqa.ie/publications.asp) indicates a much wider range than is reported in the submission. Please compare the values used in the manufacturers submission to those values for metastatic CRC reported in Sharp et al 2009 (specifically Ness 1999, van den Brink 2004, Stouthard 2000) and provide a commentary to justify the choice. It is suggested that an additional sensitivity analyses may be required using values from Sharp et al 2009.

The utility values used in the analyses are the same as those recently accepted for use as part of the STA of cetuximab for the treatment of 1st line mCRC. Clinical experts have advised that it is reasonable to assume the utility values for chemotherapy in combination with cetuximab is equivalent to chemotherapy in combination with bevacizumab. Additionally, unlike the utility values identified by either Roche's literature review (see Appendix B) or the review by Sharp et al., the utility estimates for PFS reflect the NICE reference case as they were elicited from patients from the relevant population in a clinical trial using the EQ-5D questionnaire. Roche therefore disagrees with the use of these alternative utility values as the values currently used in the base case analysis conform with the NICE reference case as well as consistency across recent NICE appraisals in 1st line treatment of metastatic colorectal cancer. Additionally previous economic analysis performed by ScHAAR in support of the former NICE appraisal of bevacizumab in the 1st line treatment of mCRC (TA118) used utility value for PFS of 0.8, which is similar to the 0.77 and 0.79 used for the PFS_T and PFS_{PT} health states respectively.

The sensitivity analysis provided in the submission considered a deviation of +/- 5% of the base case analysis. For the purpose of exploring the impact of larger deviations as observed in the Sharp analysis, a new sensitivity analysis was conducted by considering a range of +/-20% of the base case value. The results of this additional one-way sensitivity analysis is reported in appendix A.

B11. Priority question: Section 7.3.3. Please present the following results of the probabilistic sensitivity analyses: The mean and 95% CI for the incremental costs, the incremental QALYs and the ICER.

Please find the requested analysis shown in the tables below

Table 3: Original analysis results with 95 percentiles

Comparison	FOLFOX+Bev vs. FOLFOX	B-XELOX vs. XELOX	and B-XELOX vs. FOLFOX
Incremental Costs: mean	[redacted]	[redacted]	[redacted]

95% percentiles	[redacted]	[redacted]	[redacted]
Incremental QALYs: mean	[redacted]	[redacted]	[redacted]
95% percentiles	[redacted]	[redacted]	[redacted]
Incremental cost per QALY gained (mean Incr. costs / Incr. QALYs)	£41,519	£34,217	£332
95% percentiles of ICERs	(31,136; 67,859)	(26,597; 52,960)	(Dominant; 6,424)

B12. Section 7.2.3. On p165 it states that market research surveyed 50 oncologists across England and Wales but table 14 on p108 suggests that there were 38. Please clarify the sample size and methods used in the market research undertaken, and discuss whether this sample is likely to be representative.

The figures in the footnote of figure 14 on p108 are correct. The figure of 50 oncologists, quoted on p165 of the submission is therefore incorrect as it related to the original study results that included Scottish centres.

Doctors were asked to complete a patient record audit for a number of their patients in a given period, therefore the data are representative of actual patients receiving treatment (not perceptions). In total 225 patients records were captured.

B13. Could you please clarify the following regarding the economic model

- **Section 7.2.6.8. In the base case, a treatment effect is assumed to continue beyond median follow-up. There is an option to include no treatment effect after median follow up. Please clarify what this assumption means and explain how this was implemented in the model.**

  Setting the option in the model to not include a treatment effect beyond median follow up applies the same risk of death in the bevacizumab arms as in the chemotherapy alone arms beyond the point of median follow-up. This was implemented in the model by setting the lambda parameter value of the OS Weibull curve for the bevacizumab arms to equal that of the comparator arms.

- **Section 7.2.6.8. The parameter values presented in Table 25 p122 do not match the parameter values in cells C34 and C35 on the parameter estimates sheet of the model. Please clarify which values are correct.**

  We can confirm the values in the model are the correct values. Please find the corrected table 25 below.

Table 4: Weibull Parameter Estimates for OS and PFS by Treatment Arm

Efficacy Endpoint	Bevacizumab + Chemotherapy	Chemotherapy alone
Overall Survival (OS)		
Lambda	0.006119924	0.007291302
Gamma	1.547272063	1.547272063
Progression Free Survival (PFS)		
Lambda	0.0258572	0.032449402
Gamma	1.457360715	1.457360715

- **Section 7.2.6.1. Please include drug wastage costs for oxaliplatin within the modelling of drug costs p116.**

Oxaliplatin wastage is included in the further analyses presented in Appendix A. The total dose including wastage was estimated by rounding up the mean dose per cycle observed in the trial to the nearest complete 50 mg vial.

- **Section 7.2.6.8. A hazard ratio is applied to the FOLFOX PFS and OS survival curves to derive curves for FOLFIRI. It is not clear if this applies only to the extrapolated part of the FOLFOX curves (beyond 28 months) and how the HR is applied to the earlier non-extrapolated portion of the KM curve**

The hazard ratio has been applied to the entirety of the curve. For the Kaplan-Meier section of the curve the following formulae has been applied to calculate the cumulative survival for FOLFIRI based on the FOLFOX Kaplan-Meier curve.

EXP(-(-LN(S(t))*os_HR_FLI))

Where: S(t) is the cumulative hazard function at month t and os_HR_FLI is the hazard ratio of FOLFOX compared with FOLFIRI.

B14. Section 6.10. As head to head data was available, a mixed treatment comparison (MTC) was not required or undertaken by the manufacturer. However, the manufacturer provided supportive evidence from an MTC undertaken by Golfinopoulos et al. 2007. On p75 the manufacturers submission suggest that the MTC meta-analysis included results from the ECOG E3200 trial (second line setting) but did not include data from the NO16966 trial (first line setting). The Evidence Review Group notes that the MTC meta-analysis by Golfinopoulos et al (2007) included the results from the NO16966 trial with specific reference to Salt et al 2007 (Proc Am Soc Clin Oncol; 25 (170S suppl): abstr 4028). For completeness please clarify what data (e.g. which arms from the trial) from the NO16966 trial was included.

This was an oversight which was identified and believed to have been corrected in the final version of the submission. We can confirm that the ERG are correct and that the results as per the Saltz paper (2*2 pooled analysis) were included in the MTC study.

B15. Could you please clarify the following points regarding the economic analysis

- **Section 7.2.9. Please provide 95% confidence intervals for the mean dose values in Table 29 p133 and mean number of cycles per month observed in Table 33 p137. In addition, please provide for each of the six treatment groups separately. Table 29 on p133 describes a mean dose of bevacizumab for the XELOX and FOLFOX arms. Please clarify, as these arms should not involve any bevacizumab.**

There was a small amount of bevacizumab given to patients randomized to placebo in the study. Hence this is why there is an average dose per cycle presented in the chemotherapy arms of table. The total dose given in error across all patients was only 1250 mg (ie <1mg per patient in the chemo+-P arms) so would not materially impact the ICER if included.

The revised tables including the additional requested statistics will be supplied as part two of our response by the 1st September deadline.

- **Please justify the assumption that people in the PFS state post-treatment have a utility equal to healthy people in the general population.**

  It is assumed that patients in the progression-free health state will have a greater utility once they stop receiving chemotherapy until disease progression. Empirical data on the marginal utility between patients on and off treatment whilst in PFS was not identified in the literature. Clinical experts suggested that the utility would be greater in PFS when not receiving chemotherapy. The utility value whilst on 1st line treatment, captured via the NICE reference case methodology was 0.77. It was considered unlikely that the utility value would exceed that of the general population of the same age (0.79) hence a figure of 0.79 was used for patients in PFS but not receiving treatment.

