Section A: Clarification on effectiveness data

Further study reports required

A1. **Priority Question:** Further to our e-mail on 22nd February regarding the ERG's request for additional documents, please could you reconsider providing a copy of the clinical study report for the VELOUR trial.

As discussed with the NICE Secretariat team, on our recent teleconference (14th March), the original request that we received on the 22nd February did not specifically ask for the Clinical Study Report for the VELOUR study. We understood the study report requested in that note was for the utility study, which we supplied directly to the Institute on the 25th February and was accepted without further comment.

However, in response to question A1 above, we have considered the advice provided to us by the NICE Secretariat at the decision-problem meeting and in the recent teleconference. Rather than provide the full CSR, we have included with this response the Clinical study synopsis, and the table of contents from the CSR. In the event that the ERG or the Appraisal Committee has a specific clarification question that might be addressed by further reference to the CSR, we can give consideration to how the CSR (or parts thereof) might be used in meeting that request.

At the decision-problem meeting the Institute's Secretariat team provided clear guidance on the information that we should provide both within the submission template and as accompanying appendices. They recommended that only the information relevant to answering the decision-problem should be supplied, and that because the Appraisal Committee and Evidence Review Group have limited time to review and appraise the information they receive, a concise presentation without undue repetition is preferred.

The VELOUR Clinical Study Report is an extensive document that comprises approximately 1400 pages of data tabulations and supporting narrative, plus many more pages in associated appendices. It would clearly contain information superfluous to consideration of the decision-problem and would, in all likelihood, not be considered in detail in the time available to the ERG and Appraisal Committee.

A2. **Priority Question:** Please provide a full report of the meta-analysis of aflibercept adverse events referred to on p.71 of the submission, which included the VELOUR, VITAL and VANILLA trials. Please also provide full adverse event results individually from the VITAL and VANILLA trials.

Details of the meta-analysis of adverse events are provided in the Tabernero et al 2012 poster and Allegra et al 2012 posters (attached).

With regards to the individual results of the VITAL and VANILLA trials, the VITAL trial is published (Ramlau 2012) and this provides AE results from this trial. The VANILLA trial is published in abstract format (Riess 2010). Further details on the safety results of both studies are published in the FDA review of safety (Zaltrap FDA report).

When interpreting both the results of the meta-analysis and the results of the VITAL and VANILLA trials it should be noted that these are from different patient populations and involved different doses of aflibercept and different chemotherapy backbones (6 mg/kg in combination with docetaxel in NSCLC patients in VITAL; 4 mg/kg in combination with gemcitabine in pancreatic cancer patients in VANILLA). Therefore, while the safety results from these studies are in line with the VELOUR results (the FDA review of safety notes that the safety profile of aflibercept in VITAL and VANILLA is consistent with that shown in VELOUR) they are not directly relevant to the safety profile likely to be shown by aflibercept

in combination with FOLFIRI when used for the treatment of 2L metastatic colorectal cancer in the UK.

A3. Please provide the study protocol and results of the survey of UK clinical oncology experts used to estimate community-based care and personal and social care related costs included in the economic model.

The original Physician RU questionnaire is attached. It should be noted that the original questionnaire contained questions on secondary care resource use which were superseded by results from the observational study undertaken. The results of the KOL questionnaire were used in the model to estimate resource use associated with community care, resource use associated with regimen change (i.e. from stable to stable discontinued second-line and from stable on treatment to progressed), and resource use associated with AE treatment. Results for community care and regimen change resource use are provided in the attached document (Physician survey results), and are also in the model. Results for AE-associated resource use are in the model in the worksheet KOL survey.

It should be noted that the results of the KOL questionnaire were directly entered into the model adjusted to rates per 2 week cycle; this accounts for why these are not whole numbers.

A4. As indicated on p. 40 of the submission, please provide any available results for the ongoing non-randomised trial (ASQoP - AFLIBC06097) investigating the safety of aflibercept and the HRQL in patients with mCRC (described in Table A-2 of the submission).

To date, only the first interim analysis of this study has been performed which has provided the baseline data for those patients recruited. The results provided in the submission (Table B14) are the most up-to-date results available. We anticipate that further interim analyses will become available during the course of the appraisal and we have made the NICE secretariat aware of this.

A5. If available, please provide the report for the trial of aflibercept+FOLFOX in the first line treatment of patients with metastatic colorectal cancer (AFFIRM). If not available, please provide any further details of the trial and any available results.

Results from the AFFIRM trial were presented at WGIC (Pericay 2012); the abstract and conference presentation are attached. Full journal publication is planned for Q4 2013. The AFFIRM study evaluates aflibercept in combination with a different backbone (FOLFOX) in the first-line setting. This is outside the licensed indication for aflibercept and the AFFIRM trial is not directly relevant to the decision problem.

Outcomes in the VELOUR trial: Overall Survival

A6. Since the analysis is mainly based on mean survival times, please provide mean survival for those patients who had died at the time of the most recent data analysis, by treatment group, including for the subgroups. For each analysis, please state the parametric distribution used to estimate the mean.

Following clarification via the NICE secretariat, we understand that this question refers to a restricted mean analysis – i.e. the mean OS calculated directly from the area under the Kaplan-Meier curves, without any extrapolation.

a) Restricted mean OS until last death in each arm (area under KM curves)
- ITT population
Aflibercept

Restricted mean OS = [redacted] calculated until t=32.7 months (where probability of survival = [redacted]

Placebo

Restricted mean OS = [redacted] calculated until t=32.5 months (where probability of survival = [redacted]

In both arms the mean survival time and its standard error were underestimated because the largest observation was censored and the estimation was restricted to the largest event time.

b) Restricted mean OS until last death in each arm (area under KM curves)
- Liver metastases only subgroup

Aflibercept

Restricted mean OS [redacted] calculated until t=31.7 months (where probability of survival = [redacted]

Placebo

Restricted mean OS = [redacted] calculated until t=32.5 months (where probability of survival = [redacted]

In the aflibercept arm the mean survival time and its standard error were underestimated because the largest observation was censored and the estimation was restricted to the largest event time.

c) Restricted mean OS until last death in each arm (area under KM curves)
- ITT population excluding adjuvant only patients

Aflibercept

Restricted mean OS = [redacted] calculated until t=32.7 months (where probability of survival = [redacted]

Placebo

Restricted mean OS = [redacted] calculated until t=32.5 months (where probability of survival [redacted]

In both arms the mean survival time and its standard error were underestimated because the largest observation was censored and the estimation was restricted to the largest event time.

A7. Please provide log-cumulative hazard plots for overall survival equivalent to Figure B-6 (P58) with readjusted (widened) scale so as to permit visual inspection of plots beyond Log [time (14 day cycles)] ≥ 1. In addition, please reduce the size of the markers for both treatments, as the circles and squares used are too large.

Revised figures are shown below; AVE0005A refers to aflibercept.

Figure 1: Revised log-cumulative hazard plot - ITT population

[redacted]

Figure 2: Log-cumulative hazard plot - Liver metastases subgroup

Figure 3: Log-cumulative hazard plot - ITT excluding patients progressing on or within 6 months of adjuvant treatment

A8. **Priority Question:** Please complete table B9 (p. 55) by providing overall survival HR for aflibercept plus FOLFIRI versus placebo plus FOLFIRI estimates, as well as corresponding standard deviations, for the following time (t) intervals:

i) 18 < t ≤ 24 months;

ii) 24 < t ≤ 30 months;

iii) 30 < t ≤ 36 months.

Please include the number of patients censored per treatment arm for each interval (including t ≤ 6 months, 6 < t ≤ 12 months, 12 < t ≤ 18 months, 18 < t ≤ 24 months, 24 < t ≤ 30 months, and 30 < t ≤ 36 months), as well as the number of patients at risk at t = 36 months.

Number of patients (censored, death) per time interval

Description of Planned Arm=Aflibercept

Table of interval by AVAL			
interval	**AVAL(Analysis Value)**		
Frequency	**Censored**	**Death**	**Total**
t<=6	[redacted]	[redacted]	[redacted]
6<t<=12	[redacted]	[redacted]	[redacted]
12<t<=18	[redacted]	[redacted]	[redacted]
18<t<=24	[redacted]	[redacted]	[redacted]
24<t<=30	[redacted]	[redacted]	[redacted]
30<t<=36	[redacted]	[redacted]	[redacted]
t>36	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Description of Planned Arm=PLACEBO

Table of interval by AVAL			
interval	**AVAL(Analysis Value)**		
Frequency	**Censored**	**Death**	**Total**
t<=6	[redacted]	[redacted]	[redacted]
6<t<=12	[redacted]	[redacted]	[redacted]
12<t<=18	[redacted]	[redacted]	[redacted]
18<t<=24	[redacted]	[redacted]	[redacted]
24<t<=30	[redacted]	[redacted]	[redacted]
30<t<=36	[redacted]	[redacted]	[redacted]
t>36	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

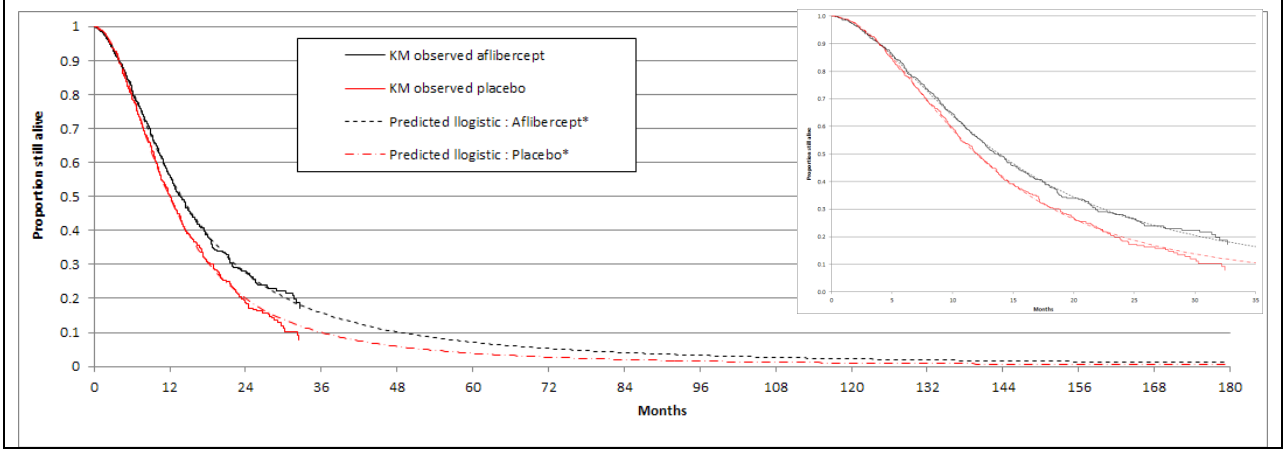
Hazard ratios (HR) by 6-month time periods estimated using a piecewise Cox proportional hazard model:

Parameter	Time (months)	Hazard Ratio	95.34% Hazard Ratio Confidence Limits	
OS	t ≤ 6	0.860	0.664	1.114
OS	6 < t ≤ 12	0.838	0.673	1.043
OS	12 < t ≤ 18	0.782	0.582	1.050
OS	18 < t ≤ 24	[redacted]	[redacted]	[redacted]
OS	24 < t ≤ 30	[redacted]	[redacted]	[redacted]
OS	30 < t ≤ 36	[redacted]	[redacted]	[redacted]

Treatment with aflibercept + FOLFIRI showed a continuous and consistent improvement in OS over time. The smaller number of patients still at risk in the last 3 intervals explains the larger confidence intervals.

