[redacted]

Premeeting briefing

Aflibercept in combination with irinotecan and fluorouracil-based therapy for the treatment of metastatic colorectal cancer which has progressed following prior oxaliplatin-based chemotherapy

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- The ERG suggested that the demographic and disease characteristics of patients in the VELOUR trial meant that they were potentially fitter and younger than those seen in UK clinical practice. Does the Committee consider the trial population to be representative of UK clinical practice?
- Assumptions to estimate mean overall survival
  - The manufacturer assumed that there were patients who experienced a sustained survival benefit following treatment with aflibercept. The ERG stated that this assumption is highly uncertain, and it considered that the available evidence suggested a constant incremental benefit at all times. What is the Committee's view on the most appropriate assumption to extrapolate overall survival?

  - The manufacturer extrapolated overall survival over 15 years to estimate mean overall survival. The ERG considered that 15 years is very long and does not reflect the duration of treatment benefit that the patient population under consideration is likely to gain. What is the Committee's view on the most appropriate extrapolation period?
- Progression-free survival in the VELOUR trial was assessed by an independent review committee. Disease progression assessed by local investigator was explored by the manufacturer in a sensitivity analysis. The ERG advised that an independent review committee may miss symptoms other than tumour growth caused by disease progression (that is, symptomatic deterioration), which may impact on duration of treatment. Which assessment of disease progression does the Committee consider more appropriate, bearing in mind the protocol stipulated review by an independent committee?
- The ERG advised that the results of the subgroup analysis comprising patients with liver metastasis only and that which excluded patients whose disease had relapsed 6 months or less after starting oxaliplatin-based adjuvant therapy should be interpreted cautiously because the former may be underpowered, and the latter was performed post-hoc so its results may be biased. What is the Committee's view on these subgroups?
- What is the Committee's view on the potential role of aflibercept plus FOLFIRI in shrinking secondary liver metastases?
- What is the Committee's view on the rigour of the estimates contributing to the end-of-life criteria for the overall population and the subgroups?
- Does the technology reflect an innovative treatment?

Cost effectiveness

- The ERG stated that the manufacturer's assumptions to extrapolate overall survival are highly uncertain, and it explored this uncertainty in additional sensitivity analyses. In these, the ERG assumed that the survival benefits of aflibercept plus FOLFIRI and FOLFIRI alone become the same beyond

the trial period (that is, treatment effect does not continue beyond the trial period), or that the survival benefits of aflibercept plus FOLFIRI and FOLFIRI alone converge over the extrapolation period. What is the Committee's view on the most appropriate assumption to extrapolate overall survival?

- Utility estimates in the analysis
  - The ERG had concerns about the generalisability of the utility study from which the manufacturer obtained the utility estimates for the model. Does the Committee consider this study to be representative of UK clinical practice?
  - The ERG considered that the utility value in the model attached to patients whose disease had progressed was too high. What is the utility estimate that the Committee considers appropriate for patients whose disease had progressed?
  - The manufacturer assumed that the utility value for patients whose disease had progressed is constant from disease progression until death. The ERG stated that this assumption is clinically implausible. Does the Committee consider the manufacturer's assumption appropriate?
  - Should the utility values be age-adjusted?
- Resource use and costs
  - The manufacturer assumed that no extra administration costs would be needed to administer aflibercept. The ERG indicated that administering aflibercept requires preparing an additional infusion at an extra cost. In addition, the ERG stated that if aflibercept is given before or after FOLFIRI, instead of at the same time, administering aflibercept would include an additional hour of infusion time. What is the Committee's view on the assumptions?
  - In the model, the manufacturer used the median estimate of resource use from its survey of clinical oncologists. The ERG indicated that mean values are most commonly used in cost-effectiveness analyses, and that

the use of medians may underestimate expected costs. Which estimate does the Committee consider more appropriate?

1 Background: clinical need and practice

1.1 Colorectal cancer originates in the lower part of the digestive system, including the colon and rectum. In locally advanced colorectal cancer, tumours grow through the bowel wall and into adjacent tissues, and cancer cells can be found in surrounding lymph nodes, but not elsewhere in the body. In metastatic disease, the cancer spreads beyond the confines of local or regional lymph nodes to other organs of the body.

1.2 Approximately 35,600 people were diagnosed with colorectal cancer in England and Wales in 2010. The prevalence of colorectal cancer increases with age (median age at diagnosis is over 70 years), from 35 per 100,000 in people younger than 60 years, to 345 per 100,000 in people over 75 years. The overall 5-year survival rate for colorectal cancer in England and Wales is more than 50%; however, large differences in duration of survival exist according to the stage of disease at diagnosis. For example, over 93% of people diagnosed with the earliest stage of the disease (Stage A on the modified Dukes' classification) in England between 1996 and 2002 survived for 5 years, but less than 7% of people diagnosed with metastatic disease. At the time of diagnosis, 20–55% of people with colorectal cancer already have metastatic disease. In addition, of the people who have undergone surgery for early-stage colorectal cancer, 50–60% will eventually develop metastatic disease, most commonly in the liver.

1.3 The management of metastatic colorectal cancer is mainly palliative, that is, to relieve symptoms, and combines specialist treatments (such as palliative surgery, chemotherapy and radiation)

with control of symptoms and psychosocial support. However, approximately 8% of people with metastatic colorectal cancer have liver metastases that are potentially respectable by surgery and, in some, chemotherapy may make these liver metastases operable.

1.4 The aim of treatment is to prolong survival and improve quality of life. People with metastatic disease in sufficiently good health (World Health Organisation performance status 2 or better) are usually treated with first-line chemotherapy and then, if their cancer progresses, second-line chemotherapy. For other people, the harms from chemotherapy may outweigh the potential benefits. Therefore, treatment depends on a person's individual circumstances.

1.5 As first-line treatment options for advanced colorectal cancer, NICE recommends oxaliplatin in combination with 5-fluorouracil plus folinic acid (FOLFOX) and capecitabine in combination with oxaliplatin (XELOX) in Colorectal cancer: the diagnosis and management of colorectal cancer (NICE clinical guideline 131). Other first-line treatment options recommended for metastatic colorectal cancer are the oral analogues of 5-fluorouracil; capecitabine or tegafur with uracil (in combination with folinic acid) (Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer [NICE technology appraisal guidance 61]). If metastatic disease is confined to the liver and is of the 'wild-type' (non-mutated) form of the Kirsten rat sarcoma viral oncogene homolog (KRAS) gene, the aim of first-line treatment is to make the metastases resectable surgically, and cetuximab may be given with FOLFOX, or irinotecan in combination with 5-fluorouracil plus folinic acid (FOLFIRI); these recommendations can be found in Cetuximab for the first-line treatment of metastatic colorectal cancer (NICE technology appraisal guidance 176).

1.6 As second-line treatment for people whose disease has progressed despite first-line treatment, Colorectal cancer: the diagnosis and management of colorectal cancer (NICE clinical guideline 131) recommends irinotecan monotherapy or FOLFIRI as an option for people who received FOLFOX as first-line treatment, and FOLFIRI as an option for people who received XELOX as first-line treatment.

2 The technology

2.1 Aflibercept (Zaltrap, Sanofi) is a recombinant human fusion protein that can block the vascular endothelial growth factor (VEGF) pathway by preferentially binding to VEGF-A, VEGF-B and placenta growth factor (PlGF), which play an important role in the formation of new blood vessels in solid tumours (angiogenesis). By preventing these factors from activating their endogenous receptors, aflibercept interferes with the process by which blood vessels and capillaries expand into tumours (vascularisation), and so inhibits tumour growth. Aflibercept in combination with FOLFIRI has a UK marketing authorisation 'for the treatment of adults with metastatic colorectal cancer that is resistant to or has progressed after an oxaliplatin-containing regimen'. The summary of product characteristics states that aflibercept should be administered as an intravenous infusion over 1 hour at a dose of 4 mg/kg of body weight, followed by the FOLFIRI regimen, every 2 weeks until the disease progresses or unacceptable toxicity occurs.