  It was also noted that in a previous NICE appraisal ScHARR used a utility value of 0.8 for PFS in first line mCRC (Tappenden et al) and hence 0.79 also appeared reasonable in light of this. It is worth noting that setting the utility value for the PFS_{PT} health state to equal that of the PFS_T health state (0.77) only increases the ICER from £34,170 to £34,677 for XELOX vs B-XELOX and therefore is not considered a major driver of the model. The results of varying the utility values by 20% are shown in Appendix A.

- **Section 7.2.9.1. In table 35 on p 139 the incidence of adverse events is described. In the Saltz et al 2008 paper adverse events of special interest to bevacizumab with incidence greater than or equal to 2% were venous thromboembolic events, hypertension, bleeding, and arterial thromboembolic events (including ischemic cardiac events). Please clarify why bleeding and arterial thromboembolic events were not included in table 35 on p139. In table 34 on p139 the unit costs for adverse events are described with references. Please include in this table the procedure/treatment/drugs which are included in these costs.**

The difference with regards arterial thromboembolic events appears to be related to rounding, with the incidence of the event being 1.98%. The incidence of bleeding was indeed slightly over 2% in the B-FOLFOX arm although as can be seen from the table below the incidence across the arms are comparable and thus inclusion of the cost of this adverse event is very unlikely to materially affect the ICER.

For those adverse event costs taken from reference costs, the component parts of these costs are not available. For other sources of AE costs, a breakdown of the costing elements will be provided by Tuesday 1st September where possible from the publications.

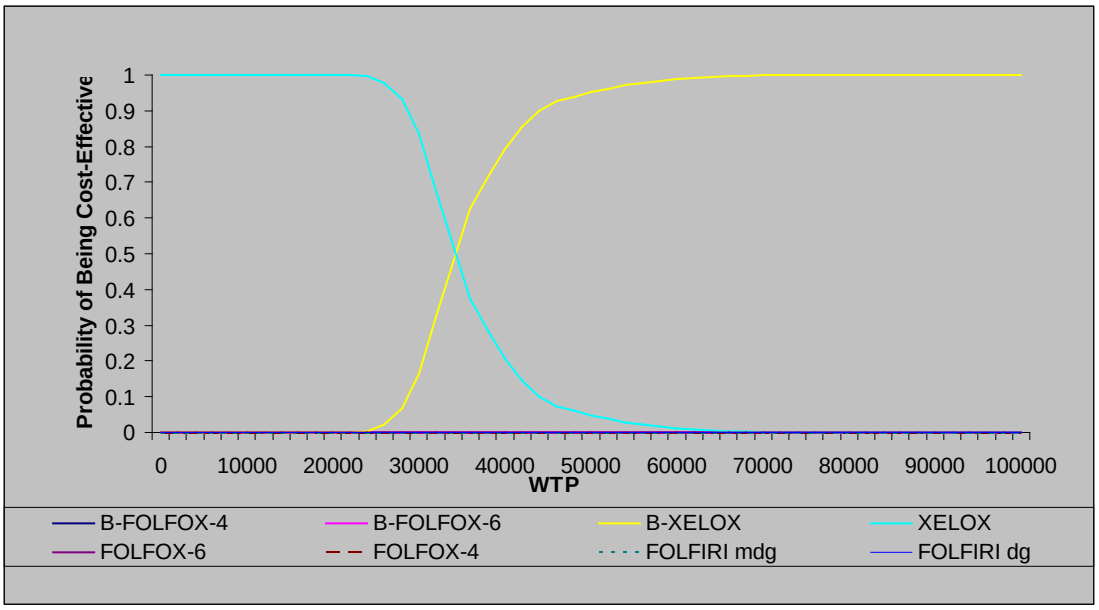
Table 5: Adverse Event Incidence

Event (Grade 3/4 unless otherwise stated)	Treatment allocation			
	XelOx+P-XelOx N=655 n (%)	FOLFOX+P-FOLFOX N=648 n (%)	B-XelOx N=353 n (%)	B-FOLFOX N=342 N (%)
Gastrointestinal perforation	3 (0.5)	1 (0.2)	3 (0.8)	1 (0.3)
Bleeding problems	13 (2.0)	7 (1.1)	6 (1.7)	7 (2.0)
Venous thromboembolic events	25 (3.8)	41 (6.3)	22 (6.2)	32 (9.4)
Arterial thromboembolic events	4 (0.6)	8 (1.2)	7 (2.0)	5 (1.5)
Hypertension	5 (0.8)	5 (0.8)	16 (4.5)	12 (3.5)
Proteinuria	12 (1.8)	-	1 (0.3)	3 (0.9)

- **Section 7.3.3. The scale on the x-axis of Figure 25 CEAC makes it unclear and difficult to interpret. Please provide Figure 25 using the intervals £0K, £10K, £20K etc on the x-axis.**

Please find the amended CEAC below.

Figure 5: Cost Effectiveness acceptability Curve



B16. <u>Could you please clarify the following information in the appendices</u>

Response to this question will be supplied in part two of our response by the 1st September

- Appendix E1. As the model submitted by the manufacturer is a cohort model the mean costs of treatment are appropriate. Please clarify whether the costs have been sampled using the quartiles described in table 51 on p182 and in table 52 rather than the standard error of the mean, which would be incorrect.

- Appendix E3. The manufacturer's submission states that a Beta Pert distribution was used to estimate uncertainty in adverse event costs. It is unclear whether the quartiles listed in Table 51 or the 50% and 150% of the mean were used as the low and high estimates. Please describe how the parameters for the beta pert distributions were calculated. Please also describe any assumptions made, including how the mode was estimated.

- Appendix E3. For the PSA a Beta (utility*1000, (1-utility)*1000) distribution was used to model the uncertainty in the utility values. Please use a Beta distribution that fits to the confidence intervals of the utility data.

1.1.1 Appendix A: Additional Analysis in response to the ERG clarification questions

In response to the comments from the ERG the following 4 modifications, have been incorporated in all the further analyses presented below:

1. A Weibull curve for PFS has been used from month 6 onwards

2. The untruncated data from the NO16966 has been used to calculate the Weibull parameter estimates for PFS and OS rather than by truncating the data at 28 months.

3. Oxaliplatin drug wastage has been included in the analyses

4. The estimation of treatment duration, and subsequent cost, has been refined to account the component drugs in each regimen being stopped at different time points. (see response to question B6 above)

In response to question B1 and B2 the following scenarios have also been explored varying the selected population from the NO16966 study:

1. All arms of the NO16966 study are included in the analysis (as used in the manufacturer's submission) i.e. comparing the pooled chemotherapy arms without bevacizumab with the pooled bevacizumab arms.

2. As per scenario 1, but excluding patients from the first part of the trial i.e. before the protocol was amended to include placebo and bevacizumab.

3. As per scenario 2 except the XELOX and FOLFOX arms of the analysis are not pooled.

Note: When limiting the analysis to the data in the 2*2 phase of the study the tails of the Kaplan-Meier curves are prone to more variation as the patient number and follow-up period is reduced, hence unlike the original analysis the Weibull has been used for the entirety of the OS curve for the 2*2 analysis.

An overlay of the Weibull curve against the Kaplan-Meier curve is presented in the results below for the 2*2 analyses.

1.1.1.1 Summary of results of additional analysis

The table below summarises the most relevant ICERs from each of the additional analysis performed. B-XELOX and XELOX represent the regimens on the efficiency frontier of the cost effectiveness plane, B-FOLFOX-6 vs FOLFOX-6 are of relevance for patients unsuitable for capecitabine and the comparison of B-XELOX vs FOLFOX-6 is of relevance as this shows the cost effectiveness of replacing the most used regimen in England and Wales with the most cost-effective of the bevacizumab regimens examined in this analysis.