A9. **Priority Question:** Please provide a figure with the fitted log-logistic functions extrapolated to 15 years with the Kaplan Meier curves overlaid. Please display both treatment arms in the same figure.

Question A9 - Overall survival (ITT) plotted to 15 years [180mths]
(insert: the same plot scaled to show only the trial follow-up period)



A10. Please add to Figures B-4 (p. 56) and B-5 (p. 57) the overall survival curve resulting from the fitting of the Gompertz distribution for which AIC/BIC results are presented in table B10 (p. 56).

B4 (p56) OS functions and Kaplan-Meier data for the ITT population: functions fitted to each treatment arm separately for aflibercept + FOLFIRI [includes the Gompertz function]

[redacted]

B4 (p56) OS functions and Kaplan-Meier data for the ITT population: functions fitted to each treatment arm separately for placebo + FOLFIRI [includes the Gompertz function]

[redacted]

B5 (p57) OS functions and Kaplan-Meier data for the ITT population: functions fitted to both treatment arms with treatment as predictor (assuming proportional hazards) for aflibercept + FOLFIRI [includes the Gompertz function]

[redacted]

B5 (p57) OS functions and Kaplan-Meier data for the ITT population: functions fitted to both treatment arms with treatment as predictor (assuming proportional hazards) for placebo + FOLFIRI [includes the Gompertz function]

[redacted]

A11. On p. 59 it states that the curves were truncated at 15 years to avoid implausibly long survival times. However, in the ERG's opinion, 15 years is still too long for this population. Therefore, please present the estimates with the analysis truncated at 5 and 10 years, along with both mean and median survival times for each model.

Mean OS data are shown in Table 1 for the ITT population, for different parametric distributions, by arm as randomised. The median survival time is unaffected by the time horizon.

Table 1: Overall Survival at different time horizons – ITT population

Overall Survival	Placebo/Folfiri (N=614)	Aflibercept/ Folfiri (N=612)	Comparison
Number of patients	614 (100%)	612 (100%)	
Number of events	460 (74.9%)	403 (65.8%)	
Median in months* [95% CI]	12.06 [11.07 ; 13.08]	13.50 [12.52 ; 14.95]	Median difference = 1.44
Median in months assuming LogLogistic (a)	[redacted]	[redacted]	[redacted]
Restricted mean over 5 years in months assuming LogLogistic (a)	[redacted]	[redacted]	[redacted]
Restricted mean over 10 years in months assuming LogLogistic (a)	[redacted]	[redacted]	[redacted]
Restricted mean over 15 years in months assuming LogLogistic (a)	18.1	22.8	Mean difference = 4.7
Median in months assuming Weibull (a)	[redacted]	[redacted]	[redacted]
Restricted mean over 5 years in months assuming Weibull (a)	[redacted]	[redacted]	[redacted]
Restricted mean over 10 years in months assuming Weibull (a)	[redacted]	[redacted]	[redacted]
Restricted mean over 15 years in months assuming Weibull (a)	14.9	17.9	Mean difference =3.0
Median in months assuming Lognormal (a)	[redacted]	[redacted]	[redacted]
Restricted mean over 5 years in months assuming Lognormal (a)	[redacted]	[redacted]	[redacted]
Restricted mean over 10 years in months assuming Lognormal (a)	[redacted]	[redacted]	[redacted]
Restricted mean over 15 years in months assuming Lognormal (a)	[redacted]	[redacted]	[redacted]
Median in months assuming Exponential (a)	[redacted]	[redacted]	[redacted]
Restricted mean over 5 years in months assuming Exponential (a)	[redacted]	[redacted]	[redacted]
Restricted mean over 10 years in months assuming Exponential (a)	[redacted]	[redacted]	[redacted]
Restricted mean over 15 years in months assuming Exponential (a)	[redacted]	[redacted]	[redacted]
Median in months assuming Gompertz (a)	[redacted]	[redacted]	[redacted]
Restricted mean over 5 years in months assuming Gompertz (a)	[redacted]	[redacted]	[redacted]
Restricted mean over 10 years in months assuming Gompertz (a)	[redacted]	[redacted]	[redacted]
Restricted mean over 15 years in months assuming Gompertz (a)	[redacted]	[redacted]	[redacted]
* Refer to Kaplan-Meier curve (a) By treatment group independently			

We consider that 15 years is an appropriate time horizon. While only a minority of patients with metastatic CRC will survive for longer than 5 years, it is important that the time horizon

is sufficient to capture survival for that minority of patients who do survive for extended periods of time.

In line with this, the model estimates that only a small minority of patients will survive beyond 5 and 10 years. In the model base-case, the probability of survival in the aflibercept arm is [redacted] years. The corresponding values for the FOLFIRI alone arm are [redacted]

The most extensive and reliable data source for 5, 10 and 15 year survival rates for mCRC is probably the SEER database in the US. This provides 1, 5, and 10-year survival rates for metastatic colorectal cancer (SEER survival monograph) recorded between 1988 – 2001. These are shown in the table below. These data show that just under 5% of mCRC patients survived for at least 10 years since diagnosis.

The data also show a decreasing hazard over time – as can be seen the difference in the 5-year and 10-year rates is small, particularly in comparison with the large decrease observed between 1 and 5 years. This supports the concept that there are indeed a small proportion of mCRC patients who do experience extended survival times, and supports the use of a time horizon beyond 10 years.

Table 2: Survival rates for Stage IV colorectal cancer from SEER database

1- Year survival rate	5-year survival rate	10-year survival rate
43.6%	6.9%	4.8%

In the UK, NICE TA118 quotes a value of 12% for the 5-year survival rate of mCRC. The UK National Cancer Intelligence Network (NCIN 2009) reports similar data to the SEER database. The NCIN report quotes a 5-year survival rate of 6.6% for Dukes D stage cancer (equivalent to Stage IV) and also shows a decreasing hazard over time since diagnosis, suggesting a small proportion of patients will survive beyond 5 – 10 years. Further data come from five-year follow-up data from the N9741 trial (Sanofi 2008). This shows a five-year survival rate of 6.6% overall; the rate for patients treated with first-line FOLFOX was 9.8%. Interestingly, an analysis of the characteristics of patients surviving to 5 years showed that only 7% of these underwent resection – i.e. the extended survival time was not necessarily due to curative surgery

There is evidence that survival rates have improved over time. A publication by Kopetz et al quoted in our submission (Kopetz 2009) undertook an analysis of survival over time in two major cancer centres in the US. This showed somewhat higher 5-year survival rates than those in the SEER database, but importantly showed an increase in survival rates over time - the 5-year overall survival rate for mCRC increased from 9.1% for patients diagnosed in 1990 through 1997, to 13.0% for 1998 – 2000, and 19.2% for those diagnosed in 2001 – 2003. Earlier increases were associated with liver resection but later improvements were not, and were considered to be most probably due to the availability of new drugs. The authors also analysed data from the SEER database and found lower absolute survival rates but a similar trend for increasing survival rates over time. This suggests that current survival rates may be somewhat higher than those quoted by SEER for the period 1988 – 2001.

These rates are for mCRC as a whole rather than a specific second-line mCRC sub-population. It might be expected that rates for second-line mCRC would be lower than for mCRC as a whole, particularly if a proportion of the longer-surviving group contains some of those patients who underwent curative resection for liver metastases. However, the

second-line population by definition have survived beyond first-line treatment and have to be relatively fit and of good performance status to be considered for sometimes lengthy courses of second-line chemotherapy, so it is not unreasonable to expect some longer-term survivorship from this group too. Taken as a whole, the datasets available suggest that a small proportion of mCRC patients do survive for longer than10 years from diagnosis and therefore a time horizon of up to 15 years is appropriate.

Outcomes in the VELOUR trial: Progression Free Survival

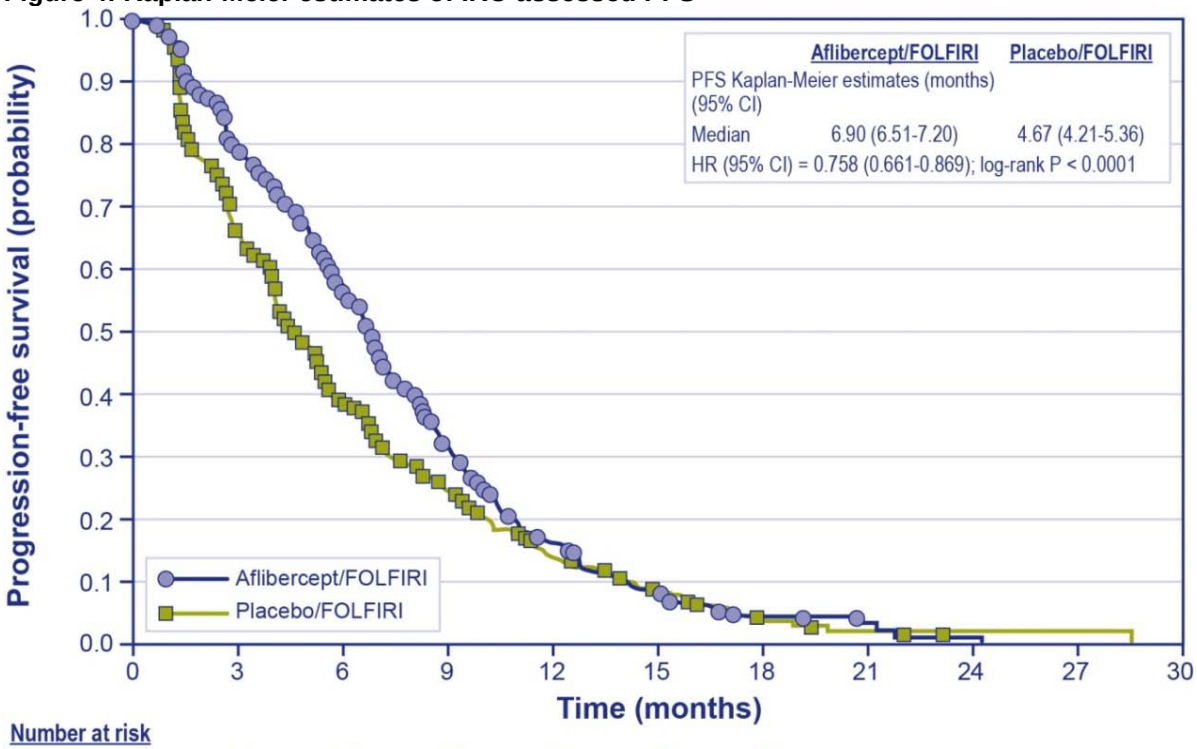
A12. Disease progression was defined as: at least a 20% increase in the sum of the longest diameter of target lesions; unequivocal increase in the size of non-target lesions; or the appearance of one or more new lesions. Please provide the rationale for this definition. Results were based on independent review committee (IRC) tumour assessment, with investigator assessment of progression used in sensitivity analysis. Please provide separate results for both IRC and investigator assessed PFS.