2.2 The summary of product characteristics lists the following most common adverse reactions for aflibercept plus FOLFIRI: leucopenia, diarrhoea, neutropenia, proteinuria, increased plasma activity of aspartate aminotransferase, stomatitis, fatigue, thrombocytopenia, increased plasma activity of alanine aminotransferase, hypertension, weight loss, decreased appetite,

epistaxis, abdominal pain, dysphonia, increased serum creatinine, and headache. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The manufacturer's submission states that the list price of aflibercept is £295.65 per 100 mg vial and £591.30 per 200 mg vial (prices excluding VAT). Based on a mean number of 2-week treatment cycles of [redacted], the manufacturer estimated that the average cost of a course of treatment with aflibercept plus FOLFIRI is [redacted] (including administration costs). This estimate takes into account a patient access scheme that the manufacturer of aflibercept has agreed with the Department of Health, and which offers a discount on the list price of aflibercept. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost effectiveness of aflibercept in combination with irinotecan and fluorouracil-based therapy within its licensed indication for the treatment of metastatic colorectal cancer which has progressed following prior oxaliplatin-based chemotherapy.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	People with metastatic colorectal cancer that is resistant to or has progressed following prior oxaliplatin-based chemotherapy.	
Intervention	Aflibercept in combination with irinotecan and fluorouracil-based therapy	Aflibercept in combination with FOLFIRI (irinotecan plus fluorouracil plus leucovorin)
Comparators	Irinotecan in combination with fluorouracil-based therapy	FOLFIRI

Outcomes	• overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life	
Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	The cost-effectiveness of aflibercept is expressed in terms of incremental cost per QALY. The time horizon for estimating clinical and cost-effectiveness is patients' lifetimes (15 years), to reflect any differences in costs or outcomes between the technologies being compared. Costs are considered from an NHS and PSS perspective.

3.2 The ERG reviewed and critiqued the decision problem in the manufacturer's submission. It stated that the decision problem in relation to the points above was appropriate and consistent with the scope developed by NICE for this appraisal.

Subgroups to be considered	None identified	Subgroups under consideration: • Patients with metastasis confined to the liver • Subgroup excluding patients progressing on or within 6 months of adjuvant treatment

3.3 The manufacturer's submission states that the subgroup of patients with liver metastasis only was recognised as a relevant clinical subgroup for metastatic colorectal cancer in Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid

or capecitabine for the treatment of metastatic colorectal cancer (NICE technology appraisal guidance 212). The manufacturer also considers in its submission the subgroup which excluded patients whose disease had relapsed 6 months or less after starting oxaliplatin-based adjuvant therapy. The manufacturer performed an analysis in this subgroup after the VELOUR trial had reported (post-hoc) as the manufacturer notes that, in the trial, 10% of the patients had cancer that had relapsed 6 months or less after starting oxaliplatin-based adjuvant therapy. The manufacturer states that this outcome typically reflects very aggressive disease and poor prognosis in a subset of patients who may have tumours with genetic changes, and who would therefore be unlikely to benefit from anti-VEGF therapy.

4 Clinical-effectiveness evidence

4.1 The manufacturer undertook a systematic literature review of studies evaluating the efficacy and safety of second-line treatments for metastatic colorectal cancer. It identified 1 relevant randomised controlled trial (RCT), the VELOUR trial, from which it obtained the key clinical evidence. The VELOUR trial was a randomised, double-blind, placebo-controlled phase III study, which was conducted in 176 centres in 28 countries, including the UK. Eligible patients were adults who had inoperable metastatic colorectal cancer, and whose disease progressed on or after treatment with only 1 prior oxaliplatin-based chemotherapy regimen. Investigators randomised patients in a 1:1 ratio to either aflibercept plus FOLFIRI (n=612) or placebo plus FOLFIRI (n=614), and they stratified randomisation by patients' wellbeing and ability to perform daily activities using the Eastern Cooperative Oncology Group Performance Status (ECOG PS) and whether or not the patient had had prior therapy with bevacizumab. Patients received either

aflibercept or placebo intravenously at a dose of 4 mg/kg over 1 hour on day 1, every 2 weeks, immediately followed by intravenous FOLFIRI. During the trial, patients could stop 1 study treatment (aflibercept or placebo, or FOLFIRI) but still receive the other components of the regimen. Treatment continued until disease progressed, unacceptable toxicity occurred (according to clinical judgment) or the patient declined further treatment. Investigators followed up the survival of patients whose disease progressed during the study, and the progression-free survival of those who stopped treatment before disease progression, until the cut-off date of the study (when 863 patients had died during the trial), and they continued to follow some patients who were experiencing adverse events up to 9 months after that date. The median follow-up for the intention-to-treat population at the time of the primary analysis was 22.28 months.

4.2 The primary end point in the VELOUR trial was overall survival, defined as time from randomisation to death from any cause. One of the secondary endpoints was progression-free survival as assessed by an independent review committee based on radiologic progression, and it was determined as time from randomisation to first observation of disease progression (at least a 20% increase in the sum of the longest diameter of target tumours, the unequivocal increase in the size of non-target tumours, or the appearance of 1 or more new tumours) or death from any cause. The manufacturer recorded, and explored in a sensitivity analysis, disease progression determined instead by local investigators assessing lesions and taking into account clinical progression (where the patients' symptoms had worsened). Other secondary end points were objective response (complete and partial responses) according to Response Evaluation Criteria In Solid Tumors

(RECIST) criteria version 1, and adverse events and abnormal laboratory findings.

4.3 The manufacturer stated that patient characteristics and history of disease at baseline were well balanced between the aflibercept and placebo groups. Of the patients randomised in the study, the median age was 61 years, 58.6% were men, 97.8% had a baseline ECOG PS of 0 or 1, and 2.2% had a baseline ECOG PS of 2. The marketing authorisation of aflibercept stipulates prior treatment with an oxaliplatin-containing regimen; in the VELOUR trial, of patients randomised to aflibercept plus FOLFIRI or placebo plus FOLFIRI, 90.2% and 89.4%, respectively, had received prior oxaliplatin-based chemotherapy for locally advanced or metastatic disease. Approximately 10% of patients (9.8% and 10.4% of patients randomised to aflibercept plus FOLFIRI or placebo plus FOLFIRI, respectively) had received prior oxaliplatin-based chemotherapy in the adjuvant setting. Some 30.4% of patients (373) had received oxaliplatin-based regimens in combination with bevacizumab.

4.4 The manufacturer determined that it needed 863 death events to detect a statistically significant 20% risk reduction in the aflibercept group compared with the placebo group (the cut-off date of the study). To estimate time-to-event parameters, the manufacturer used survival analysis, and it calculated hazard ratios and confidence intervals for the primary and subgroup analyses using a Cox proportional hazards model. It also established heterogeneity of treatment effect among subgroups using a Cox proportional hazards model, and provided an interaction test for each subgroup analysis. If a patient neither died nor experienced disease progression during the trial, the manufacturer censored the patient at the date of when the tumour was last assessed or at the cut-off date of the study.

4.5 At the cut-off date of the study, 403 patients (65.8%) randomised to aflibercept and 460 patients (74.9%) randomised to placebo had died. Median overall survival was 1.44 months higher for aflibercept than placebo (aflibercept 13.50 months, placebo 12.06 months), and the corresponding hazard ratio was 0.817 (95.34% CI 0.713 to 0.937, p=0.0032), suggesting a reduction in the risk of death of 18.3% with aflibercept compared with placebo. The probabilities of overall survival at 6, 12, 18, 24 and 30 months were consistently higher in the aflibercept group than in the placebo group; at 6 months the probability of overall survival was 4% higher, and it was 86% higher at 30 months. The manufacturer also calculated hazard ratios for overall survival by 6-month periods up until 18 months, and it combined all time points thereafter in 1 hazard ratio. This analysis showed that hazard ratios improved over time, implying that the longer patients received aflibercept, the more incremental benefit they gained. In response to clarification, the manufacturer provided further hazard ratios and the number of patients at risk of dying by 6-month periods after 18 months (table 1).