Removing the two arms from the first phase of the NO16966 study, that did not contain placebo or bevacizumab had the largest impact on the ICER of all the requested modifications. As discussed in detail in our response to question A2 we believe that the pooled 2*2 analyses underestimates the treatment effect of bevacizumab and thus over estimates the ICERs due to the unexpectedly good performance of the P-FOLFOX arm of the study.

Basing the analysis of B-XELOX vs XELOX on the results of the B-XELOX and P-XELOX arms of the study results in an ICER similar to that of the analysis in the submission (ie Chemotherapy+Bevacizumab vs Chemotherapy+-Placebo).

Table 6: Summary of scenario analysis

		COMPARATOR	
Analysis	**Intervention**	**XELOX**	**FOLFOX-6**
Chemo+Bev vs Chemo+-Placebo (all 6 arms)	**B-XELOX**	£35,912	Dominant
	B-FOLFOX-6		£36,569
Chemo+Bev vs Chemo+Placebo (2*2 only)	**B-XELOX**	£48,111	Dominant
	B-FOLFOX-6		£39,771
XELOX+Bev vs XELOX+Placebo (2*2 only) **FOLFOX+Bev vs FOLFOX+Placebo (2*2 only)**	**B-XELOX**	£35,662	Dominant
	B-FOLFOX-6		£62,714

Scenario 1: Revised pooled analysis using all 6 arms of NO16966

Table 7: Total cost for each intervention per patient

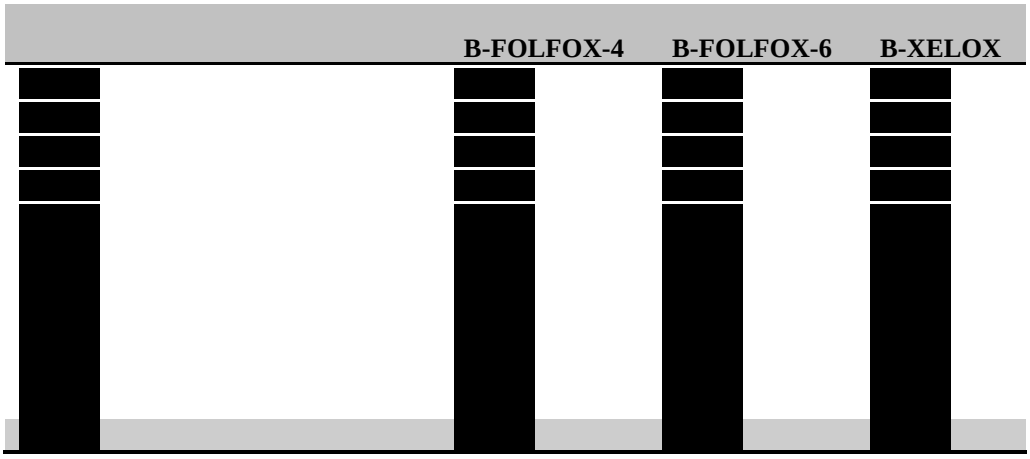


Table 8: cost for each comparator per patient

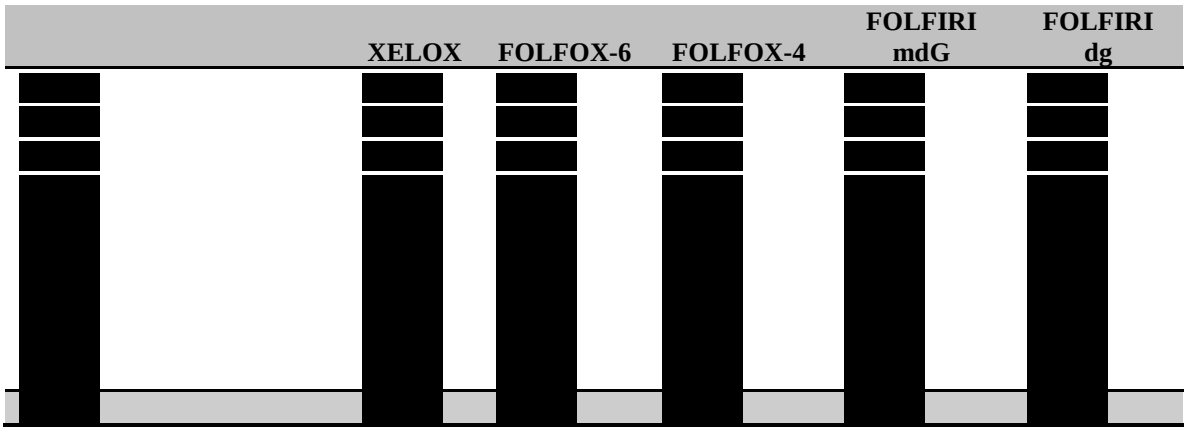


Figure 6: Simultaneous incremental results

Table 9: Time (months) spent in each health state till death per patient (undiscounted)

Table 10: QALYs per patient

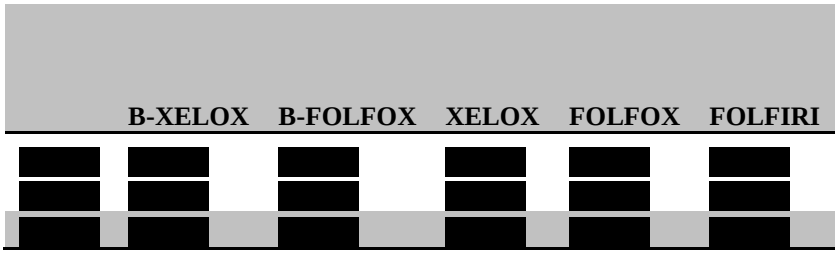


Table 11: Incremental QALYs per patient

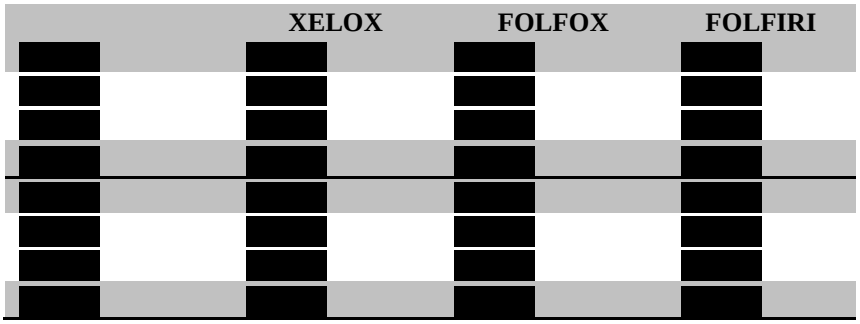


Table 12: Mean Incremental cost per patient

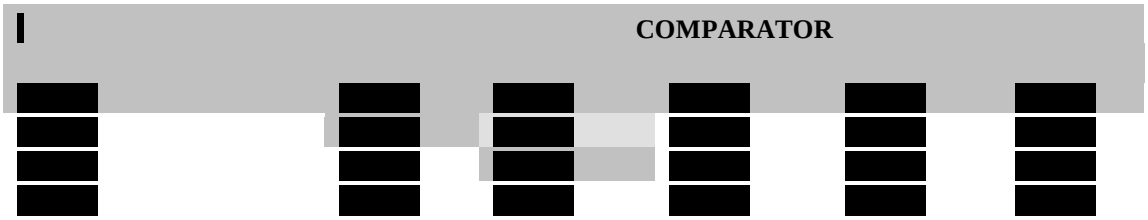


Table 13: Mean ICERs (£/QALY) per patient

	COMPARATOR				
Intervention	**XELOX**	**FOLFOX-6**	**FOLFOX-4**	**FOLFIRI mdG**	**FOLFIRI dg**
B-XELOX	£35,912	Dominant	Dominant	£14,778	Dominant
B-FOLFOX-6	£73,557	£36,569	£23,517	£42,282	£26,753
B-FOLFOX-4	£100,939	£63,920	£50,964	£62,300	£46,771