The definition of disease progression was as per RECIST criteria, which is an internationally recognised standard set of criteria for defining disease progression. IRC assessment provides an objective, unbiased assessment of disease progression.

As reported in our original submission, addition of aflibercept to FOLFIRI increased IRC-assessed PFS relative to placebo plus FOLFIRI. The median PFS gain was 2.23 months – 6.90 (95% CI 6.51 – 7.20) months for aflibercept plus FOLFIRI versus 4.67 (95% CI: 4.21 – 5.36) for placebo plus FOLFIRI, based on independent assessment of radiologic progression. The HR was 0.758 (95% CI: 0.661 – 0.869) (Figure 5). NB - for 42 patients (26 aflibercept + FOLFIRI, 16 placebo + FOLFIRI) who died prior to the implementation of the IRC review or who refused consent for this review, the investigator's tumour assessment was used (Sanofi data on file, 2011).

[redacted]

Figure 4: Kaplan-Meier estimates of IRC-assessed PFS



Number at risk

Aflibercept:	612	420	247	99	43	17	7
Placebo:	614	355	171	94	46	24	9

CI, confidence interval; FOLFIRI, fluorouracil/leucovorin/irinotecan; HR, hazard ratio; ITT, intention to treat; PFS, progression-free survival.
Intention-to-treat population; cut-off date: 6 May 2010.
Source: Van Cutsem et al., 2012; Sanofi data on file, 2011.

In a sensitivity analysis, PFS was determined and analysed using the investigators' assessment of lesions, and also considering clinical progression as an event. The results of this analysis are presented in Figure 6. Estimation of PFS in this sensitivity analysis was based on [redacted] in the aflibercept arm. Whilst the stratified log-rank hazard ratio indicates an improvement in PFS in favour of aflibercept over placebo (HR [redacted]

[redacted]

A13. Please report the mean and median PFS with 95% CI for the following parametric and non-parametric functions, Kaplan Meier, Weibull, log-normal, log-logistic, exponential and Gompertz. Please report values for both treatment arms.

ITT population		Aflibercept + FOLFIRI	Placebo + FOLFIRI	Difference
Median PFS (in months)	Kaplan-Meier – median	6.9	4.7	2.2
	Weibull	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]
	Exponential	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]
Mean PFS (in months)	Weibull	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]
	Exponential	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]

A14. Please report the mean and median PFS with 95% CI for the functions mentioned above, but assuming the proportional hazards assumption. Please report values for both treatment arms.

ITT population		Aflibercept + FOLFIRI	Placebo + FOLFIRI	Difference
Median PFS (in months)	Kaplan-Meier – median	**6.9**	**4.7**	**2.2**
	Weibull	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]
	Exponential	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]
Mean PFS (in months)	Weibull	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]
	Exponential	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]

A15. Please present equivalent results for the Gompertz distribution in table B20 (p. 85).

AIC and BIC test results for PFS functions, ITT population

Function	Aflibercept + FOLFIRI		Placebo + FOLFIRI		Both arms (proportional hazards)	
	AIC	BIC	AIC	BIC	AIC	BIC
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Values in red font indicate the lowest AIC and BIC values.

AIC, Akaike information criterion; BIC, Bayesian information criterion; FOLFIRI, fluorouracil/leucovorin/irinotecan; IRC, independent review committee; ITT, intention-to-treat; PFS, progression-free survival.

Note: PFS was as determined by IRC.

Outcomes in the VELOUR trial: Response rate

A16. Table B5 states the primary and secondary outcomes and how they were measured, but not the timings. The journal article by Van Cutsem et al. (2012) states that disease assessment was performed every 6 weeks until documented progression. Please confirm that this disease assessment was for response rate, as well as disease progression.

To confirm, disease assessment every 6 weeks included response rate as well as progression.

Outcomes in the VELOUR trial: Time to Treatment Discontinuation

A17. Please provide legible figures for B-13 and B-14 by using different colours for the curves.

B13 Time to second-line treatment discontinuation functions and Kaplan-Meier data, ITT population

[redacted]

B14 Time to early second-line treatment discontinuation functions and Kaplan-Meier data, ITT population

[redacted]

A18. Please provide the mean and median times to FOLFIRI discontinuation in each arm and the mean and median time to aflibercept discontinuation, for any reason for discontinuation, and for each reason for discontinuation separately (i.e. adverse event, disease progression, patient request, etc).

The following data are presented for the safety population, by arm as actually received.

Duration of exposure to FOLFIRI

Duration of exposure is calculated from 1st dose of any FOLFIRI components (5-FU infusion or Bolus, Irinotecan, Leucovorin) to last dose of any FOLFIRI component + 2 weeks. The reason for stopping treatment is reason for stopping FOLFIRI in case of premature discontinuation of FOLFIRI. Otherwise it is reason for stopping overall treatment.

	Duration of exposure to FOLFIRI (weeks)	Placebo/Folfiri (N=605)	Aflibercept/Folfiri (N=611)
Safety population	N	604	611
	Mean (SD)	[redacted]	[redacted]
	Median	18.4	21.3
	Min ; Max	2 ; 135	2 ; 106
Stopping reason : any	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min ; Max	[redacted]	[redacted]
Stopping reason : adverse event	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min ; Max	[redacted]	[redacted]
Stopping reason : disease progression	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min ; Max	[redacted]	[redacted]
Stopping reason : poor compliance to protocol	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min ; Max	[redacted]	[redacted]
Stopping reason : subject lost to follow-up	N	[redacted]	
	Mean (SD)	[redacted]	
	Median	[redacted]	
	Min ; Max	[redacted]	
Stopping reason : other	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min ; Max	[redacted]	[redacted]

Duration of exposure to AFLIBERCEPT/PLACEBO

Duration of exposure is calculated from 1st dose of Aflibercept/Placebo to last dose of Aflibercept/Placebo + 2 weeks.
Reason for stopping treatment is reason for stopping Aflibercept/Placebo in case of premature discontinuation of Aflibercept/Placebo. Otherwise it is reason for stopping overall treatment.

	Duration of exposure to AFLIBERCEPT/PLACEBO (weeks)	**Placebo/Folfiri (N=605)**	**Aflibercept/Folfiri (N=611)**
Safety population	N	605	611
	Mean (SD)	[redacted]	[redacted]
	Median	18	17.9
	Min ; Max	2 ; 135	2 ; 85
Stopping reason : any	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min ; Max	[redacted]	[redacted]
Stopping reason : adverse event	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min ; Max	[redacted]	[redacted]
Stopping reason : disease progression	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min ; Max	[redacted]	[redacted]
Stopping reason : poor compliance to protocol	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min ; Max	[redacted]	[redacted]
Stopping reason : subject lost to follow-up	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min ; Max	[redacted]	[redacted]
Stopping reason : other	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min ; Max	[redacted]	[redacted]

A19. **Priority Question:** Please provide more detail on further lines of treatments, namely:

a) Proportion of patients in each treatment arm:

i) On any active treatment and on each specific active treatment after discontinuation;

ii) Who underwent liver metastases resection (for ITT and liver metastases only subgroup).

b) Mean number of cycles of any subsequent active treatment by treatment arm:

i) After early discontinuation of the second line treatment;

ii) After progression.

Overall, [redacted] patients in the ITT population received at least one further anti-cancer therapy ([redacted] of the aflibercept arm). The proportions of patients receiving different types of first further therapy were balanced between the two arms, with the majority of patients receiving systemic anti-cancer therapy.

[redacted] in the aflibercept arm underwent a surgery of liver metastasis. This information is not available broken down by subgroup.

Information on further treatments as recorded in VELOUR is presented in Table 3 and Table 4.

Table 3: First further anti-cancer therapy – ITT population

	Placebo/Folfiri (N=614)	**Aflibercept/Folfiri (N=612)**
At least one further therapy [n(%)]		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Type of first further therapy [n(%)]		
Systemic anti-cancer treatment	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]
Surgery	[redacted]	[redacted]

Table 4: All further systemic anti-cancer treatment – ITT population

	Placebo/Folfiri (N=614)	Aflibercept/Folfiri (N=612)
Any further therapy	[redacted]	[redacted]
Surgery	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]
Systemic anti-cancer treatment	[redacted]	[redacted]
Biologics / Small molecules	[redacted]	[redacted]
Cetuximab	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]
Panitumumab	[redacted]	[redacted]
Other	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]
Fluoropyrimidine	[redacted]	[redacted]
Irinotecan	[redacted]	[redacted]
Other	[redacted]	[redacted]
Oxaliplatin	[redacted]	[redacted]
Other[a]	[redacted]	[redacted]

Although data were available from the VELOUR trial for the distribution of subsequent therapies, they were not always available for duration or dosage; owing to missing or unclear data (i.e. data on dosage was missing in more than [redacted] of cases). In addition, in some cases only the class or type of drug (e.g. anti-tumour necrosis factor monoclonal antibody, antineoplastic agents, monoclonal antibodies or protein kinase inhibitors) was recorded in the CRF, not the drug. For these reasons, and because subsequent treatment patterns may vary between countries, the UK resource use study was used to provide distribution, dosage, and treatment duration for subsequent therapies.

A20. **Priority Question:** Please clarify the difference between "Time to second-line treatment discontinuation" and "Time to second-line early discontinuation". In addition, please explain how does "Time second-line treatment discontinuation" curve differs from the PFS curve.

The VELOUR trial protocol required the second-line study drug (aflibercept + FOLFIRI or placebo + FOLFIRI) to be stopped at progression; however, in the trial, many patients switched treatment before progression due to AEs, patient requests, or investigator decisions.

Time to second-line early discontinuation refers to these patients who discontinued early due to adverse events or patient choice but who had not progressed.
Time to second-line treatment discontinuation refers to treatment discontinuation overall – i.e. it includes both those patients who discontinued early and those who discontinued due to progression. The PFS curve differs from the Time to Treatment Discontinuation curve in that because PFS is based on progression/ death, the event times for those patients who discontinued treatment early – i.e. prior to progression – are different. These are shown graphically in Figure 7 and Figure 8.
Early discontinuations were estimated from all patients who have discontinued before progression, which is 47% and 34% of all patients in the ITT patient population for the aflibercept+FOLFIRI and the FOLFIRI arm respectively.

Figure 5: Discontinuation curves and PFS - Aflibercept plus FOLFIFI – ITT population

[redacted]

[redacted]

Figure 6: Discontinuation curves and PFS - placebo plus FOLFIRI – ITT population

[redacted]

A21. For both “Time to second-line treatment discontinuation” and “Time to second-line early discontinuation”, please present the following descriptive statistics for non-parametric curves: mean, median, standard deviation and number of observations by treatment arm.