Table 1 Hazard ratios for overall survival by 6-month periods

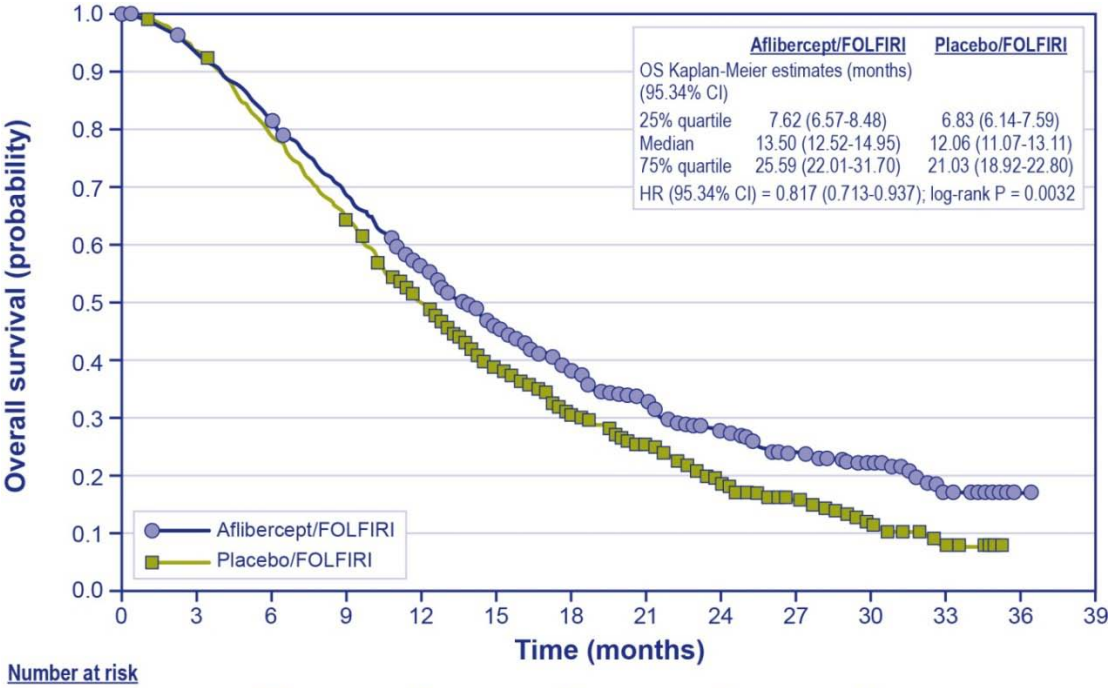
Time (months)	HR[a] (95.34% CI[b]) Aflibercept vs. placebo	Number of deaths	
		Aflibercept	Placebo
$t^c \leq 6$	0.860 (0.664-1.114)	[redacted]	[redacted]
$6 < t^c \leq 12$	0.838 (0.673-1.043)	[redacted]	[redacted]
$12 < t^c \leq 18$	0.782 (0.582-1.050)	[redacted]	[redacted]
$t^c > 18$	0.676 (0.463-0.988)		
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[a]HR, hazard ratio; [b]CI, confidence interval; [c]t, time

4.6 The manufacturer noted that the Kaplan-Meier curves for overall survival (figure 1) separated early and continued to separate over time, suggesting that there were patients who experienced a sustained benefit following treatment with aflibercept. The manufacturer indicated that therefore the difference in median overall survival of 1.44 months may underestimate the overall clinical benefit of adding aflibercept to FOLFIRI. Because of this, the manufacturer estimated the mean overall survival post hoc by fitting separate parametric functions to the trial data for each treatment group, and extrapolating to provide complete curves. It modelled each treatment group separately, rather than modelling treatment as a covariate, because the log-cumulative hazard plots (page 58 of the manufacturer's submission, a diagnostic plot used to evaluate the validly of assuming that a hazard ratio between 2 treatments remains constant over time) were not parallel and crossed over one another. The manufacturer considered the log-logistic function to provide the best fit for overall survival for the 2 treatment groups. The log-logistic function, however, gave a long tail (implying that some patients will live implausibly long), so the manufacturer truncated the curves at 15 years. This approach estimated that aflibercept would extend mean overall survival over placebo by 4.7 months. Without the truncation of the curves, the estimate was 6.6 months. In response to clarification, the manufacturer provided estimates with the analysis truncated at 5 years and 10 years; in this analysis the differences in mean overall survival between the aflibercept and placebo groups were [redacted] and [redacted] respectively. The manufacturer also provided mean overall survivals restricted to patients who had died before the most recent data analysis for each treatment group (that is, an analysis based on actual data rather than an extrapolated

model). This analysis estimated a difference in mean overall survival of [redacted] in favour of aflibercept.

Figure 1 Kaplan-Meier curves of overall survival for the VELOUR trial



Number at risk

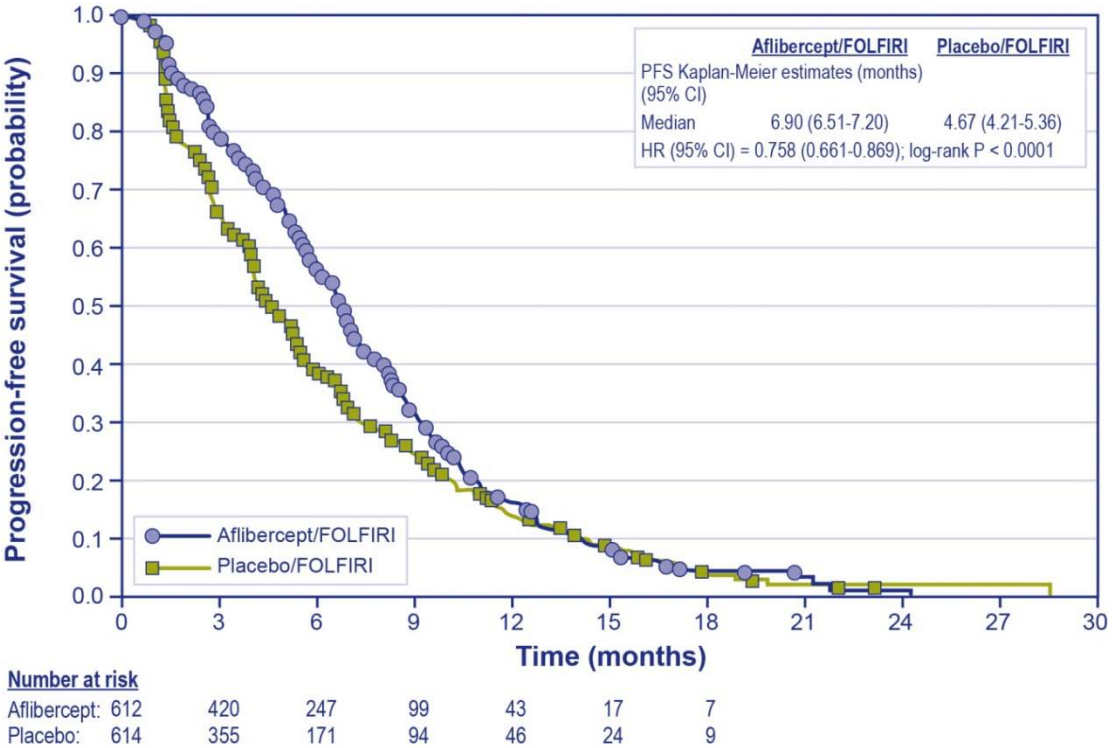
Aflibercept:	612	498	311	148	75	33
Placebo:	614	485	286	131	51	14

Survival probability (%)

Aflibercept:	81.9	56.1	38.5	28.0	22.3
Placebo:	79.1	50.3	30.9	18.7	12.0

4.7 The manufacturer found that adding aflibercept to FOLFIRI also prolonged progression-free survival compared with adding placebo to FOLFIRI (figure 2). The difference in median progression-free survival was 2.23 months (aflibercept 6.90 months, placebo 4.67 months, hazard ratio 0.758 [95% CI 0.661 to 0.869]). For response rate (complete and partial responses), the manufacturer carried out an analysis in 1,061 patients based on the assessment of an independent review committee. It found that aflibercept improved response rate compared with placebo, with a response rate of 19.8% (95% CI 16.4 to 23.2) in the aflibercept group and 11.1% (95% CI 8.5 to 13.8) in the placebo group.