Table 14: One-way sensitivity analysis of B-XELOX vs XELOX to changes to mean parameter estimates (base case £35,912)

Parameter modified	Base value	Low value	High value	ICER Low	ICER High
Utility Values					
PFS_T Utility value	0.77	0.616	0.924	£38,689	£33,507
PFS_{PT} Utility value	0.79	0.632	0.948	£39,274	£33,080
Progression Utility Value	0.68	0.544	0.816	£37,510	£34,444
Survival Analysis					
Weibull OS Survival curves (1) or mix of KM and Weibull (0)	0	0	1	£35,912	£38,802
Weibull PFS Survival curves (1) or mix of KM and Weibull (0)	0	0	1	£35,912	£34,526
assume treatment effect post follow-up 0 = yes 1 = no	0	0	1	£35,912	£35,912
Time horizon (years)	8	5	10	£39,768	£35,777
Clinical Practice Assumptions					
% pts requiring hospital transport	30%	0%	50%	£35,847	£35,955
% pts with CVAD insertion 0 = UK expert opinion, 1=recorded in trial	0	0	1	£35,912	£36,146
Unit Costs					
Cost of CVAD installation	£502	£301	£703	£35,911	£35,913
Cost of hospital funded transport per visit	£29	£18	£41	£35,886	£35,938
Cost per consultation with oncologist	£125	£75	£175	£35,469	£36,354
Cost of a CT scan	£135	£81	£189	£35,694	£36,129
Cost of administration day 1 of cycle	£317	£190	£444	£34,736	£37,087
Pharmacy cost (complex infusion)	£42	£25	£59	£34,875	£36,948
Pharmacy cost (simple infusion)	£25	£15	£35	£35,837	£35,986
Cost of Progressive Disease Health State	£600	£360	£840	£35,007	£36,817
Total B Cape Ox Adverse Event costs	£248	£149	£347	£36,502	£35,321
Total FOLFOX Adverse Event costs	£334	£200	£467	£35,117	£36,706

Figure 7: Tornado diagram for B-XELOX vs XELOX

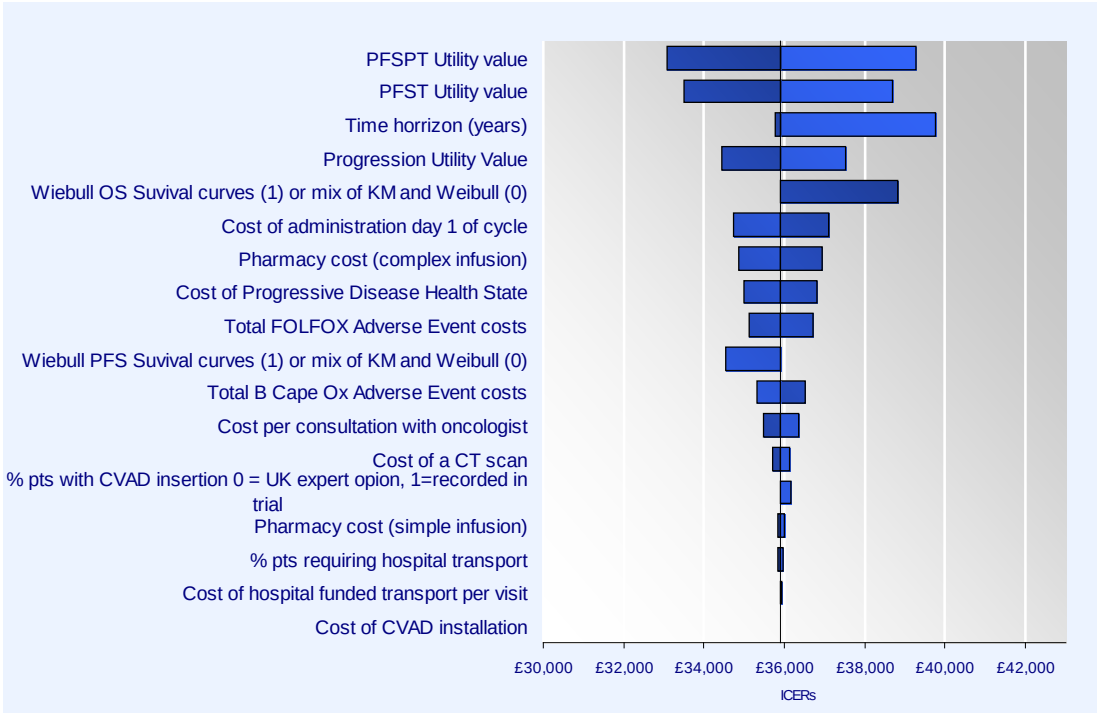
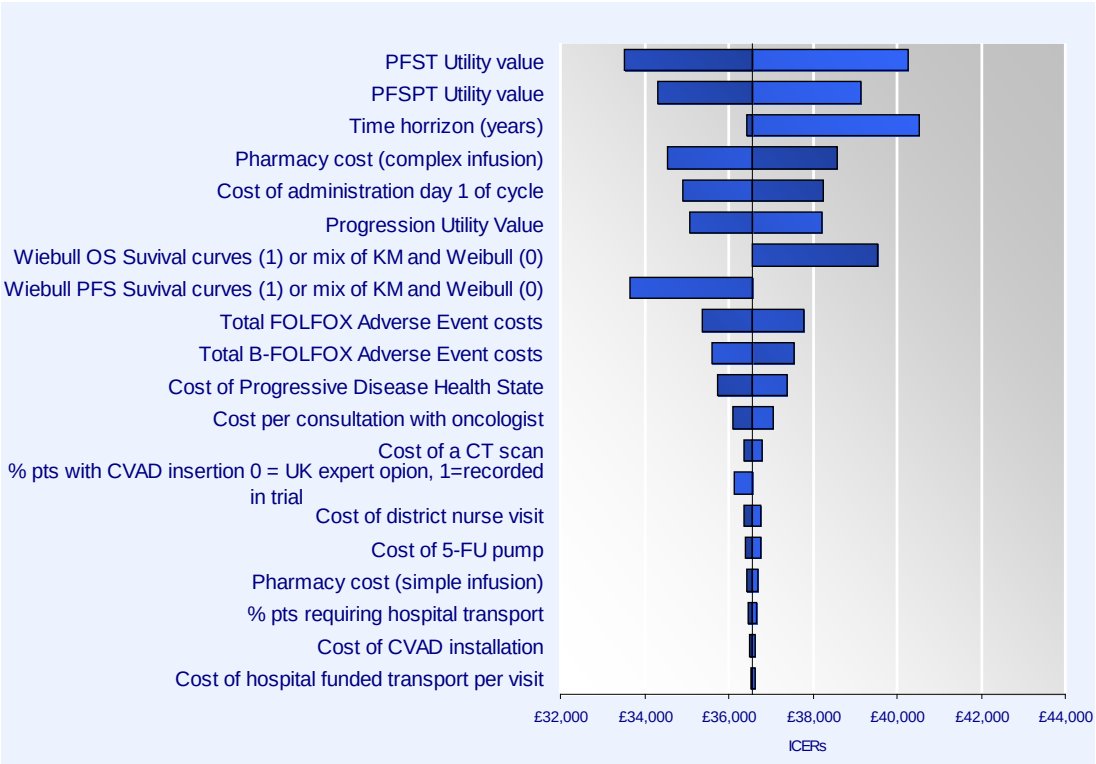


Table 35: One-way sensitivity analysis of B-FOLFOX-6 vs FOLFOX-6 to changes to mean parameter estimates (base case £ 36,569)