All tables are derived from KM data

Time to second-line treatment discontinuation – ITT population

Summary of the Number of Censored and Uncensored Values					
Stratum	Planned Arm	Total	Failed	Censored	Percent Censored
1	PLACEBO	[redacted]	[redacted]	[redacted]	[redacted]
2	AFLIBERCEPT	[redacted]	[redacted]	[redacted]	[redacted]
Total		[redacted]	[redacted]	[redacted]	[redacted]

Planned Arm	Mean	Standard Error	Median	95% Confidence Interval- Lower	95% Confidence Interval- Upper
PLACEBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AFLIBERCEPT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Time to early treatment discontinuation – ITT population

Summary of the Number of Censored and Uncensored Values					
Stratum	Planned Arm	Total	Failed	Censored	Percent Censored
1	PLACEBO	[redacted]	[redacted]	[redacted]	[redacted]
2	AFLIBERCEPT	[redacted]	[redacted]	[redacted]	[redacted]
Total		[redacted]	[redacted]	[redacted]	[redacted]

Planned Arm	Mean	Standard Error	Median	95% Confidence Interval- Lower	95% Confidence Interval- Upper
PLACEBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AFLIBERCEPT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Time to second-line treatment discontinuation – ITT population excluding adjuvant only patients

Summary of the Number of Censored and Uncensored Values					
Stratum	Planned Arm	Total	Failed	Censored	Percent Censored
1	PLACEBO	[redacted]	[redacted]	[redacted]	[redacted]
2	AFLIBERCEPT	[redacted]	[redacted]	[redacted]	[redacted]
Total		[redacted]	[redacted]	[redacted]	[redacted]

Planned Arm	Mean	Standard Error	Median	95% Confidence Interval- Lower	95% Confidence Interval- Upper
PLACEBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AFLIBERCEPT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Time to early treatment discontinuation –ITT population excluding adjuvant only patients

Summary of the Number of Censored and Uncensored Values					
Stratum	Planned Arm	Total	Failed	Censored	Percent Censored
1	PLACEBO	[redacted]	[redacted]	[redacted]	[redacted]
2	AFLIBERCEPT	[redacted]	[redacted]	[redacted]	[redacted]
Total		[redacted]	[redacted]	[redacted]	[redacted]

Planned Arm	Mean	Standard Error	Median	95% Confidence Interval- Lower	95% Confidence Interval- Upper
PLACEBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AFLIBERCEPT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Time to second-line treatment discontinuation – Liver mets only population

Summary of the Number of Censored and Uncensored Values					
Stratum	Planned Arm	Total	Failed	Censored	Percent Censored
1	PLACEBO	[redacted]	[redacted]	[redacted]	[redacted]
2	AFLIBERCEPT	[redacted]	[redacted]	[redacted]	[redacted]
Total		[redacted]	[redacted]	[redacted]	[redacted]

Planned Arm	Mean	Standard Error	Median	95% Confidence Interval- Lower	95% Confidence Interval- Upper
PLACEBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AFLIBERCEPT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Time to early treatment discontinuation – Liver mets only population

Summary of the Number of Censored and Uncensored Values					
Stratum	Planned Arm	Total	Failed	Censored	Percent Censored
1	PLACEBO	[redacted]	[redacted]	[redacted]	[redacted]
2	AFLIBERCEPT	[redacted]	[redacted]	[redacted]	[redacted]
Total		[redacted]	[redacted]	[redacted]	[redacted]

Planned Arm	Mean	Standard Error	Median	95% Confidence Interval- Lower	95% Confidence Interval- Upper
PLACEBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AFLIBERCEPT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A22. It is stated in p. 88 of the submission that further details for the time to second-line treatment discontinuation were provided in appendix 14, but this appendix refers only to PFS and OS data. Please provide these missing details in appendix 14.

This statement was made in error. Please clarify if any further details relating to time to treatment discontinuation or the parametric functions fitted to this are required, however we consider this is fully described in the main dossier.

A23. Please clarify which survival curves (parametric or non-parametric) were used for "time to second-line treatment discontinuation" and "time to early second-line treatment discontinuation" for the cost-effectiveness analysis results (reproduced in tables 10-24 and 10-24 in appendix 16) of the i) liver metastases only subgroup, and ii) ITT excluding patients relapsing within 6 months of adjuvant therapy subgroup. Please, could you also justify the rationale for selecting the survival curves for each subgroup.

As detailed in section 7.9.3 of the submission parametric survival functions were fitted to subgroup-specific data in the same way as described for the ITT population in sections 6.5.3 and 7.3.1. The information provided below should be read in conjunction with the response to question A24 which contains all the relevant tables and figures.

Liver Metastases Only Subgroup

Time to Treatment Discontinuation

The Weibull distribution was the best fitting distribution to the observed treatment discontinuation for aflibercept + FOLFIRI. The log-normal distribution was the best fit and log-logistic the second best fit for the FOLFIRI group according to the AIC and BIC. When the two treatment groups were modelled together and treatment was used as a predictor Log-normal provided the best fit. However, in the absence of a strong justification, it is not appropriate to apply different functions to two treatment groups for the same endpoint (Latimer, 2011). Therefore, consistent with what was done for the ITT population for Time to Treatment Discontinuation and for PFS, the Weibull functions with treatment arms modelled separately were selected for the base-case analysis.

Time to Early Treatment Discontinuation (by IRC PFS)

The best fitting distribution for Aflibercept + FOLFIRI was Weibull, followed by log-logistic and then log-normal distribution. Log-normal distribution was the best fit and log-logistic the second best fit for the FOLFIRI group according to the AIC and BIC results. The Weibull was used as the base-case.

ITT Excluding Adjuvant Subgroup

Time to Treatment Discontinuation

The Weibull distribution was the best fitting distribution to the observed treatment discontinuation for the aflibercept + FOLFIRI group. The log-normal distribution was the best fit and log-logistic the second best fit for the FOLFIRI group according to the AIC and BIC. When the two treatment arms were modelled together and treatment was used as a predictor Weibull distribution provided the best fit.

Weibull provided a very good fit for the Aflibercept + FOLFIRI arm, while predictions from log-normal and log-logistic distributions deviated significantly at the tail (i.e. after cycle 20). For the FOLFIRI group log-normal, log-logistic and Weibull distributions provided a close fit to the observed data, while predictions deviated slightly from the observed data at the tail.

As the Weibull function was overall the best fit for both arms, consistent with the ITT group, the Weibull functions with treatment arms modelled separately were selected for the base-case analysis.

Time to Early Treatment Discontinuation

The Weibull distribution was the best fitting distribution to the observed early treatment discontinuation for the Aflibercept + FOLFIRI group. Log-normal distribution was the best fit and Weibull the second best fit for the FOLFIRI group according to the AIC and BIC results. When the two treatment groups were modelled together and treatment was used as a predictor Weibull provided the best fit.

For both treatment groups Weibull provided a very good fit while predictions from log-normal and log-logistic distributions deviated slightly at the tail (i.e., after cycle 15) , Consistent with the ITT and liver metastases subgroup, Weibull with treatment arms modelled separately was used in the base-case.

A24. Please provide tables equivalent to tables B21 and B22 (p. 88), as well as figures equivalent to figures B-13 and B-14 (p. 89) for the i) liver metastases only, and ii) ITT excluding patients relapsing within 6 months of adjuvant therapy. Please ensure that figures are legible and that different colours are used for each curve.

i) Liver metastases only subgroup

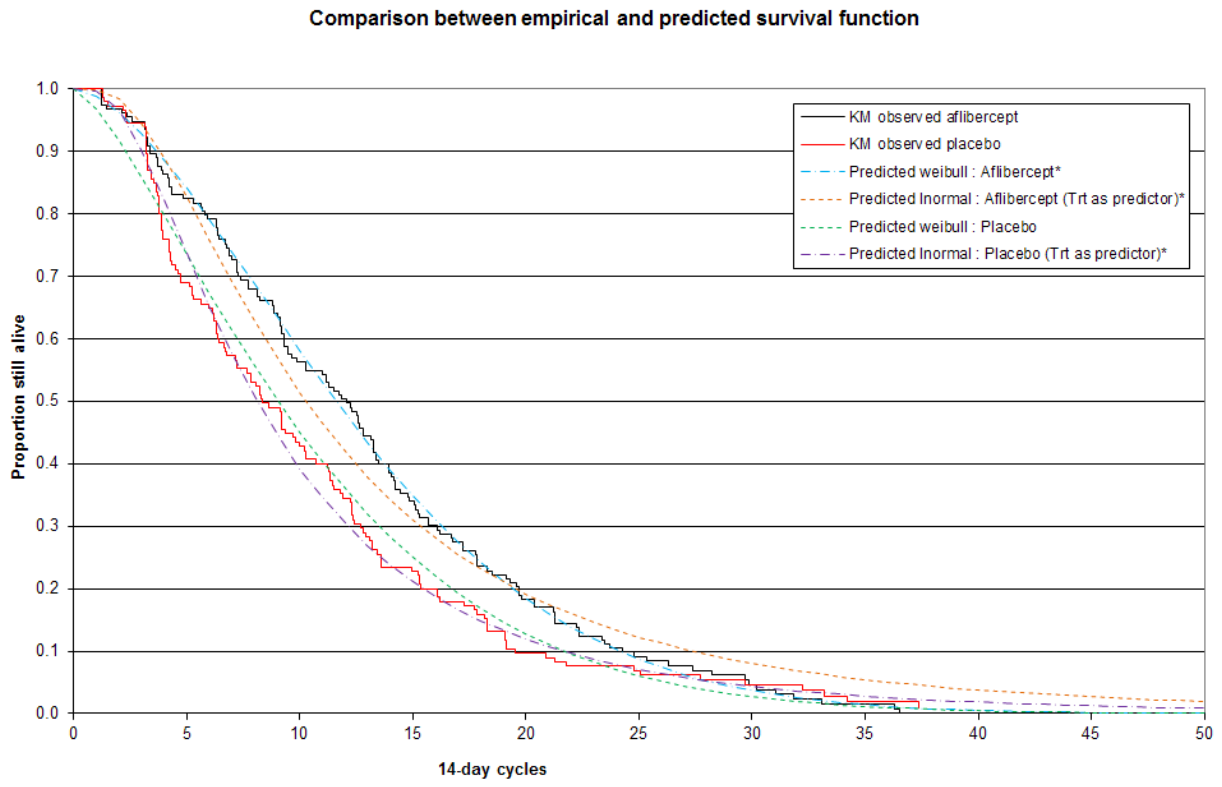
AIC and BIC test results for time to second-line treatment discontinuation functions

Function	Aflibercept + FOLFIRI		Placebo + FOLFIRI		Both arms (proportional hazards)	
	AIC	BIC	AIC	BIC	AIC	BIC
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Values in red font indicate the lowest AIC and BIC values.