Figure 2 Kaplan-Meier estimates of progression-free survival for the VELOUR trial



4.8 A summary of the results of the efficacy analysis in the overall population is provided in table 2.

Table 2 Summary of the efficacy results of the VELOUR trial

			Placebo + FOLFIRI	Aflibercept + FOLFIRI
Descriptive statistics and estimate variability	Median OS[a] (months, 95% CI[b])		12.1 (11.07 to 13.11)	13.5 (12.52 to 14.95)
	Median PFS[c] (months, 99% CI[b])		4.67 (4.07 to 5.55)	6.90 (5.88 to 7.85)
	Survival probability (95% CI[b])	6 months	0.79 (0.76 to 0.82)	0.82 (0.79 to 0.85)
		12 months	0.50 (0.46 to 0.54)	0.56 (0.52 to 0.60)
		24 months	0.19 (0.15 to 0.23)	0.28 (0.24 to 0.32)
Effect estimate per comparison	Primary end point (OS[a]) Aflibercept vs. placebo		*Hazard Ratio (95% CI[b])*	0.81 (0.71 to 0.94)
	Secondary end point (PFS[c]) Aflibercept vs. placebo		*Hazard Ratio (99% CI[b])*	0.76 (0.58 to 1.00)

[a]OS, overall survival; [b]CI, confidence interval; [c]PFS, progression-free survival

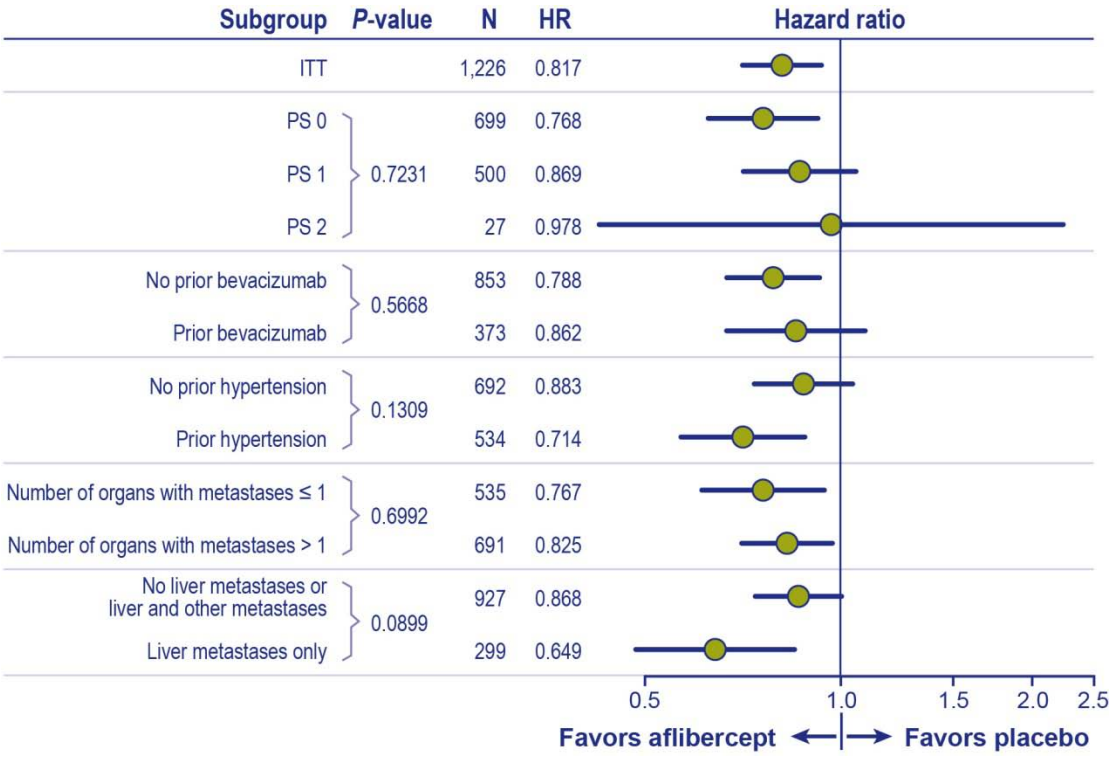
4.9 The manufacturer performed pre-specified subgroup analyses according to the following:

- Baseline characteristics: presence of liver metastasis, location of primary tumour, number of metastatic organs, prior history of hypertension
- Stratification variables: ECOG PS, prior bevacizumab treatment
- Demographic characteristics: age, gender, race, geographical region

4.10 The manufacturer carried out an analysis of overall survival based on the pre-specified subgroups (figure 3). It found no evidence of heterogeneity in treatment effect (non-significant interaction test), except in the subgroup of patients with liver metastasis only (p value for interaction was 0.0899, statistically significant at the 10% level). In patients with liver metastasis only, there was a statistically significant difference in median overall survival of [redacted] (aflibercept [redacted], placebo [redacted]); the hazard ratio for this subgroup was 0.649 (95.34% CI 0.492 to 0.855) compared with a hazard ratio of 0.868 (95.34% CI 0.742 to 1.015) in patients who had no liver metastasis or in whom the cancer spread to the liver and other organs. In response to clarification, the manufacturer provided the difference in mean overall survival for patients who had died before the most recent data analysis for each treatment group; this was [redacted] in favour of aflibercept. In the post-hoc subgroup analysis which excluded patients whose disease had relapsed 6 months or less after starting oxaliplatin-based adjuvant therapy, the difference in median overall survival was 1.9 months in favour of aflibercept. In this subgroup, the unadjusted hazard ratio was 0.78 (95% CI 0.68 to 0.90) compared with 1.09 (95% CI 0.70 to 1.69) in patients whose disease had relapsed 6 months or less after starting adjuvant therapy, but the effect difference between

these subgroups was not statistically significant (p value for interaction was [redacted]). The restricted mean analysis suggested that overall survival was [redacted]. The European Public Assessment Report notes that there was a numerically less beneficial effect on overall survival within the aflibercept group than the placebo group for patients previously treated with bevacizumab. However, it concluded that this could be due to random variation because the study was not powered to demonstrate superiority of aflibercept over placebo in any subgroup.

Figure 3 Overall survival by pre-specified subgroups (prognostic, prior treatment and performance status)



4.11 Similarly, the only statistically significant subgroup effect in the analysis of progression-free survival was that of the presence of liver metastasis only (p value for interaction was [redacted]). In patients who had liver metastasis only, there was a difference in median

progression-free survival of [redacted] (aflibercept [redacted], placebo [redacted], unadjusted hazard ratio [redacted]). This estimate compares with a difference of [redacted] (aflibercept [redacted], placebo [redacted], unadjusted hazard ratio [redacted]) in patients who had no liver metastasis or in whom the cancer spread to the liver and elsewhere. In the post-hoc subgroup analysis which excluded patients whose disease had relapsed 6 months or less after starting oxaliplatin-based adjuvant therapy, the unadjusted hazard ratio was [redacted] compared with [redacted] in patients whose disease had relapsed 6 months or less after starting adjuvant therapy, but the subgroup effect was not statistically significant (p value for interaction was [redacted]).