Parameter modified	Base value	Low value	High value	ICER Low	ICER High
Utility Values					
PFS_T Utility value	0.77	0.616	0.924	£40,252	£33,505
PFS_{PT} Utility value	0.79	0.632	0.948	£39,145	£34,312
Progression Utility Value	0.68	0.544	0.816	£38,202	£35,071
Survival Analysis					
Weibull OS Survival curves (1) or mix of KM and Weibull (0)	0	0	1	£36,569	£39,542
Weibull PFS Survival curves (1) or mix of KM and Weibull (0)	0	0	1	£36,569	£33,668
assume treatment effect post follow-up 0 = yes 1 = no	0	0	1	£36,569	£36,569
Time horizon (years)	8	5	10	£40,537	£36,431
Clinical Practice Assumptions					
% pts requiring hospital transport	30%	0%	50%	£36,454	£36,646
% FOLFOX pts with ambulatory pump	95%	50%	100%	£36,569	£36,569
% pts with CVAD insertion 0 = UK expert opinion, 1=recorded in trial	0	0	1	£36,569	£36,145
Unit Costs					
Cost of CVAD installation	£502	£301	£703	£36,511	£36,628
Cost of hospital funded transport per visit	£29	£18	£41	£36,523	£36,616
Cost of 5-FU pump	£35	£21	£49	£36,386	£36,753
Cost per consultation with oncologist	£125	£75	£175	£36,088	£37,051
Cost of a CT scan	£135	£81	£189	£36,351	£36,788
Cost of district nurse visit	£37	£22	£52	£36,374	£36,765
Cost of administration day 1 of cycle	£317	£190	£444	£34,906	£38,233
Cost of administration day 2 of cycle	£227	£136	£318	£36,569	£36,569
Cost of inpatient stay of administration	£1,052	£631	£1,473	£36,569	£36,569
Pharmacy cost (complex infusion)	£42	£25	£59	£34,555	£38,584
Pharmacy cost (simple infusion)	£25	£15	£35	£36,437	£36,702
Cost of Progressive Disease Health State	£600	£360	£840	£35,741	£37,398
Total B-FOLFOX Adverse Event costs	£407	£244	£569	£37,541	£35,598
Total FOLFOX Adverse Event costs	£504	£303	£706	£35,365	£37,774

Figure 8: Tornado diagram for B-XELOX vs XELOX



Scenario 2: Pooled analysis excluding patients in first part of NO16966 (i.e. only results from the 2*2 part of study utilised)

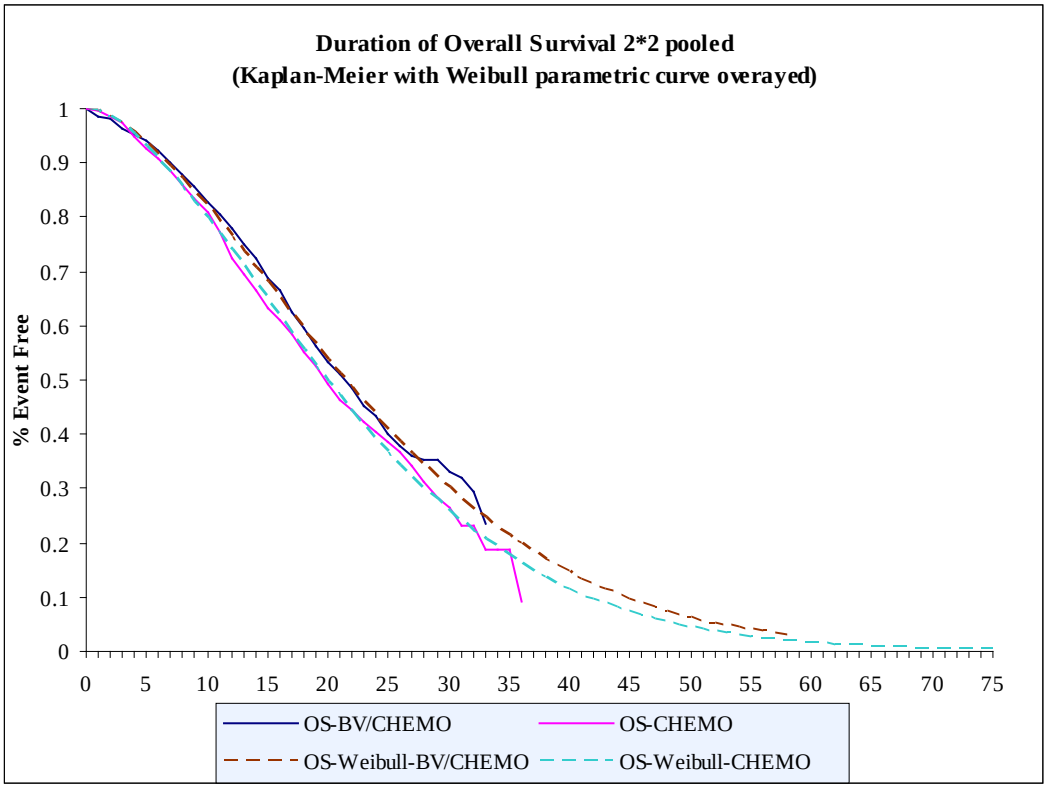


Table 16: Total cost for each intervention per patient

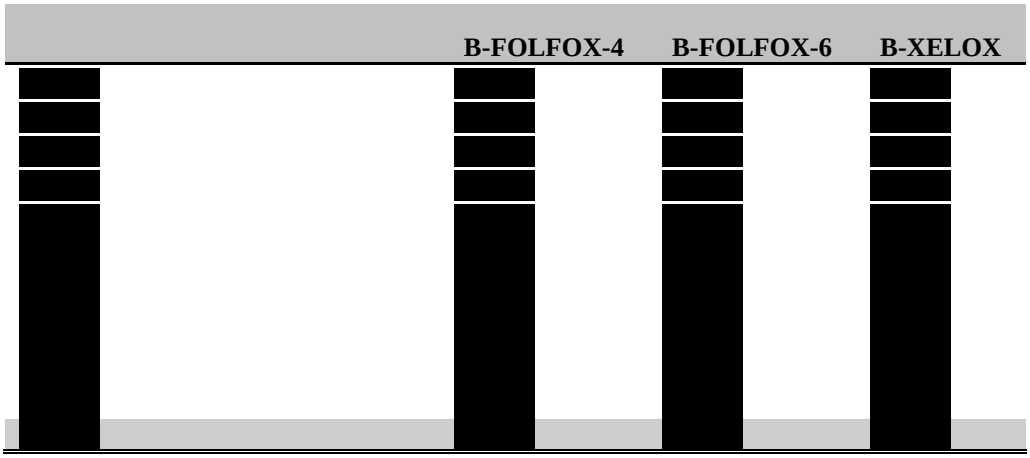


Table 17: cost for each comparator per patient

	XELOX	FOLFOX-6	FOLFOX-4	FOLFIRI mdG	FOLFIRI dg
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 9: Simultaneous incremental results

[redacted]

Table18: Time (months) spent in each health state till death per patient (undiscounted)

	B-XELOX	B-FOLFOX	XELOX	FOLFOX	FOLFIRI
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 19: QALYs per patient