AIC, Akaike information criterion; BIC, Bayesian information criterion; FOLFIRI, fluorouracil/leucovorin/irinotecan;

Time to second-line treatment discontinuation functions and Kaplan-Meier data, Liver mets only [supplemental to Figure B-13]



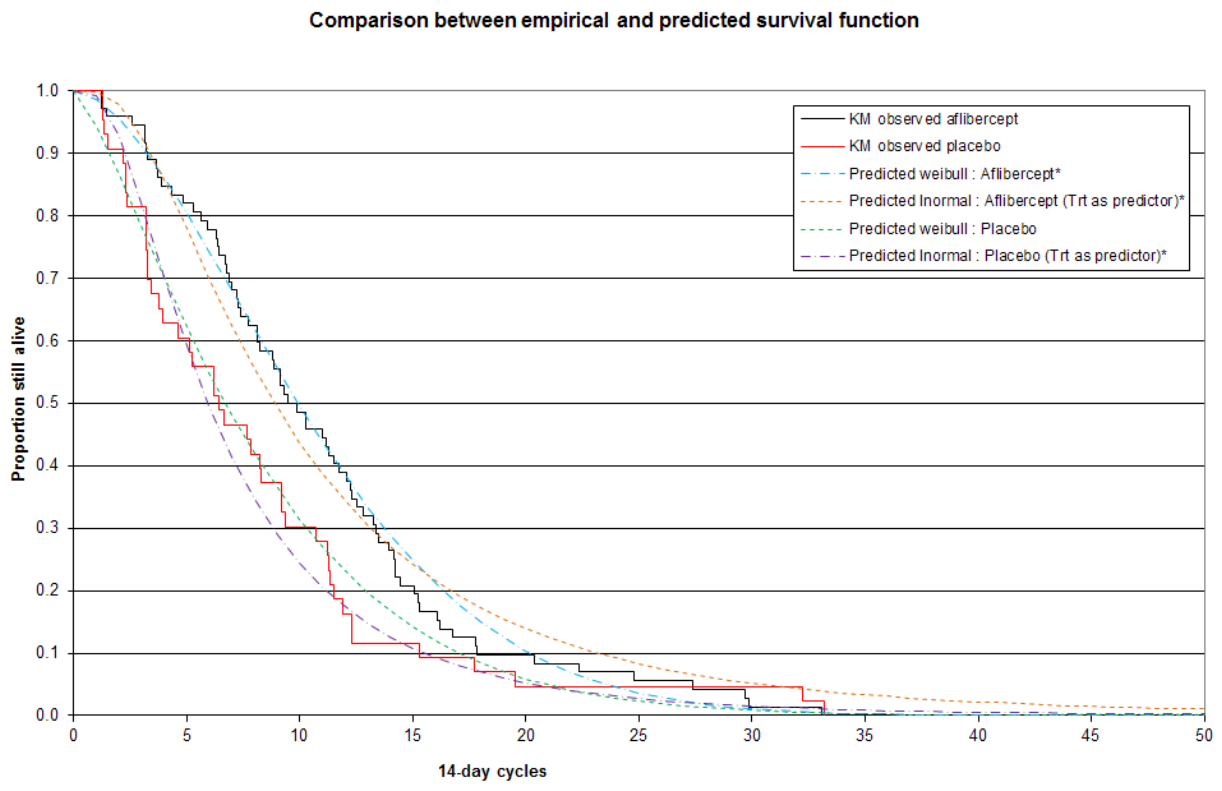
AIC and BIC test results for time to early second-line treatment discontinuation functions, Liver metastases only population

Function	Aflibercept + FOLFIRI		Placebo + FOLFIRI		Both arms (proportional hazards)	
	AIC	BIC	AIC	BIC	AIC	BIC
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Values in red font indicate the lowest AIC and BIC values.

AIC, Akaike information criterion; BIC, Bayesian information criterion; FOLFIRI, fluorouracil/leucovorin/irinotecan;

Time to early second-line treatment discontinuation functions and Kaplan-Meier data, Liver mets only [supplemental to Figure B-14]



ITT Excluding Adjuvant Only Population

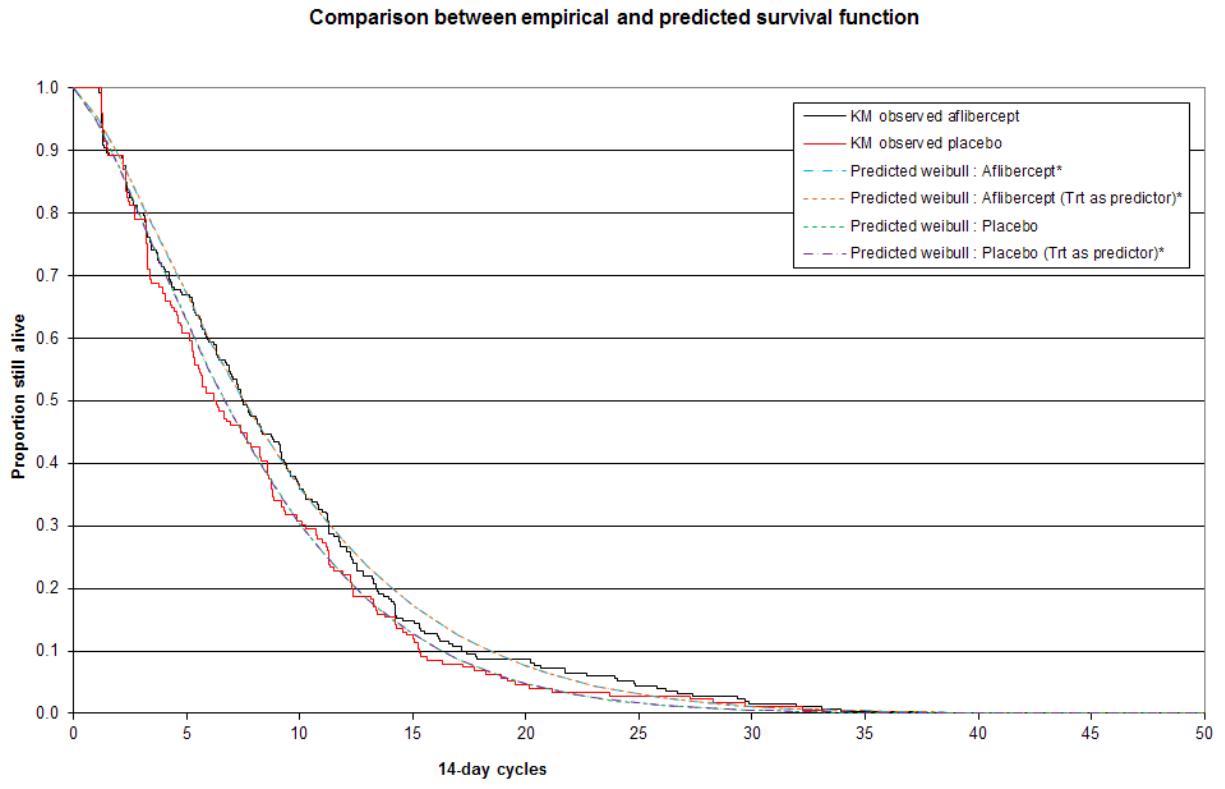
AIC and BIC test results for time to second-line treatment discontinuation functions, ITT Excluding Adjuvant Only population

Function	Aflibercept + FOLFIRI		Placebo + FOLFIRI		Both arms (proportional hazards)	
	AIC	BIC	AIC	BIC	AIC	BIC
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Values in red font indicate the lowest AIC and BIC values.

AIC, Akaike information criterion; BIC, Bayesian information criterion; FOLFIRI, fluorouracil/leucovorin/irinotecan; ITT, intention-to-treat.

Time to second-line treatment discontinuation functions and Kaplan-Meier data, ITT excl. adjuvant [supplemental to Figure B-13]



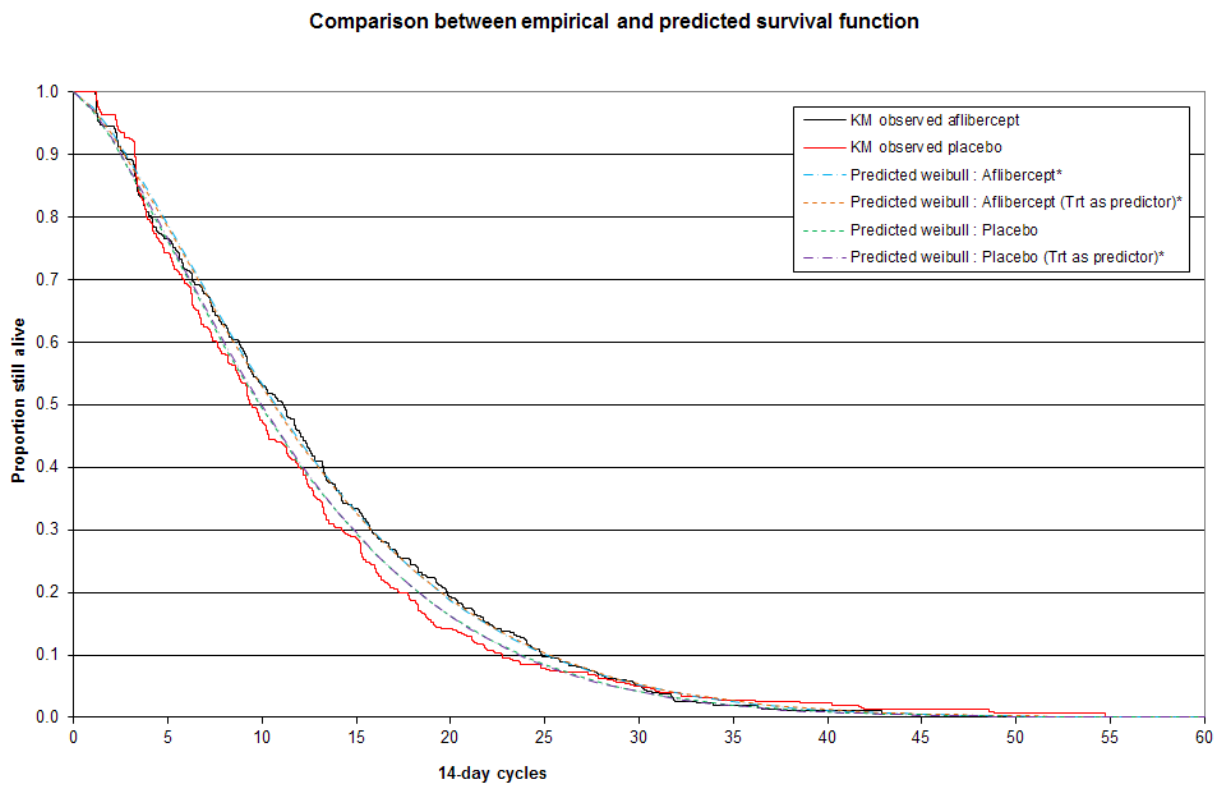
AIC and BIC test results for time to early second-line treatment discontinuation functions, ITT Excluding Adjuvant Only population

Function	Aflibercept + FOLFIRI		Placebo + FOLFIRI		Both arms (proportional hazards)	
	AIC	BIC	AIC	BIC	AIC	BIC
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Values in red font indicate the lowest AIC and BIC values.

AIC, Akaike information criterion; BIC, Bayesian informartion criterion; FOLFIRI, fluorouracil/leucovorin/irinotecan; ITT, intention-to-treat.

Time to early second-line treatment discontinuation functions and Kaplan-Meier data, ITT excl. adjuvant [supplemental to Figure B-14]



Patient Sub-groups

A25. Please provide duration of second-line treatment, number of administrations per cycle, dose intensity per administration, weight and BSA distributions, and AE probabilities for the i) liver metastases only subgroup, and ii) ITT excluding patients relapsing within 6 months of adjuvant therapy subgroup. These data could not be found in Appendix 15.