4.12 The incidence of adverse events of any grade (according to Common Terminology Criteria for Adverse Events v3.0) was similar in the aflibercept and placebo groups of the VELOUR trial (99.2% and 97.9% respectively), but the incidence of some adverse events was considerably higher in the aflibercept group (for example, 41.4% of patients receiving aflibercept experienced hypertension [any grade] compared with 10.7% of those receiving placebo). Grades 3–4 adverse events occurred in 33.6% more patients in the aflibercept group, and those that occurred at least twice as much in the aflibercept group than in the placebo group, in order of decreasing relative incidence, were: hypertension (19.3% versus 1.5%), proteinuria (7.8% versus 1.2%), hand-foot syndrome (2.8% versus 0.5%), headache (1.6% versus 0.3%), arterial thromboembolic events (1.8% versus 0.5%), weight loss (2.6% versus 0.8%), stomatitis and ulceration (13.8% versus 5.0%), diarrhea (19.3% versus 7.8%) and decreased platelet count (3.4% versus 1.6%). Typical anti-VEGF adverse events and adverse events associated with FOLFIRI occurred at an increased

frequency in the aflibercept group. The manufacturer indicated that the adverse events of aflibercept plus FOLFIRI were generally reversible and manageable using current clinical practice, although adverse events (mainly physical weakness, infections, diarrhea and hypertension) led to permanent discontinuation of study treatment in 26.8% of patients in the aflibercept group compared with 12.1% of those in the placebo group (following discontinuation, [redacted] of patients in the aflibercept group and [redacted] of those in the placebo group had surgery to remove liver metastases; the manufacturer stated that this information is not available for subgroups). Furthermore, the European Public Assessment Report notes that the toxicity potential of aflibercept resulted in dose modifications of FOLFIRI and cycle delays, but these data were not provided in the manufacturer's submission.

4.13 The manufacturer performed a meta-analysis of aflibercept adverse events by pooling safety data from 3 RCTs (VELOUR, VITAL and VANILLA). The VITAL trial evaluated aflibercept plus docetaxel in patients with non-small cell lung cancer, and in the VANILLA trial, patients received aflibercept plus gemcitabine for metastatic pancreatic cancer. Overall, the meta-analysis included data from 2,662 patients (1,333 receiving aflibercept and 1,329 receiving placebo). The manufacturer used a fixed-effect logistic regression model to carry out the analysis, and when statistical evidence did not find inconsistency of treatment effect across studies, it provided summary statistics for the relative safety of aflibercept. The results of the analysis were framed so that risk ratios (RR) greater than 1 favoured placebo. The manufacturer found that, among patients treated with aflibercept, 0.4% and 0.5% experienced Grade 4 hypertension and nephrotic syndrome respectively. It also found that the addition of aflibercept to concurrent chemotherapies did not increase the risk of venous thromboembolism but it did increase the

risk of Grade 3–4 adverse events related to anti-VEGF therapy. This increased risk was statistically significant for hypertension (RR 9.21, 95% CI 5.91 to 14.36), proteinuria (RR 8.37, 95% CI 4.37 to 16.06) and hemorrhage (RR 2.04, 95% CI 1.20 to 3.47). The incidence of adverse events typically associated with the background chemotherapy used in the 3 RCTs also increased with the addition of aflibercept, most notably for events of neutropenia (including neutropenic complications), various gastrointestinal toxicities and physical weakness.

4.14 Health-related quality of life data were not collected in the VELOUR trial. The manufacturer included evidence from 2 studies, neither of them are RCTs. The first of these, the ASQoP study, was an international, single-arm, open-label study primarily to evaluate the safety of aflibercept in patients with metastatic colorectal cancer whose disease progressed following treatment with an oxaliplatin-based regimen, and secondarily to establish the health-related quality of life in this population. The manufacturer stated that the study enrolled [redacted] patients out of a planned total of 900 patients (including 50 patients from the UK), and [redacted]. The second study was the 'mCRC utilities study', which was an observational, cross-sectional study conducted by the manufacturer to estimate utility values in patients with metastatic colorectal cancer who would be eligible for treatment with aflibercept plus FOLFIRI as per the licensed indication, or who had progressed to subsequent phases of the disease. The study took place in the Netherlands ([redacted]) and the UK ([redacted]), and collected EQ-5D data. The manufacturer used these data as its main source to estimate health-related quality of life for the cost-effectiveness analysis.

ERG critique and exploratory analyses

4.15 The ERG stated that the manufacturer presented a well conducted systematic review of clinical evidence, and used a comprehensive search strategy which is unlikely to have missed any relevant studies. It also stated that the manufacturer's submission included sufficient detail about the VELOUR trial and that the criteria used to assess the quality of the trial were appropriate. The ERG noted, however, that minimal details of the meta-analysis of aflibercept adverse events were provided, and it was unclear whether the manufacturer had assessed the quality of the VITAL and VANILLA trials.

4.16 The ERG indicated that the VELOUR trial was of good quality and that it was directly relevant to the decision problem. Baseline patient characteristics and disease history were well balanced between the aflibercept and placebo groups in the ERG's opinion. However, the ERG highlighted that patients in the trial were potentially fitter and younger than those seen in UK practice because of the following:

- In the UK, patients whose disease progresses after a break in treatment during intermittent first-line palliative chemotherapy are likely to be offered repeat treatment with the first-line chemotherapy regimen. If their disease progresses while receiving this treatment, or within 6 to 8 weeks of completing it, they would then move to second-line treatment. Although the manufacturer's submission does not state how many cycles of first-line oxaliplatin-based chemotherapy patients in the VELOUR trial had undergone, the ERG indicated that the trial population may be healthier than patients in clinical practice who may have received several cycles of first-line treatment.

- The ERG noted that, between 2007 and 2009, around 72% of all patients with colorectal cancer cases diagnosed in the UK were aged 65 years or over. In the VELOUR trial, people aged 65 years or over constituted only 33.5% of the aflibercept group and 38.9% of the placebo group.
- The proportion of patients with an ECOG PS of 2 in the VELOUR trial was 2.2%, which is lower than that reported in other trials in the second-line setting and in UK clinical practice according to the ERG's clinical advisory board.
- In the VELOUR trial 42–44% of patients had metastasis in only 1 organ. The ERG's clinical advisory board considered this proportion to be higher than that seen in clinical practice.

4.17 The ERG noted that the hazard ratios for overall survival by 6-month periods had very wide confidence intervals at the later time points of the VELOUR trial because many patients were not alive at these later time points, so the number of patients at risk of dying was very small (around 5% at 30 months). The ERG stated that the wide confidence intervals reflect imprecise estimates, and that the interpretation of the hazard ratios toward the end of the trial is highly uncertain, particularly at 30 and 36 months.

4.18 The ERG acknowledged the uncertainty around the hazard ratios for overall survival at the later time points of the VELOUR trial, but it did not agree with the manufacturer's interpretation of the survival curves, and considered that the hazard ratios were still consistent with the proportional hazards assumption, and so with a constant incremental benefit at all times (proportional hazards assumes that a hazard ratio between 2 treatments remains constant over time). The ERG stated that assuming a continued separation of the survival curves is highly uncertain given that no data were available for more than 36 months follow-up, and particularly that the

progression-free survival curves separate then converge at around 12 months.

4.19 To estimate mean overall survival, the manufacturer modelled each treatment group separately (rather than modelling treatment as a covariate) because the log-cumulative hazard plots were not parallel and crossed over one another. The ERG, conversely, noted that the curves were very close to being parallel, so it considered that it is uncertain whether the hazards varied over time, although the ERG accepted that using a proportional hazards approach is subject to judgment. The ERG suggested that it would be reasonable to assume that the survival curves would converge before 5 years, in line with the clinical experience with treating metastatic colorectal cancer.