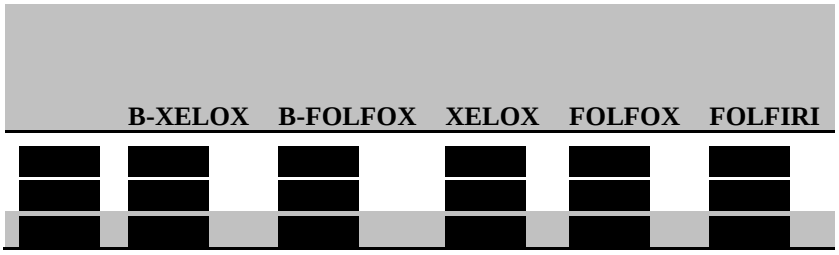


Table 20: Incremental QALYs per patient

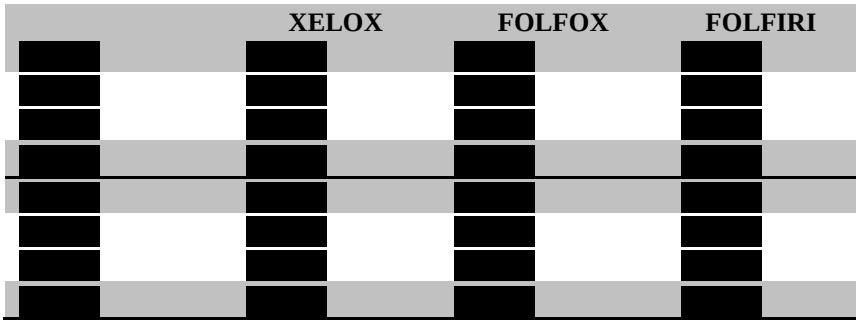


Table 21: Mean Incremental cost per patient

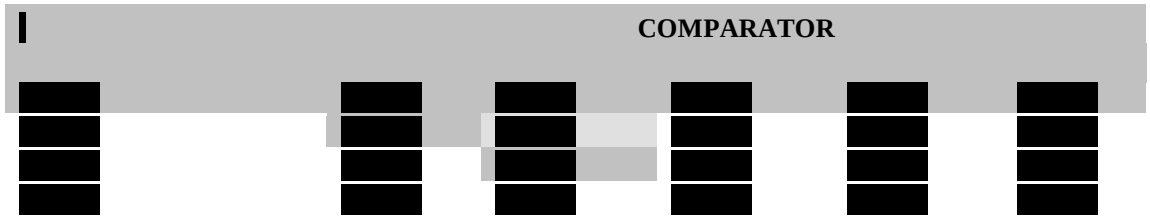
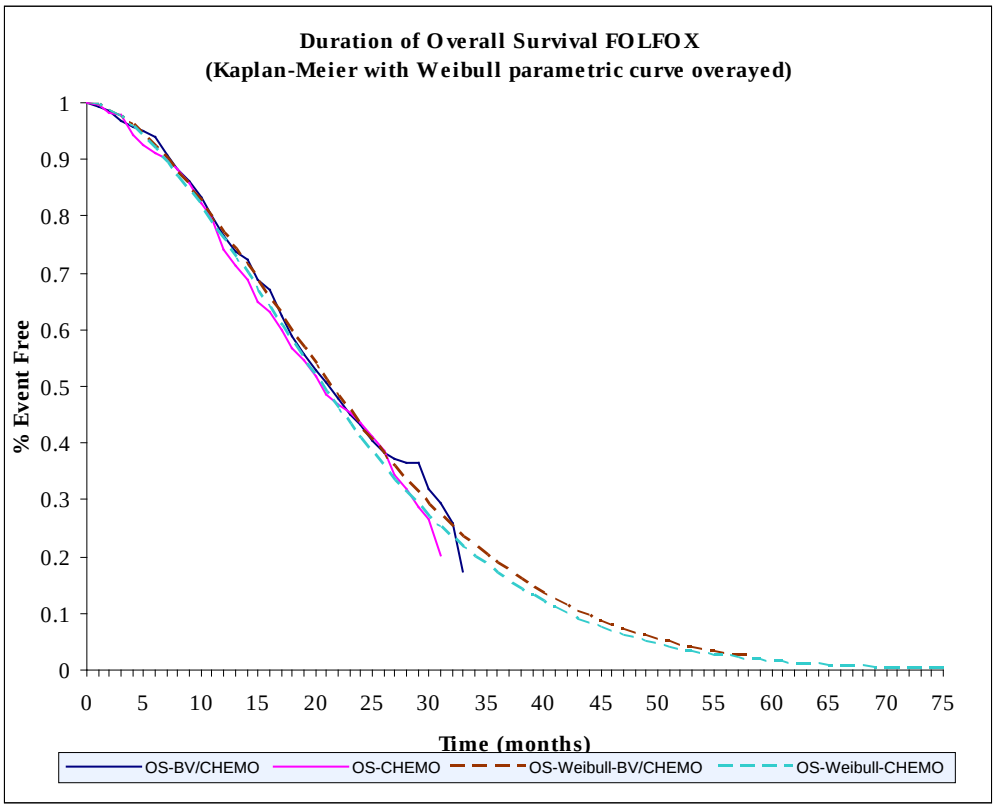


Table 22: Mean ICERs (£/QALY) per patient --- currently using truncated and oxaliplatin

	COMPARATOR				
Intervention	**XELOX**	**FOLFOX-6**	**FOLFOX-4**	**FOLFIRI mdG**	**FOLFIRI dg**
B-XELOX	£48,111	Dominant	Dominant	£10,600	Dominant
B-FOLFOX-6	£111,220	£39,771	£15,315	£50,195	£25,892
B-FOLFOX-4	£157,115	£85,426	£61,152	£79,022	£54,718