Please find below the data requested for the liver metastases only and ITT excluding adjuvant only subgroups. There were two typos, firstly the reference should have been to Appendix 14 and secondly the text should have referred to AE frequencies not probabilities.

Treatment Duration, Dose, and Number of Administrations

Mean of second line treatment dose per administration for ITT and subgroups of interest is summarised in Table 5.

Table 5: Second-line Treatment Dose per Administration

		ITT		Liver Metastases Only		ITT Excluding Adjuvant Only	
		Aflibercept + FOLFIRI	FOLFIRI	Aflibercept + FOLFIRI	FOLFIRI	Aflibercept + FOLFIRI	FOLFIRI
Aflibercept	mg/kg	[redacted]		[redacted]		[redacted]	
Folinic acid	(mg/m2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5-FU	(mg/m2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Irinotecan	(mg/m2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Mean and standard error of second line treatment duration for ITT and subgroups of interest is summarised in Table 6

Table 6: Second-line Treatment Duration (overall treatment study exposure)

		Duration in Weeks	Standard Error
ITT	**Aflibercept + FOLFIRI**	[redacted]	[redacted]
	FOLFIRI	[redacted]	[redacted]
Liver metastases only	**Aflibercept + FOLFIRI**	[redacted]	[redacted]
	FOLFIRI	[redacted]	[redacted]
ITT excluding adjuvant only	**Aflibercept + FOLFIRI**	[redacted]	[redacted]
	FOLFIRI	[redacted]	[redacted]

Average total number of second-line treatment administrations for ITT and subgroups of interest is summarised in Table 7.

Table 7: Total Number of Second-line Treatment Administrations

	ITT		Liver Metastases Only		ITT Excluding Adjuvant Only	
	Aflibercept + FOLFIRI	**FOLFIRI**	**Aflibercept + FOLFIRI**	**FOLFIRI**	**Aflibercept + FOLFIRI**	**FOLFIRI**
Aflibercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Folinic acid	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5-FU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Irinotecan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Inputs Used to Calculate Weight Reparation

Mean weight and BSA and standard error of all weights and BSA at baseline and treatment phase in patients in Western Europe for ITT and subgroups of interest is summarised in Table 8.

Table 8: Mean weight and BSA of all weights and BSA at baseline and treatment phase - Western Europe

ITT (Safety)	**Weight (kg)**	**BSA (m^2)**
N	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SE	[redacted]	[redacted]
Liver metastases only		
N	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SE	[redacted]	[redacted]
ITT Excluding Adjuvant Only		
N	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SE	[redacted]	[redacted]

Weight distributions according to available vial combinations for ITT and subgroups of interest in patients from Western Europe are summarised in Table 9.

Table 9: Weight distributions according to available vial combinations - Western Europe

Group	Vial Dose (mg)	CAT	Frequency Count	Percent of Total Frequency
ITT (Safety)	200	[25.84 51.68]	[redacted]	[redacted]
	300	[51.68 77.52]	[redacted]	[redacted]
	400	[77.52 103.36]	[redacted]	[redacted]
	500	[103.36 129.2]	[redacted]	[redacted]
	600	[129.2 -]	[redacted]	[redacted]
Liver metastases only	200	[25.91 51.81]	[redacted]	[redacted]
	300	[51.81 77.72]	[redacted]	[redacted]
	400	[77.72 103.63]	[redacted]	[redacted]
	500	[103.63 129.53]	[redacted]	[redacted]
ITT Excluding Adjuvant Only	200	[25.84 51.68]	[redacted]	[redacted]
	300	[51.68 77.52]	[redacted]	[redacted]
	400	[77.52 103.36]	[redacted]	[redacted]
	500	[103.36 129.2]	[redacted]	[redacted]
	600	[129.2 -]	[redacted]	[redacted]

Rate of AEs While on Second Line Treatment

Rate of grade III and IV treatment emergent AEs while on second line treatment for ITT and subgroups of interest are summarised in Table 10.

Table 10: Frequency of Adverse Events

Sum Person 14-Day Cycles Under Treatment	**8,188.57**	**7,631.29**	**2,134.57**	**1,692.50**	**7,431.71**	**6,885.50**
	ITT		**Liver Metastases Only**		**ITT excluding adjuvant only**	
	Afliberce pt + FOLFIRI	**FOLFIRI**	**Afliberce pt + FOLFIRI**	**FOLFIRI**	**Afliberce pt + FOLFIRI**	**FOLFIRI**
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dehydration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neuropathy peripheral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infections	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hand-foot syndrome	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GI perforation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Section B: Clarification on cost-effectiveness data

Utility Study

B1. Please provide the mean and median time since progression for those patients in the utility study that had progressed.

Time from progression of 2nd line treatment to informed consent is displayed in the table below (interim analysis):

-	-	Health state : progression
		[redacted]
Time from progression 2nd line to informed consent (Months)	N	[redacted]
	Mean (SD)	[redacted]
	Median	[redacted]
	Min ; Max	[redacted]
	Q1 - Q3	[redacted]
21st December 2012 data base		

B2. Please provide the mean and median time since diagnosis for those patients in the utility study that had progressed, as well as for those that were in stable states.

The mean and median time from diagnosis to date of informed consent are provided in the utility study report supplied in response to the ERG request of 22nd Feb, and are provided in the table below.

Table 11: Time from diagnosis to consent, observational utilities study

-	-	Health state : 2nd line stable (N= 36)	Health state : 3rd line stable / BSC (N= 3)	Health state : progression (N= 32)	Overall (N= 71)
Time from diagnosis to date of informed consent (Months)	N	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]	[redacted]
	Min ; Max	[redacted]	[redacted]	[redacted]	[redacted]
	Q1 ; Q3	[redacted]	[redacted]	[redacted]	[redacted]

Adverse events

B3. On p. 89 it is mentioned that six additional rare events were included in the evaluation, as they were considered relevant by the clinical advisory board. Please name those events, and provide further explanation on the rationale underlying the clinical advisory board recommendation to include them.

The rare events were as follows:

- Gastrointestinal perforation
- Haemorrhage
- Febrile neutropenia
- Peripheral neuropathy
- Urinary tract infections
- Hand-foot syndrome

The rationale for inclusion was that while the incidence of these was rare in the VELOUR study these can have a serious impact on both utility and QoL. For example febrile neutropenia is generally recognised as a clinically serious consequence of neutropenia (laboratory neutropenia itself does not necessarily have a serious impact on the patient). Haemorrhage and gastrointestinal perforation are recognised as rare but serious adverse events associated with anti-angiogenic therapies.

Costs

B4. Please clarify what is included in 'regimen changes' costs for Stable, discontinued second-line therapy, and Progressed health states respectively, presented in table B24 (p. 93-94).

The resource use data for regimen change costs was sourced from the KOL questionnaire. Resource use estimates were applied to NHS unit costs to calculate total costs. Resource use and unit costs applied are shown in the tables below for Stable, discontinued second-line therapy, and Progressed following second-line treatment.

Table 12: Regimen change costs, Stable - discontinued second-line therapy

One off cost at time of regimen change	**Resource use estimate**	**Unit costs (£)**	**Total cost (£)**
Hospitalization			
% requiring ITU stay	[redacted]		
Length of ITU stay	[redacted]	654	
% requiring General Ward stay	[redacted]		
Length of General ward stay	[redacted]	302.82	[redacted]
	[redacted]		
Number of physician visit at hospital	[redacted]		
Oncologist	[redacted]	123.71	
Nurse	[redacted]	35	
Pain specialist	[redacted]	114.63	
Specialist nurse	[redacted]	43	
Palliative care team	[redacted]	270.05	[redacted]
	[redacted]		
Number of physician visit - community based	[redacted]		
GP	[redacted]	48	
District nurse	[redacted]	51	
Palliative care team	[redacted]	270.05	[redacted]
	[redacted]		
Imaging	[redacted]		
Contrast enhanced CT of chest, abdomen or pelvis	[redacted]	119.98	
Colonoscopy	[redacted]	276.32	
MRI of the pelvis	[redacted]	163.49	
PET-CT of the whole body	[redacted]	779.63	
Other, please specify	[redacted]		
	[redacted]	0	[redacted]
Laboratory tests at time of regimen change	[redacted]		
Calcium (Ca++)	[redacted]	1.23	
Full blood count (FBC)	[redacted]	3.09	
Glucose level	[redacted]	1.23	
Liver function test	[redacted]	8.61	
Renal function test	[redacted]	12.30	
Serum carcinoembryonic antigen tests	[redacted]	1.23	
Other, please specify	[redacted]	0	[redacted]
	[redacted]		
One off cost at time of regimen change	[redacted]		[redacted]

Table 13: Regimen change costs, progression

One off cost at time of progression	Resource use estimate	Unit costs (£)	Total cost(£)
Hospitalization			
% requiring ITU stay	[redacted]		
Length of ITU stay	[redacted]	654	
% requiring Genral Ward stay	[redacted]		
Length of General ward stay	[redacted]	302.82	[redacted]
Number of physician visit at hospital			
Oncologist	[redacted]	123.71	
Nurse	[redacted]	35	
Pain specialist	[redacted]	114.63	
Specialist nurse	[redacted]	43	
Palliative care team	[redacted]	270.05	[redacted]
Number of physician visit - community based			
GP	[redacted]	48	
District nurse	[redacted]	51	
Palliative care team	[redacted]	270.05	[redacted]
Imaging	[redacted]		
Contrast enhanced CT of chest, abdomen or pelvis	[redacted]	119.98	
Colonoscopy	[redacted]	276.32	
MRI of the pelvis	[redacted]	163.49	
PET-CT of the whole body	[redacted]	779.63	
Other, please specify	[redacted]	0	[redacted]
Laboratory tests at time of progression	[redacted]		
Calcium (Ca++)	[redacted]	1.23	
Full blood count (FBC)	[redacted]	3.09	
Glucose level	[redacted]	1.23	
Liver function test	[redacted]	8.61	
Renal function test	[redacted]	12.30	
Serum carcinoembryonic antigen tests	[redacted]	1.23	
Other, please specify	[redacted]		
One off cost at time of progression	[redacted]	[redacted]	[redacted]

Model

B5. **Priority Question:** Please provide a version of the economic model that incorporates the use of the Gompertz distribution to model PFS and OS for the ITT population and subgroups. The model should include data that allows the modelling of the curves separately or as a proportional hazards model. If this is not possible please provide the full set of distribution parameters, variance and covariance matrices, and Cholesky decomposition matrices for the Gompertz distribution.

Unfortunately it was not possible to provide a full version of the economic model incorporating the Gompertz distribution in the time available. A full set of parameters and variance/covariance matrices for PFS and OS are provided in attached documents. The Gompertz distribution was not included in the original submission due to the fact that according to AIC and BIC criteria, it is a relatively poor fit to the data.

B6. **Priority Question:** In the Efficacy Inputs sheet cell F7 there is a comment stating that the Kaplan Meier option is not available in the current version of the model. Nonetheless, there is a Kaplan Meier option on the drop-down list. Please clarify what does this option refer to, and if it is not to the Kaplan Meier curve for OS, please include a version of the model that incorporates the OS Kaplan Meyer curve from VELOUR study to model OS for ITT and subgroups.