4.20 The ERG noted that the estimate of mean overall survival varied considerably (from 3 months to [redacted]) depending on which parametric function the manufacturer used (table 4.6, page 49 of the ERG report). The ERG stated that this makes the difference in mean overall survival estimated by the manufacturer (4.7 months) unreliable. Because of this, the ERG requested at clarification stage mean estimates of overall survival restricted to patients who had died before the most recent data analysis for each treatment group (that is, results based on actual data rather than an extrapolated model), which estimated a difference in mean overall survival of [redacted] in favour of aflibercept. The ERG indicated that this figure is likely to be an underestimate given that some patients with long survival times were excluded. The ERG stated that it is unclear which estimate (4.7 months or [redacted]) is more accurate.

4.21 The manufacturer used the log-logistic function to estimate mean overall survival, and it truncated the curves at 15 years to obtain plausible estimates. The ERG considered that 15 years is very long for the patient population under consideration because the treatment benefit is unlikely to extend beyond 5 years. Because of this, the ERG requested at clarification stage that the manufacturer produce estimates with the analysis truncated at 5 years and 10 years. When the data were truncated at 5 years, the results from the different functions were more consistent, with a difference in mean overall survival of [redacted] between treatment groups. The ERG indicated that mean survivals are longer than median survivals because the former takes into account the few patients with relatively long survival durations.

4.22 Progression-free survival in the VELOUR trial was a secondary end point assessed by an independent review committee. The ERG advised that independent review committee assessment may miss symptoms other than tumour growth caused by disease progression, which may determine how long a patient receives treatment, and influence costs. The ERG noted that when disease progression determined by investigator assessment was explored in a sensitivity analysis, and took into account symptomatic deterioration (as would happen in clinical practice), the results were less favourable ([redacted] months difference in median progression-free survival compared with [redacted] months with independent review committee). The ERG explained that the outcome progression-free survival has the advantage over overall survival in that it is not confounded by treatment received after disease progression.

4.23 The ERG stated that, while there was no evidence of significant interaction between treatment groups for most of the subgroup analyses, the results suggested that patients with less advanced

disease in the VELOUR trial (ECOG PS equal 0, number of organs with metastasis less than or equal to 1, and patients with liver metastasis only) may be more likely to benefit from treatment with aflibercept than those with more severe cancer. The ERG, however, advised that the generalisability of the subgroup analyses should be considered in light of the differences between patients in the VELOUR trial and those in clinical practice in the UK.

4.24 Table 3 summarises the different estimates of overall survival produced by the manufacturer in its submission, and at clarification stage. All the estimates are expressed in terms of the incremental survival benefit offered by aflibercept over placebo.

Table 3 Summary of the estimates of incremental overall survival offered by aflibercept

	Overall population	Subgroup liver metastasis only (pre-specified)	Subgroup excluding those whose disease had relapsed 6 months or less after starting oxaliplatin-based therapy (post hoc)
Median OS[a]	1.44	[redacted]	1.90
Mean OS[a] (log-logistic)			
Truncation at 5 y[b]	[redacted]	-	-
Truncation at 10 y[b]	[redacted]	-	-
Truncation at 15 y[b]	4.70	-	-
No truncation	6.60	-	-
Restricted mean OS[a]	[redacted]	[redacted]	[redacted]

[a]OS, overall survival; [b]y, years

4.25 The ERG highlighted the number of grade 3-4 adverse events were more frequent with aflibercept than with placebo (83.5% compared with 62.5%).

[redacted]

[redacted] Treatment-emergent adverse events led to permanent discontinuation of treatment in 26.8% patient in aflibercept group and 12.1% patients in placebo group.

5 Comments from other consultees

5.1 Patient experts stated that if this new technology is more effective than existing treatments in treating colorectal metastases, either in terms of halting the progress of the disease or potentially reversing it, this would obviously be of great benefit to patients. Importantly, this new technology could improve a patient's quality of life by reducing the physical symptoms of the disease. This could in turn lead to the patient feeling better and reduce their stress, which could improve their mental health and their capacity to continue to work and socialise. The patient experts highlighted the importance of an increased sense of well-being, despite having an incurable disease, to allow patients to feel more positive about their situation, which in turn gives some short-term benefits for a patients' family and friends. The patient experts also noted that this technology works in a different way to existing technologies, and so may be more effective than existing alternatives for some patients, which could lead to a significant improvement in their condition and change the prognosis for some people by enabling surgery to take place on previously inoperable tumours.

5.2 Patient experts noted that not all patients may achieve the same level of benefit from this technology. However, they also noted that any benefit may be associated with side effects such as tiredness and nausea, but weighing up the harms and benefits of the treatment would be a matter of individual choice. Patient experts

stated that there were other considerations to be taken account of as to whether to undergo treatment such as the impact upon work and the impact on others in assisting with travel to the hospital. The patient experts highlighted the importance of involving and enabling the patient to have a realistic and collaborative relationship with the multidisciplinary team so that decisions regarding treatment, particularly in the issue of futility, are openly and respectfully raised and addressed.

5.3 Patient experts stated that they hope treatment with this technology will mean a better outcome in terms of prognosis, length of life, and the subsequent positive effects this has on the patient and their family. Patient experts stated that new technologies should be available on the NHS to everyone who may benefit from them, at least in the first instance, to give the patient the best chance of having a better quality of life and potentially a longer life than they otherwise would. A key difference this technology would give would be to extend the range of treatments for metastatic colorectal cancer and therefore if this treatment was not on offer then outcomes for patients would be unchanged.

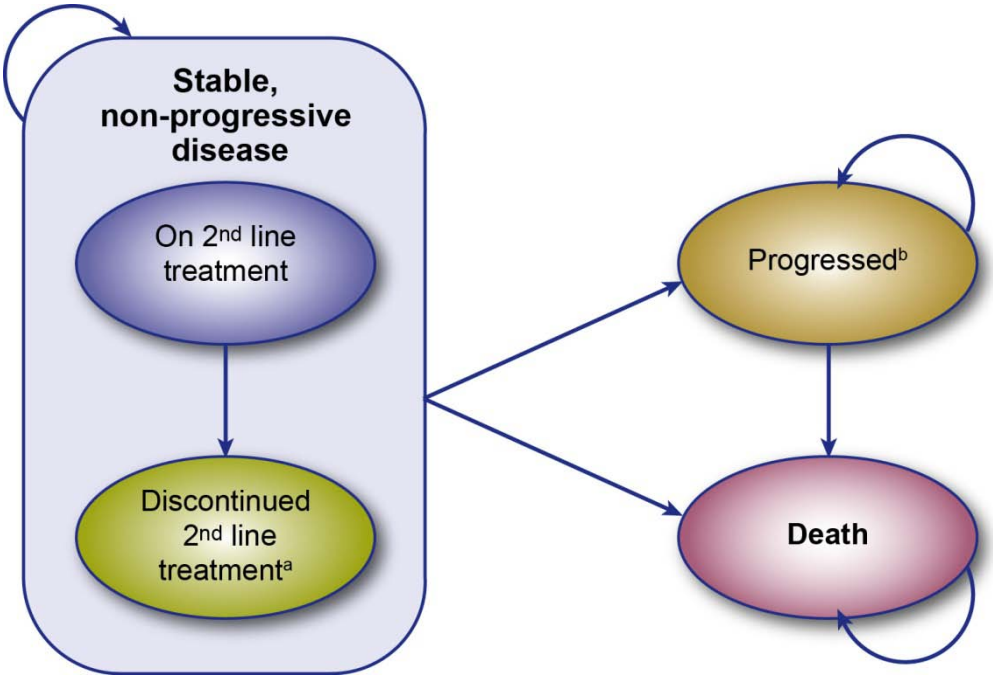
6 Cost-effectiveness evidence

6.1 The manufacturer did not identify any published economic evaluations relevant to the decision problem. It submitted a de novo economic model to establish the cost effectiveness of aflibercept in patients with metastatic colorectal cancer who are eligible for second-line combination chemotherapy, and who were previously treated with an oxaliplatin-based regimen. The manufacturer also performed subgroup analyses for patients with liver metastasis only, and for a subgroup which excluded patients who had received oxaliplatin-based therapy in the adjuvant setting and whose

disease relapsed within the following 6 months. The manufacturer conducted the analysis from an NHS and personal social services perspective and chose a lifetime horizon of 15 years. It used a fortnightly treatment cycle to reflect the treatment schedules of aflibercept and FOLFIRI, and applied a half-cycle correction. Costs and health effects were discounted at an annual rate of 3.5%.