Scenario 3: As per scenario 2 except the arms are un-pooled



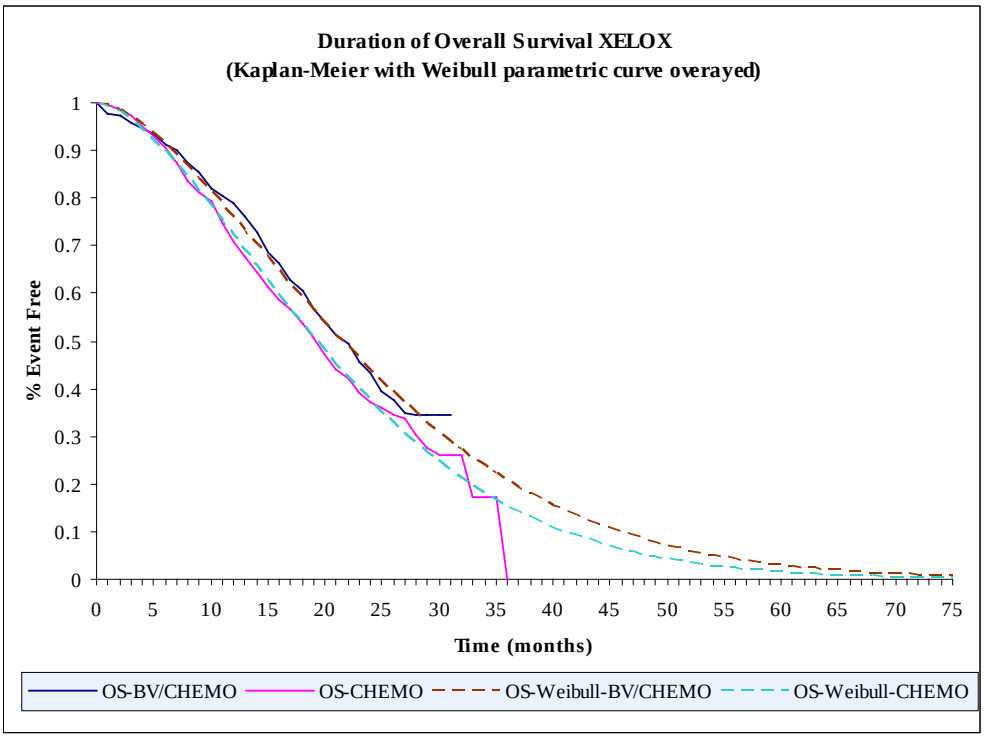


Table 23: Total cost for each intervention per patient

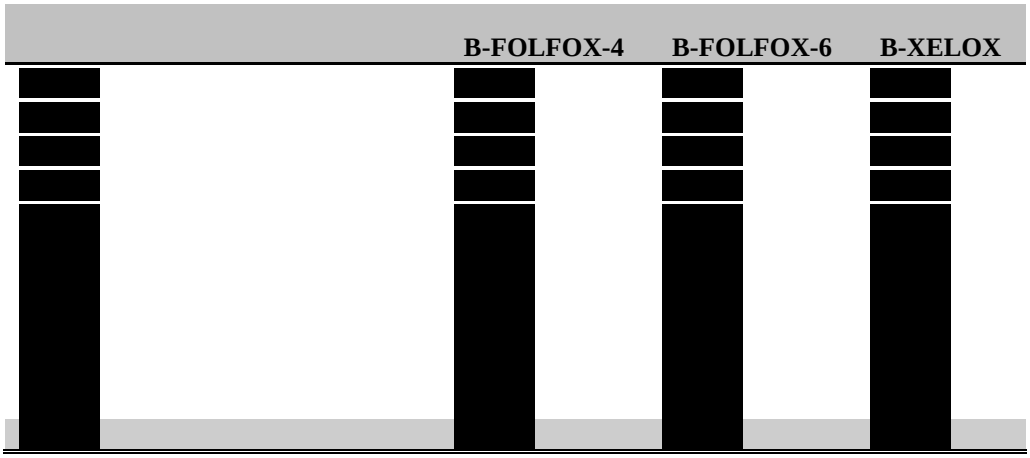


Table 24: cost for each comparator per patient

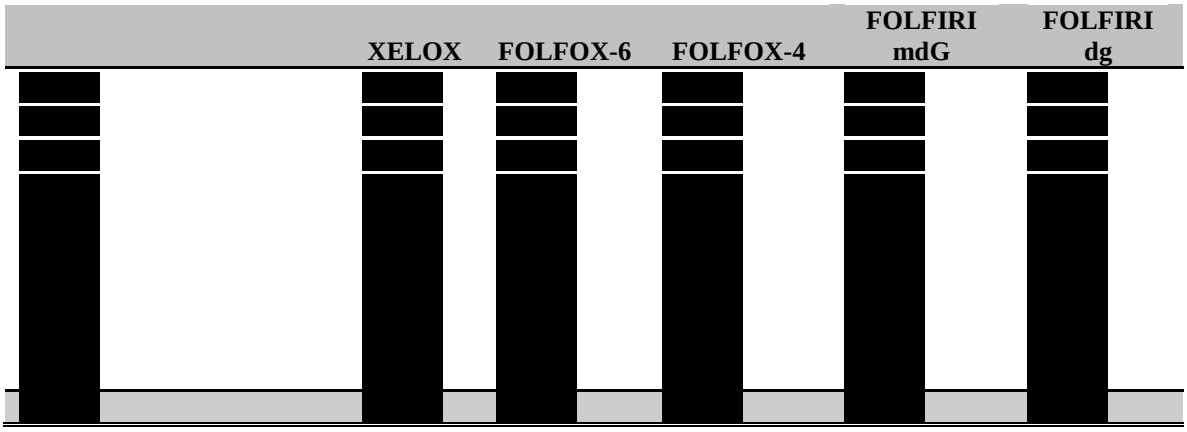


Figure 10: Simultaneous incremental results

Table 25: Time (months) spent in each health state till death per patient (undiscounted)

	B-XELOX	B-FOLFOX	XELOX	FOLFOX	FOLFIRI
Total					

Table 26: QALYs per patient

	B-XELOX	B-FOLFOX	XELOX	FOLFOX	FOLFIRI

Table 27: Incremental QALYs per patient

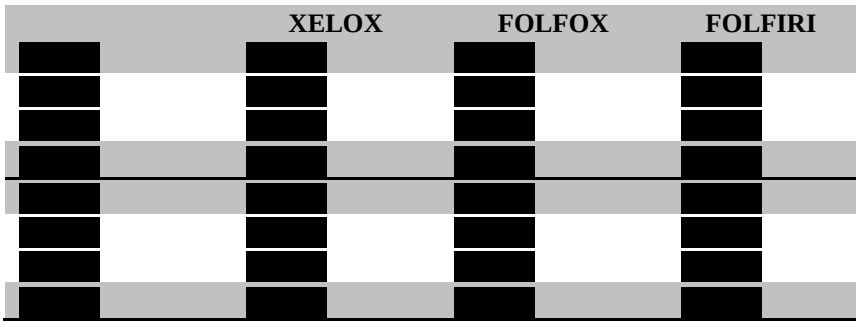


Table 28: Mean Incremental cost per patient

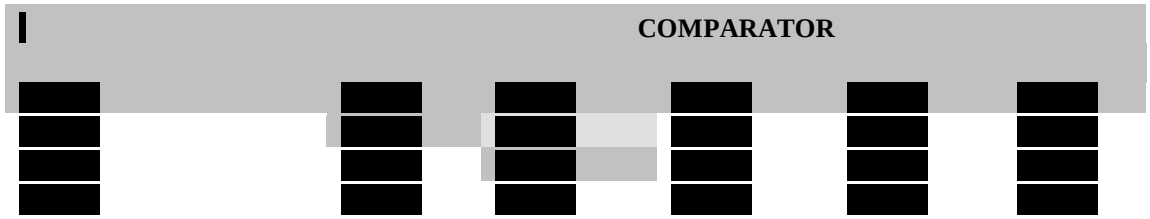


Table 29: Mean ICERs (£/QALY) per patient --- currently using truncated and oxaliplatin

	COMPARATOR				
Intervention	**XELOX**	**FOLFOX-6**	**FOLFOX-4**	**FOLFIRI mdG**	**FOLFIRI dg**
B-XELOX	£35,662	Dominant	Dominant	£8,975	Dominant
B-FOLFOX-6	£96,045	£62,714	£10,030	£66,485	£31,080
B-FOLFOX-4	£134,424	£95,813	£101,630	£107,507	£72,102

Appendix B Literature review for utility values

Methods

A literature review was conducted across a number databases, including PubMed, the Tuft's Cost Effectiveness Analysis (CEA) Registry (formerly the Harvard Center for Risk Analysis CEA), and the National Institute for Health and Clinical Excellence (NICE). The search was supplemented by hand reviews of bibliographies and known utility sources and reviews. The Tuft's CEA registry was reviewed for all utility values reported in each of the three cancers (renal cell carcinoma, pancreatic cancer and colorectal cancer); all references were retrieved in full and reviewed for utility scores. NICE oncology guidance and development history was reviewed with a focus on supportive Health Technology Assessments for reference to utility values. The PubMed database was reviewed for utility scores. The PubMed search terms included: Economics [MeSH]; Quality-Adjusted Life Years [MeSH]; Quality of Life [MeSH]; Costs and Cost Analysis [MeSH]; Standard gamble; Time trade off; Utility score; Utility value; Health utilities; Health utility; Kidney Neoplasms [MeSH] OR Carcinoma, Renal Cell [MeSH]; Pancreatic Neoplasms [MeSH]; Colorectal Neoplasms [MeSH].

Where utilities were arbitrarily assigned by the authors they have been ignored. In the case of arbitrary utility assignment, authors generally ranked the disease health state as 0.5. Papers which only cited utilities from other studies were ignored and the original source collected and tabled.