The formatting in the model is unclear; this option does indeed refer to the Kaplan-Meier curve for OS. However, this option is only available for the ITT population and not for the subgroups, hence the original, somewhat confusing label.

B7. There are two possible Kaplan Meier curves estimates for the "Early 2nd line treatment discontinuation while in stable health state" curve in the Efficacy Inputs sheet: i) IRC,and ii) Investigator. However, in the submission there is no mention that this parameter could take different values depending on IRC or investigator assessment (as was the case for PFS). Please clarify the rationale for the inclusion of these curves and the differences between them.

The reason for this is that patients are defined as having "Early 2nd line discontinuation" based on whether or not they discontinued prior to progression. Because progression could be defined according to IRC review or investigator assessment, time to early second line discontinuation could be affected according to the definition of progression taken. We have used IRC definition throughout as our clinical and economic base-case as the most objective and unbiased measurement, and therefore we have solely used the IRC defined curve in our results.

Results

B8. Please provide equivalent results to those presented in table 10-24 (p. 60 in Appendices) for the patient subgroups that had no liver metastases and those that had metastases in the liver and other locations.

Unfortunately, we are not able to undertake these extensive new analyses in the time available. Moreover, we do not understand how they would help in the Committee's consideration of the evidence, as at present we have no compelling clinical or statistical argument to recommend the subgroups proposed in question B8 over those already presented for consideration by the Appraisal Committee.

In line with the decision problem outlined in the NICE scope we present the licensed population (ITT population) as the base-case.

Two subgroups were proposed in our submission for additional consideration in the economic analysis because of a compelling clinical argument;

i) the subgroup of patients with metastases confined to the liver on the basis that this was the only pre-specified subgroup that showed an interaction by treatment effect;

ii) the subgroup that excluded patients who had progressed following adjuvant therapy, on the grounds that the excluded group is a patient population known to have a poor prognosis and which may have genetic changes that make them less sensitive to chemotherapy (this subgroup was discussed with the EMA and has been included in the SPC).

Both of these subgroups have been highlighted by clinicians as representing clinically relevant subpopulations, and both were discussed at the Decision Problem meeting with NICE as relevant subgroups for the Committee to consider.

B9. Please provide equivalent results to those presented in table 10-25 (p. 62 in Appendices) for the patient subgroup that corresponds to patients who had relapsed on or within 6 months of adjuvant treatment in the VELOUR trial, and who were excluded from the ITT population in the post-hoc subgroup analysis.

The same answer applies as for B8.

B10. Please report the ICER using the OS HR from the covariate models and the ICERs for the 5% and 95% CI bounds of these HRs.

ICER estimates using the proportional hazards OS functions (fitted with treatment as a covariate) are presented below. These results were not included in the submission so as to keep the document concise, and a case had been made that because there is evidence of mild non-proportionality of hazards, treatments modelled separately was the most appropriate approach.

The log-cumulative hazards plots are non-parallel and cross over one another (Figure B6 of the submission). Furthermore, the piecewise model calculating HRs by 6-month periods showed improvement in the HR over time, consistent with the survival curves that continue to separate past the median time point, indicating that the magnitude of the aflibercept treatment effect continues to increase over time (Ruff 2013) (Table B9 of the submission). Therefore, the proportional hazards functions may be considered to provide an inferior fit to the log-logistic functions fitted to each treatment group separately, which were used for the base-case analysis in the submission.

Similar findings were observed for the ITT excluding adjuvant therapy subgroup. For the isolated liver metastases subgroup, the log-cumulative hazard plots for the two treatment arms were reasonably parallel indicating that the proportional hazards assumption may be valid. However, the curves crossed over one another early in the follow-up period.

Item B10 also requests ICER estimates for the 5% and 95% CI bounds of the HRs from the covariate models. We are not totally clear what is being requested. If the request is for ICER estimates using the 95% confidence intervals for the treatment effect (i.e. the 2.5% and 97.5% points on the distribution), we would point out that the uncertainty in the treatment effect is explored via the probabilistic sensitivity analysis which draws the intercept, scale and treatment parameters from correlated normal distributions by use of the variance-covariance matrix and Cholesky decomposition. This approach is preferred over a simplistic analysis applying the 2.5% and 97.5% bounds of the HR distribution as correlations between the survival function parameters, as well as uncertainty in other model parameters, are accounted for. The results of the PSA using the OS functions fitted with treatment as a covariate are presented below,

expressed as the probability of cost-effectiveness at a willingness-to-pay threshold of £50,000/QALY.

Table 14: Results of scenario analyses: ITT population

Parameter	Base-case	Scenario	Incremental costs[a]	Incremental QALYs[a]	ICER	Prob CE[a]
Base case results			8,816	0.2429	36,294	
OS function	8,029	0.1366	8,029	0.1366	58,784	32.38%
	8,013	0.1315	8,013	0.1315	60,941	30.02%
	8,241	0.1495	8,241	0.1495	55,116	37.58%

[a] Probability of cost-effectiveness at a willingness-to-pay threshold of £50,000/QALY

Table 15: Results of scenario analyses: Liver metastases only population

Parameter	Base-case	Scenario	Incremental costs[a]	Incremental QALYs[a]	ICER	Prob CE[a]
Base case results			11,283	0.3600	31,340	
OS function	Log-logistic, separate treatment groups	Loglogistic, proportional hazards	10,861	0.3013	36,044	85.98%
		Log-normal, proportional hazards	11,013	0.3110	35,412	85.30%
		Weibull, proportional hazards	10,795	0.2802	38,525	85.72%

[a] Probability of cost-effectiveness at a willingness-to-pay threshold of £50,000/QALY

Table 16: Results of scenario analyses - ITT excluding adjuvant population

Parameter	Base-case	Scenario	Incremental costs[a]	Incremental QALYs[a]	ICER	Prob CE[a]
Base case results			8,828	0.2640	33,436	
OS function	Log-logistic, separate treatment groups	Loglogistic, proportional hazards	8,073	0.1608	50,221	53.60%
		Log-normal, proportional hazards	8,095	0.1596	50,722	49.98%
		Weibull, proportional hazards	8,282	0.1725	48,020	61.62%

[a] Probability of cost-effectiveness at a willingness-to-pay threshold of £50,000/QALY

Sensitivity analyses

B11. Please report base case values and upper and lower bounds for all parameters explored in the one way sensitivity analyses for ITT and both subgroups analyses.

These are shown in the Table 14 below. As a point of clarification, the Tornado diagram presented in the submission only included the 20 parameters with the largest impact on the ICER (as otherwise the diagram would have been extremely large).

Table 17: Upper and lower bounds for deterministic sensitivity analyses

Parameter	Base Case	Lower Bound	Upper Bound
Average weight	75.31	52.83	98.11
Body surface area	1.85	1.30	2.42
Drug cost per cycle			
Aflibercept + FOLFIRI	[redacted]	[redacted]	[redacted]
FOLFIRI	[redacted]	[redacted]	[redacted]
Administration cost per cycle			
Aflibercept + FOLFIRI	[redacted]	[redacted]	[redacted]
FOLFIRI	[redacted]	[redacted]	[redacted]
Treatment cost: Stable, non progressive on 2nd line treatment			
Aflibercept + FOLFIRI	[redacted]	[redacted]	[redacted]
FOLFIRI	[redacted]	[redacted]	[redacted]
Treatment cost: Discontinued 2nd line treatment			
Active treatment	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]
Treatment cost: Progressive disease			
Active treatment	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]
Cost of regimen change			
Discontinued 2nd line treatment	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]
Utility per health state			
Stable, no progression			
On 2nd line treatment	[redacted]	[redacted]	[redacted]
Discontinued 2nd line treatment	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]
Disutility loss due to AE per cycle			
Aflibercept + FOLFIRI	0.01	0.01	0.02
FOLFIRI	0.01	0.01	0.02
Cycle rate of adverse events (number of events observed/total number of cycles administered)			
Aflibercept + FOLFIRI	0.12	0.06	0.12
FOLFIRI	0.06	0.03	0.06
Weigthed average costs for adverse events per comparator			

Parameter	Base Case	Lower Bound	Upper Bound
Aflibercept + FOLFIRI	[redacted]	[redacted]	[redacted]
FOLFIRI	[redacted]	[redacted]	[redacted]
Early 2nd line treatment discontinuation - FOLFIRI vs. Aflibercept + FOLFIRI	[redacted]	[redacted]	[redacted]
2nd line treatment discontinuation - FOLFIRI vs. Aflibercept + FOLFIRI	[redacted]	[redacted]	[redacted]
Time to progression: FOLFIRI vs. Aflibercept + FOLFIRI	[redacted]	[redacted]	[redacted]
Overall survival - FOLFIRI vs. Aflibercept + FOLFIRI	[redacted]	[redacted]	[redacted]
Subsequent treatment Cost			
Pre-progression	[redacted]	[redacted]	[redacted]
Post progression	[redacted]	[redacted]	[redacted]
Dosage per administration			
Aflibercept+FOLFIRI			
Aflibercept	[redacted]	[redacted]	[redacted]
Folinic acid	[redacted]	[redacted]	[redacted]
5-FU	[redacted]	[redacted]	[redacted]
Irinotecan	[redacted]	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]	[redacted]
Panitumumab	[redacted]	[redacted]	[redacted]
Mitomycin	[redacted]	[redacted]	[redacted]
Cetuximab	[redacted]	[redacted]	[redacted]
D5W	[redacted]	[redacted]	[redacted]
FOLFIRI			
Aflibercept	[redacted]	[redacted]	[redacted]
Folinic acid	[redacted]	[redacted]	[redacted]
5-FU	[redacted]	[redacted]	[redacted]
Irinotecan	[redacted]	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]	[redacted]
Panitumumab	[redacted]	[redacted]	[redacted]
Mitomycin	[redacted]	[redacted]	[redacted]
Cetuximab	[redacted]	[redacted]	[redacted]
D5W	[redacted]	[redacted]	[redacted]
Number of administrations			
Aflibercept+FOLFIRI			
Aflibercept	[redacted]	[redacted]	[redacted]
Folinic acid	[redacted]	[redacted]	[redacted]
5-FU	[redacted]	[redacted]	[redacted]
Irinotecan	[redacted]	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]	[redacted]
Panitumumab	[redacted]	[redacted]	[redacted]
Mitomycin	[redacted]	[redacted]	[redacted]
Cetuximab	[redacted]	[redacted]	[redacted]