6.2 The manufacturer developed a state-transition Markov cohort model simulating 3 states: stable disease, progressed disease and death (figure 4). The manufacturer further split the stable disease health state into ‘on second-line treatment’ and ‘discontinued second-line treatment’ sub-states to distinguish between patients who received second-line treatment until their disease progressed, and those who stopped second-line treatment before their disease progressed. All simulated patients entered the model in the stable disease health state and in the ‘on second-line treatment’ sub-state. Patients could then continue treatment and remain in the ‘on second-line treatment’ sub-state, or move to the ‘discontinued second-line treatment’ sub-state; they could also move to the progressed disease health state and stop second-line treatment, or die. Patients could not receive second-line treatment once treatment stopped, but they could receive further active therapy (systemic anti-cancer treatment, radiotherapy or surgery) or best supportive care. The manufacturer stated that the duration of second-line treatment in the model is based on the mean durations in the VELOUR trial to take into account dose delays or removal of 1 or both components of treatment (aflibercept/FOLFIRI or FOLFIRI) as observed in the trial. The manufacturer modelled adverse events as events (rather than health states) and it applied a utility decrement (disutility) for each adverse event.

Figure 4 The manufacturer's model



6.3 The manufacturer's model included parameters for overall survival, progression-free survival and time to discontinuing treatment (for both, before and after disease progression). To estimate the survival parameters, the manufacturer fitted alternative parametric functions (Weibull, log-normal, log-logistic and exponential) to Kaplan-Meier data from the VELOUR trial, and extrapolated the curves beyond the trial period for overall survival and time to discontinuing treatment, but not for progression-free survival because the disease had progressed in all patients during the trial. In extrapolating those curves, the manufacturer assumed non-proportional hazards (that is, the hazard ratios between aflibercept and FOLFIRI varied over time) so it modelled each treatment group separately. The manufacturer chose the base-case survival functions based on the results of statistical tests, visual inspection of the fit to the data and the clinical plausibility of the extrapolated portion of the curve. For overall survival, the manufacturer used the log-logistic function, and it assumed that the incremental survival

benefit of aflibercept plus FOLFIRI increases until around 12 months after starting treatment, and then decreases over the 15-year time horizon, but does not cease at any point during the extrapolation period (that is, the survival curves converge over the time horizon, but do not fully converge). The manufacturer used the Weibull function for progression-free survival (estimating a mean incremental benefit of [redacted] with aflibercept over placebo) and time to treatment discontinuation. Other parametric functions were explored in scenario analyses. For further details see pages 84-89 of the manufacturer's submission.

6.4 The manufacturer noted that the model predicted median overall survival and median progression-free survival similar to those from the VELOUR trial. The largest difference was for progression-free survival in the FOLFIRI group, which the model overestimates compared with the survival time observed in the trial ([redacted] and 4.67 months respectively).

6.5 Adverse events in the model included Grade 3–4 adverse events that affected more than 5% of patients in the VELOUR trial, together with 6 rarer adverse events (gastrointestinal perforation, haemorrhage, febrile neutropenia, peripheral neuropathy, urinary tract infections and hand-foot syndrome) that the manufacturer's clinical advisory board considered important. For further details of the number of adverse events see table B23 on page 90 of the manufacturer's submission. The subgroup analyses incorporated data specific to each subgroup.

6.6 The manufacturer applied utility values in the model from its observational utility study, in which investigators assigned a total of [redacted] patients (including [redacted] from the UK) to 1 of the following 3 groups: patients with stable disease who are receiving second-line

treatment (▇), and patients who formerly received second-line treatment but stopped it because of an adverse event (▇) or because their disease progressed (▇). Because the sample size of the group of patients who experienced an adverse event and stopped treatment was very small, the manufacturer did not use the utility estimates from this group, and instead assumed that all patients with stable disease have the same utility, equal to the utility of patients with stable disease who are receiving second-line treatment. The manufacturer obtained descriptions of health states from patients using the EQ-5D system, and derived the utility weights by applying UK valuation of health states estimated using the time trade-off method. For all patients with stable disease, the mean utility value was ▇ (SD=▇), and for patients with progressed disease, it was ▇ (SD=▇). The manufacturer assumed that the utility in the progressed disease state is independent of time spent in the state. The manufacturer explained that, despite the age and health of patients, these values are relatively high because candidates for second-line chemotherapy must be fit enough to receive treatment.

6.7 The manufacturer also identified relevant utility studies from a systematic review of the literature. It did not use the values in those studies to source the model, but used them to compare the estimates from its utility study, and noted that they were reasonably consistent. The utility estimates in the literature that the manufacturer considered relevant ranged from 0.73 to 0.81 for stable disease (compared with ▇ in the model), and from 0.68 to 0.69 for the progressed disease (compared with ▇ in the model). One other study, Best et al. (2010), reported utility values of 0.51 for stable metastatic disease and 0.21 for progressed metastatic disease, but the manufacturer did not consider this study relevant because the population included patients receiving adjuvant

chemotherapy and patients in remission. The manufacturer indicated that the results of the ASQoP study are still immature; however, it provided an interim analysis of [redacted] (out of a planned total of 900), which showed that the mean baseline utility score was [redacted] (SD=[redacted]).

6.8 The manufacturer obtained the disutilities associated with adverse events from the published literature, and supplemented these with clinical expert opinion. It calculated the average disutility per adverse event assuming that an adverse event causes the same disutility regardless of the type of cancer. This gave an average disutility per adverse event of -0.0127 for patients receiving aflibercept, and -0.0108 for those receiving FOLFIRI.

6.9 The costs of aflibercept plus FOLFIRI and FOLFIRI alone in the model did not depend on the duration of second-line treatment; the manufacturer calculated them separately based on data from the VELOUR trial to reflect the dose delays (for example because of an adverse event) and dose modifications observed in the trial. It assumed that any unused drug in a vial was discarded (wasted) for aflibercept and irinotecan (component of FOLFIRI), but explored in scenario analyses the possibility of no drug wastage, and of reducing the dose to the nearest number of whole vials for patients who would otherwise use less than 5% of the amount contained in a vial. The cost of aflibercept plus FOLFIRI per administration (every 2 weeks) in the model was [redacted] for aflibercept and [redacted] for FOLFIRI, including the patient access scheme discount. For further details on the intervention and comparator costs see table B35 on page 130 of the manufacturer's submission.

6.10 To estimate management costs (including supportive medications, clinician and nurse visits [hospital and community], imaging,

laboratory tests, hospitalisations, palliative care, and personal and social care), the manufacturer conducted a retrospective observational study in [redacted], and undertook a questionnaire-based survey of 6 UK clinical oncologists (both unpublished studies). In the observational study, the manufacturer collected resource use data from patients who received oxaliplatin-based chemotherapy followed by FOLFIRI as second line, and used those data to estimate total management costs per 2-week cycle for different groups of patients (the manufacturer advised that every patient would eventually receive end-of-life care regardless of prior treatment, so it did not include resource use at end of life in the model). The clinician survey aimed to gather data on community-based care, and on personal and social care. In this, the manufacturer elicited the average treatment practices of each oncologist to obtain data on managing patients with metastatic colorectal cancer. It also used the results of the survey, together with NHS reference costs, to estimate the costs associated with adverse events. The cost of subsequent therapies patients could receive after stopping second-line treatment or experiencing disease progression was calculated based on the manufacturer's resource use study, and was assumed to be independent of the type of second-line treatment. For further details on the health state costs see pages 131-134 of the manufacturer's submission.