Table 1: PubMed search string

Most Recent Queries	Result	Sans 'Cost Analysis'
("Kidney Neoplasms"[MeSH] OR "Carcinoma, Renal cell"[MeSH]) AND (("Health utility" OR "health utilities" OR "utility value" OR "utility score") OR ("standard gamble" OR "time trade off") OR ("Costs and Cost Analysis"[MeSH]) OR ("Quality-Adjusted Life Years"[MeSH]) OR ("Quality of Life"[MeSH] AND "Economics"[MeSH]))	72	0
("Pancreatic Neoplasms"[MeSH]) AND (("Health utility" OR "health utilities" OR "utility value" OR "utility score") OR ("standard gamble" OR "time trade off") OR ("Costs and Cost Analysis"[MeSH]) OR ("Quality-Adjusted Life Years"[MeSH]) OR ("Quality of Life"[MeSH] AND "Economics"[MeSH]))	103	10
("Colorectal Neoplasms"[MeSH]) AND (("Health utility" OR "health utilities" OR "utility value" OR "utility score") OR ("standard gamble" OR "time trade off") OR ("Costs and Cost Analysis"[MeSH]) OR ("Quality-Adjusted Life Years"[MeSH]) OR ("Quality of Life"[MeSH] AND "Economics"[MeSH]))	898	85
("Kidney Neoplasms"[MeSH]) AND ("standard gamble" OR "time trade off")	0	
("Pancreatic Neoplasms"[MeSH]) AND ("standard gamble" OR "time trade off")	2	
("Colorectal Neoplasms"[MeSH]) AND ("standard gamble" OR "time trade off")	7	

Results

The review identified a large number of studies in each of the cancer areas. However, many of these did not report utility values. Many of the studies were also excluded on the basis of their focus on surgery, screening, or diagnostics, and not on drug interventions.

Within the NICE sub-search no utility values were identified for renal or pancreatic cancer. Manufacturer's submission did report utility values for colorectal cancer; the full referenced papers for the utility values used were collected and tabled (see Table 2). The values from Petrous et al. (1997) and Ness et al. (1999) were used in many of the submissions from different manufacturers. The Tuft's CEA registry also identified a number of studies which reported utility values in the three target cancers. These papers were gathered and reference utility values tabled (Table 2). The PubMed search identified 72 renal cancer abstract; 103 pancreatic cancer abstract; and 898 colorectal abstracts (the colorectal abstracts were subsequently reduced to n=346 by limiting the abstracts to English publications within the last 10 years) (see Table 1). These abstracts were reviewed for suitability and studies were selected for full review.

Fifty-one full papers were collected and evaluated on the basis of a reported utility value for one or more of each of the three target cancers. In total 0 papers reported a utility value for renal cancer; 2 for pancreatic cancer; and 10 for colorectal cancer. Of these identified values only 4 papers reported values that could be considered potentially useful for this study (Ness; van den Brink; Petrou; Miller) (0 renal; 0 pancreatic; 4 colorectal).

Table 2: Utility values identified in literature

Author	Year	Health State	Cancer	Perspective	Utility range	Technique
Ward et al.	2001	Time in clinical benefit	Pancreatic	n/a	1.0 (0.7-1.0)	Q-Twist
		Time to disease progression when not in clinical benefit	Pancreatic	n/a	0.5 (0.3-0.7)	Q-Twist
		Time from disease progression to death.	Pancreatic	n/a	0.5 (0.1-0.6)	Q-Twist
Arguedas et al.	2002	Long term pancreatic carcinoma with jaundice	Pancreatic	Health care workers	0.10-0.50	SG
		Long term pancreatic carcinoma without jaundice	Pancreatic	Health care workers	0.20-0.65	SG
		Short term endoscopic retrograde cholangio-pancreatography complications	Pancreatic	Health care workers	0.05-0.30	SG
		Short term occlusion complications	Pancreatic	Health care workers	0.05-0.50	SG
Norum et al.	1997	Colorectal cancer survivors (mean 16 months post surgery + chemotherapy)	Colorectal	Societal	0.83	VAS; EQ-5D
Petrou et al. (see Jones et al. 2001)	1997	Partial response	Colorectal	Nurses	1.0	SG
		Stable disease	Colorectal	Nurses	0.95	SG
		Progressive disease	Colorectal	Nurses	0.575	SG
		Terminal disease	Colorectal	Nurses	0.10	SG
Ness et al.	1999	Stage I rectal or stage I/II colon cancer treated with resection only	Colorectal	Patients	0.74 (0.69-0.78)	SG
		Stage III colon cancer treated with resection and chemotherapy without significant side effects	Colorectal	Patients	0.70 (0.63-0.77)	SG
		Stage III colon cancer treated with resection and chemotherapy with significant side effects	Colorectal	Patients	0.63 (0.56-0.70)	SG
		Stage II/III rectal cancer treated with resection/chemotherapy/radiation therapy	Colorectal	Patients	0.59 (0.54-0.64)	SG
		Stage II/III rectal cancer treated with resection/chemotherapy/radiation therapy/permanent ostomy	Colorectal	Patients	0.50 (0.44-0.56)	SG
		Stage IV metastatic/unresectable disease without ostomy	Colorectal	Patients	0.24 (0.16, 0.32)	SG
		Stage IV metastatic/unresectable disease with ostomy	Colorectal	Patients	0.27 (0.18, 0.36)	SG
Miller et al.	2000	Locally recurrent rectal cancer;	Colorectal	Healthcare	0.69 +/-	SG

		Disease recurrence		professionals	0.24	
		Locally recurrent rectal cancer; Disease recurrence	Colorectal	Patients	0.72 (+/- 0.22)	SG
		Locally recurrent rectal cancer; Surgical resection	Colorectal	Healthcare professionals	0.69 (+/- 0.24)	SG
		Locally recurrent rectal cancer; Surgical resection	Colorectal	Patients	0.83 (+/- 0.18)	SG
		Locally recurrent rectal cancer; Pain and complication	Colorectal	Healthcare professionals	0.50 (+/- 0.29)	SG
		Locally recurrent rectal cancer; Pain and complication	Colorectal	Patients	0.78 (+/- 0.27)	SG
Ramsey et al.	2000	Colorectal cancer survivors (13->60 months from diagnosis)	Colorectal	Patients	0.72-0.95	HUI
Hamashima et al.	2002	Postoperative rectal cancer without stoma	Colorectal	Societal	0.865 (+/- 0.220)	EQ-5D
		Postoperative rectal cancer with stoma	Colorectal	Societal	0.842 (+/- 0.191)	EQ-5D
Ramsey et al.	2002	Colorectal cancer survivors (5->15 years from diagnosis)	Colorectal	Societal	0.84-0.86	HUI
Ko et al.	2003	Colon Cancer <1 yr from diagnosis	Colorectal	Patients	0.67	Health and Activities Limitation Index (HALex)
		Colon cancer 1 year from diagnosis	Colorectal	Patients	0.68	Health and Activities Limitation Index (HALex)
		Colon cancer 5 years from diagnosis	Colorectal	Patients	0.71	Health and Activities Limitation Index (HALex)
van den Brink et al.	2004	Randomization to pre-operative radiotherapy or surgery	Colorectal	Societal	0.78	EQ-5D
		Surgery to discharge (surgery + radiotherapy)	Colorectal	Societal	0.9-0.11	EQ-5D
		Surgery to discharge (surgery)	Colorectal	Societal	0.17-0.21	EQ-5D
		>9 months post surgery	Colorectal	Societal	0.86-0.89	EQ-5D
		Macroscopically incomplete local resection or distant metastases at surgery	Colorectal	Societal	0.73-0.80	EQ-5D
		Local recurrence (surgery + radiotherapy)	Colorectal	Societal	0.67	EQ-5D
		Local recurrence (surgery)	Colorectal	Societal	0.67	EQ-5D
		Distant recurrence (surgery + radiotherapy)	Colorectal	Societal	0.70	EQ-5D
		Distant recurrence (surgery)	Colorectal	Societal	0.64	EQ-5D
		Local + distant recurrence (surgery + radiotherapy)	Colorectal	Societal	0.48	EQ-5D

		Local + distant recurrence (surgery)	Colorectal	Societal	0.45	EQ-5D
Hillner et al.	2005	Metastatic colorectal carcinoma, first line therapy	Colorectal	Patients	0.82	Utility transformation from unknown QoL rating scale
		Metastatic colorectal carcinoma, second line or palliative treatment	Colorectal	Patients	0.5	Utility transformation from unknown QoL rating scale

Cost Effectiveness References

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