Parameter	Base Case	Lower Bound	Upper Bound
D5W	[redacted]	[redacted]	[redacted]
FOLFIRI	[redacted]	[redacted]	[redacted]
Aflibercept	[redacted]	[redacted]	[redacted]
Folinic acid	[redacted]	[redacted]	[redacted]
5-FU	[redacted]	[redacted]	[redacted]
Irinotecan	[redacted]	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]	[redacted]
Panitumumab	[redacted]	[redacted]	[redacted]
Mitomycin	[redacted]	[redacted]	[redacted]
Cetuximab	[redacted]	[redacted]	[redacted]
D5W	[redacted]	[redacted]	[redacted]
Administration cost of subsequent treatment			
Pre-progression	[redacted]	[redacted]	[redacted]
Post progression	[redacted]	[redacted]	[redacted]
BSC drug cost per cycle	[redacted]	[redacted]	[redacted]
* Note: parametric distributions varied by +/- 2 SE (-1.96, 1.96)			
Parametric distribution parameters: Early 2nd line treatment discontinuation while in stable health state			
Aflibercept + FOLFIRI			
Mu (lognormal)	[redacted]	[redacted]	[redacted]
Sigma (lognormal)	[redacted]	[redacted]	[redacted]
Lambda/ Exp (Weibull)	[redacted]	[redacted]	[redacted]
p/ Gamma (Weibull)	[redacted]	[redacted]	[redacted]
Lambda (loglogistic	[redacted]	[redacted]	[redacted]
Gamma (loglogistic)	[redacted]	[redacted]	[redacted]
FOLFIRI			
Mu (lognormal)	[redacted]	[redacted]	[redacted]
Sigma (lognormal)	[redacted]	[redacted]	[redacted]
Lambda/ Exp (Weibull)	[redacted]	[redacted]	[redacted]
p/ Gamma (Weibull)	[redacted]	[redacted]	[redacted]
Lambda (loglogistic	[redacted]	[redacted]	[redacted]
Gamma (loglogistic)	[redacted]	[redacted]	[redacted]
Parametric distribution parameters: Time to Progression			
Aflibercept + FOLFIRI			
Mu (lognormal)	[redacted]	[redacted]	[redacted]
Sigma (lognormal)	[redacted]	[redacted]	[redacted]
Lambda/ Exp (Weibull)	[redacted]	[redacted]	[redacted]
p/ Gamma (Weibull)	[redacted]	[redacted]	[redacted]
Lambda (loglogistic	[redacted]	[redacted]	[redacted]
Gamma (loglogistic)	[redacted]	[redacted]	[redacted]

Parameter	Base Case	Lower Bound	Upper Bound
FOLFIRI			
Mu (lognormal)	[redacted]	[redacted]	[redacted]
Sigma (lognormal)	[redacted]	[redacted]	[redacted]
Lambda/ Exp (Weibull)	[redacted]	[redacted]	[redacted]
p/ Gamma (Weibull)	[redacted]	[redacted]	[redacted]
Lambda (loglogistic	[redacted]	[redacted]	[redacted]
Gamma (loglogistic)	[redacted]	[redacted]	[redacted]
Parametric distribution parameters: Overall survival			
Aflibercept + FOLFIRI			
Mu (lognormal)	[redacted]	[redacted]	[redacted]
Sigma (lognormal)	[redacted]	[redacted]	[redacted]
Lambda/ Exp (Weibull)	[redacted]	[redacted]	[redacted]
p/ Gamma (Weibull)	[redacted]	[redacted]	[redacted]
Lambda (loglogistic	[redacted]	[redacted]	[redacted]
Gamma (loglogistic)	[redacted]	[redacted]	[redacted]
FOLFIRI			
Mu (lognormal)	[redacted]	[redacted]	[redacted]
Sigma (lognormal)	[redacted]	[redacted]	[redacted]
Lambda/ Exp (Weibull)	[redacted]	[redacted]	[redacted]
p/ Gamma (Weibull)	[redacted]	[redacted]	[redacted]
Lambda (loglogistic	[redacted]	[redacted]	[redacted]
Gamma (loglogistic)	[redacted]	[redacted]	[redacted]
Parametric distribution parameters: 2nd line treatment discontinuation			
Aflibercept + FOLFIRI			
Mu (lognormal)	[redacted]	[redacted]	[redacted]
Sigma (lognormal)	[redacted]	[redacted]	[redacted]
Lambda/ Exp (Weibull)	[redacted]	[redacted]	[redacted]
p/ Gamma (Weibull)	[redacted]	[redacted]	[redacted]
Lambda (loglogistic	[redacted]	[redacted]	[redacted]
Gamma (loglogistic)	[redacted]	[redacted]	[redacted]
FOLFIRI			
Mu (lognormal)	[redacted]	[redacted]	[redacted]
Sigma (lognormal)	[redacted]	[redacted]	[redacted]
Lambda/ Exp (Weibull)	[redacted]	[redacted]	[redacted]
p/ Gamma (Weibull)	[redacted]	[redacted]	[redacted]
Lambda (loglogistic	[redacted]	[redacted]	[redacted]
Gamma (loglogistic)	[redacted]	[redacted]	[redacted]

Section C: Textual clarifications and additional points

C1. In Section 4, the submission states that aflibercept is the only drug to demonstrate a statistically significant OS benefit in combination with FOLFIRI in such patients (patients with mCRC who have been treated with an oxaliplatin-based therapy). Please provide the supporting references for this statement.

The clinical systematic review did not identify any trials other than VELOUR which demonstrated a significant OS benefit for an agent in combination with FOLFIRI. Two studies were identified of agents in combination with FOLFIRI - Peeters 2010, evaluating the addition of panitumumab to FOLFIRI, and Peeters 2011 which evaluated the addition of AMG286 to FOLFIRI. Neither showed a significant OS benefit. The recent TML trial which evaluated continuation of bevacizumab treatment beyond progression after first-line therapy included a subgroup of patients treated with FOLFIRI following oxaliplatin but this only represented 16% of the total sample (Benouna 2012). While it is not possible to state definitively that there are no possible unpublished trials demonstrating a significant OS benefit, to the best of our knowledge the VELOUR trial is the only trial to demonstrate a statistically significant OS benefit in combination with FOLFIRI in oxaliplatin-treated patients.

C2. Please clarify the a priori subgroup relating to liver metastases. On p. 49 (Baseline characteristics) it suggests the subgroups are whether patients had liver metastases or not.

The wording on p49 is unclear, the subgroup is patients who had only liver metastases; the converse group is patients who had no liver metastases or who had metastases beyond the liver.

C3. Please explain why the drug name aflibercept (and related terms) was not searched for in the search strategy.

The reason for this is that there was no limitation with regards to the intervention. We were looking for second line interventions (regardless of the intervention).

C4. Please state which host was used for the EMBASE search strategy, and explain why MESH terms were used, rather than EMTREE terms in the EMBASE search at line 1.

The EMBASE search was conducted through the following interface: http://www.embase.com/search/advanced. The terms used in our search of MEDLINE (via PubMed) were translated into free text and tested in EMBASE. We also investigated the use of corresponding EMTREE terms to search EMBASE. However, the inclusion of EMTREE terms did not result in any additional hits beyond those identified via free text terms (line 1 to line 4). In addition, free text terms were not affected by any potential indexing errors or bias. Therefore, the free text terms were utilised rather than the EMTREE terms, and this also provided consistency between searches of MEDLINE (via PubMed) and EMBASE.

C5. There is some text missing on the row referring to the Wiering (2011) study on table B26 (p. 107). Please complete the table.

Due to a formatting error the complete text for Wiering (2011) did not appear. The full entry for Wiering is given below:

Wiering, 2011	145 patients with a history of proven colorectal cancer treated by surgical resection and suspicion of up to 4 potentially resectable colorectal liver metastases without evidence of extrahepatic metastatic disease. Laparotomy for hepatic resection was generally performed within 4 weeks after inclusion. Surgical treatment was performed only if it was deemed feasible to remove all liver lesions adequately. None of the patients received pre-operative chemotherapy.	The EQ-5D was used as a generic value-based HRQL instrument. The EQ-5D index was obtained by applying predetermined weights to the 5 domains derived from the general public (Dolan, 1997). Baseline EQ-5D forms were completed in hospital, and subsequent forms were sent to the patient's postal address 3 weeks and 6 weeks after surgery and every 3 months thereafter for the next 3 years.	**Health state**	**Mean/no. observations (SD)**
			Disease-free	0.78/891 (0.23)
			Non-curative	0.67/162 (0.31)
			Recurrence	0.74/450 (0.25)
			Without chemotherapy	0.82/205 (0.17)
			With chemotherapy	0.68/245 (0.28)

AWMSG, All Wales Medicines Strategy Group; BSC, best supportive care; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EQ-5D, EuroQoL 5-dimension health questionnaire; FACT, Functional Assessment of Cancer Therapy; FOLFIRI, irinotecan plus 5-fluorouracil/leucovorin; FOLFOX, oxaliplatin plus 5-fluorouracil/leucovorin; FOLFOX4, leucovorin 200 mg/m^2 as a 2-hour infusion, followed by bolus 5-fluorouracil 400 mg/m^2 and a 22-hour infusion of 5-fluorouracil 600 mg/m^2 for 2 consecutive days every 14 days, plus a 2-hour infusion of 85 mg/m^2 of oxaliplatin on day 1, given simultaneously with leucovorin; HRQL, health-related quality of life; HUI, Health Utility Index; KRAS, Kirsten rat sarcoma viral oncogene homolog; mCRC, metastatic colorectal cancer; NICE, National Institute for Health and Clinical Excellence; PFS, progression-free survival; QoL, quality of life; SD, standard deviation; SF-36, Short-Form 36-Item Health Survey; TTO, time trade-off; UK, United Kingdom; US, United States; VAS, visual analogue scale; XELOX, capecitabine and oxaliplatin.

[a] Includes information about recruitment, country, sample size, response rate, and interventions received (if any).

[b] Includes elicitation methods (including instrument used), valuation methods, and any mapping performed.

[c] Includes tabulation of 95% CIs or another measure of uncertainty.

C6. Please complete table B4 (p. 44-45) for demographic characteristics by including geographical region (Western Europe, Eastern Europe, North America, South America or other), and mean age, for each treatment group.

Summary of patient demographics and patient characteristics at baseline – ITT population

Study EFC10262 (VELOUR) Baseline characteristic	Placebo+FOLFIRI (N=614)	Aflibercept 4mg/kg+FOLFIRI (N=612)
Age (Years)		
Number	614	612
Median	61.0	61.0
Mean (SD)	60.2 (10.8)	59.5 (10.5)
Min : Max	19 : 86	21 : 82
Region		
Number	614	612
Western Europe	217 (35.3%)	208 (34.0%)
Eastern Europe	136 (22.1%)	161 (26.3%)
North America	75 (12.2%)	63 (10.3%)
South America	56 (9.1%)	62 (10.1%)
Other countries	130 (21.2%)	118 (19.3%)

Note: Other countries = Australia, New Zealand, South Africa and Korea

C7. Please clarify why the mean treatment duration with Aflibercept+FOLFIRI in the VELOUR study is reported as 10.4 cycles in table A-3 (p. 23) and 12.1 cycles in table B35 (p. 131).

To clarify this, the mean treatment duration was [redacted] cycles, in which some or all of the prescribed regimen was received. However, patients may have missed or delayed cycles of any one component of the treatment.

The actual mean number of cycles received was [redacted] cycles of treatment over a [redacted] cycle duration). As outlined in Table B35 and its footnotes, in some cycles patients may have skipped some of the individual regimen components thus the mean and median number of aflibercept cycles differs from the mean and median for irinotecan and 5-FU.