6.11 The manufacturer's deterministic base-case results (table 4) show that the addition of aflibercept to FOLFIRI provides an additional 0.2429 quality-of-life years gained (QALYs). This benefit is achieved with an additional cost of £8,816, resulting in an incremental cost-effectiveness ratio (ICER) of £36,294 per quality-adjusted life year (QALY) gained for aflibercept plus FOLFIRI compared with FOLFIRI alone.

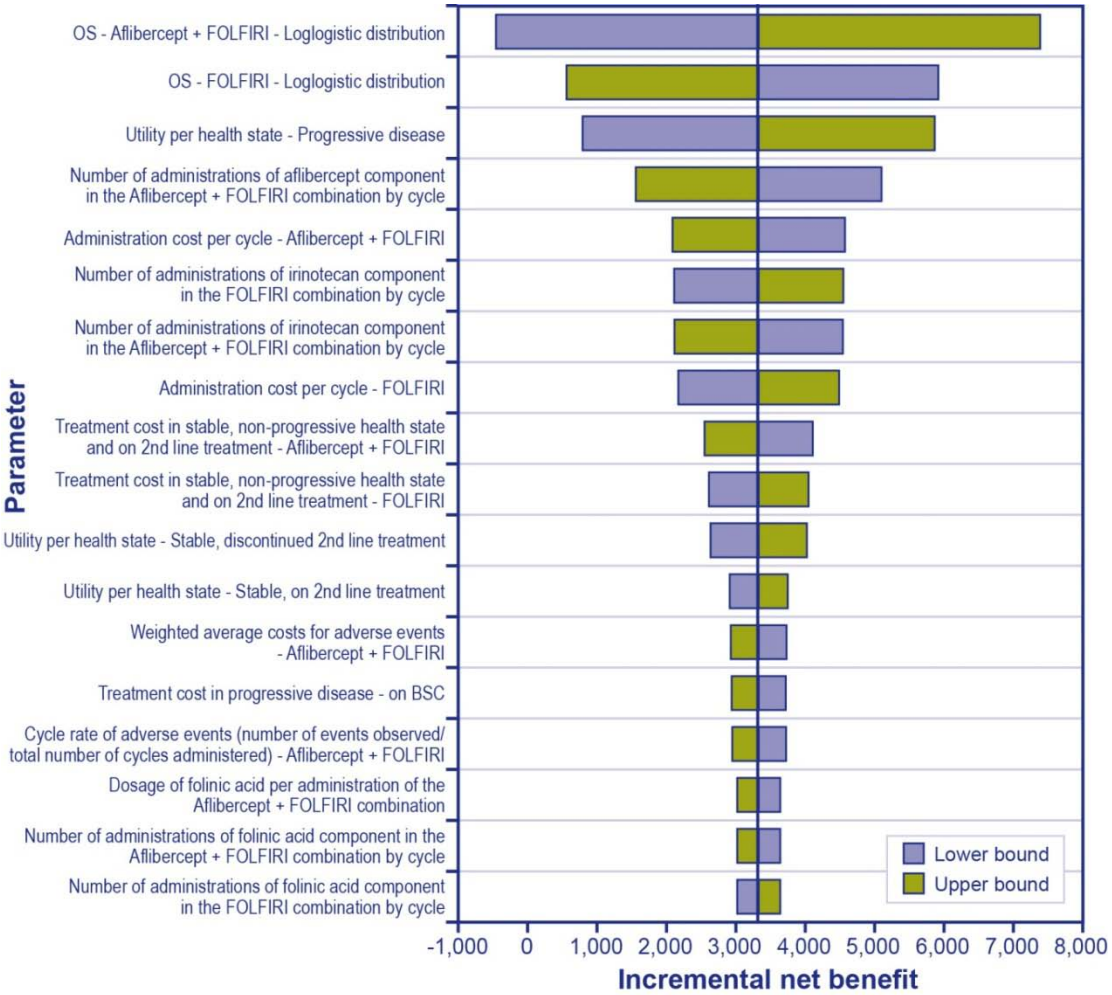
Table 4 The manufacturer's base case results

	Total costs (£)	Total LYG[a]	Total QALYs[b]	Incr.[c] costs (£)	Incr.[c] LYG[a]	Incr.[c] QALYs[b]	ICER[d] (£/QALY[b])
FOLFIRI	[redacted]	[redacted]	[redacted]	—	—	—	—
Aflibercept + FOLFIRI	[redacted]	[redacted]	[redacted]	8,816	0.3378	0.2429	36,294

[a]LYG, life years gained; [b]QALY, quality-adjusted life years; [c]Incr., incremental; [d]ICER, incremental cost-effectiveness ratio

6.12 The manufacturer presented deterministic sensitivity analyses for the 20 parameters with the largest impact on the ICER. In these, it varied 1 parameter at a time by [redacted] above and below its base-case value. The results were expressed in terms of net monetary benefit (incremental net monetary benefit greater than 0 suggests that aflibercept plus FOLIRI is cost effective compared with FOLFIRI at a threshold of £50,000 per QALY gained), and they showed that the ICER is most sensitive to the parametric function for overall survival, the utility value for the progressed disease health state, and the number of administrations of second-line treatment drugs (figure 5).The manufacturer explained that improving overall survival and progression-free survival increased incremental QALYs in favour of aflibercept, but these also brought about additional drug costs and increased the costs incurred after disease progression as a result of prolonged overall survival.

Figure 5 Results of the manufacturer's one-way sensitivity analyses



6.13 The manufacturer carried out a probabilistic sensitivity analysis to summarise the uncertainty in the ICER. This showed that the probability of aflibercept plus FOLFIRI being cost effective when compared with FOLFIRI is less than 5% at a threshold of £20,000 per QALY gained, 22% at £30,000 per QALY gained, and 68% at £40,000 per QALY gained.

6.14 The manufacturer investigated the structural uncertainty in the model by fitting alternative parametric functions for overall survival and progression-free survival, and by directly applying patient-level data from the VELOUR trial to model progression-free survival (as

the disease had progressed in all patients during the trial). It also performed scenario analyses to test the sensitivity of the ICER to alternative assumptions around drug wastage. In these, it explored the possibility of no drug wastage, and that of reducing the dose to the nearest number of whole vials for patients who would otherwise use less than 5% of the amount contained in a vial. The ICERs from these analyses ranged from [redacted] per QALY gained (assuming no drug wastage) to £49,805 per QALY gained (using the Weibull function to model overall survival). See page 147 in the manufacturer's submission for further detail.

6.15 The manufacturer provided subgroup analyses to establish the cost effectiveness of aflibercept plus FOLFIRI compared with FOLFIRI alone in patients with liver metastasis only, and in a subgroup which excluded those who had received oxaliplatin-based therapy in the adjuvant setting and relapsed within the following 6 months. In comparison with the deterministic base-case ICER of £36,294 per QALY gained, the ICERs were £30,474 per QALY gained and £32,480 per QALY gained respectively (table 5). At a threshold of £30,000 per QALY gained, the probability of aflibercept plus FOLFIRI being cost effective compared with FOLFIRI in both subgroups is around 50% (numerical values not provided in the manufacturer's submission).

Table 5 Manufacturer's base case results for the subgroup analyses

	Total costs (£)	Total LYG[a]	Total QALYs[b]	Inc.[c] costs (£)	Inc.[c] LYG[a]	Inc.[c] QALYs[b]	ICER[d] (£/QALY[b])
Isolated liver metastases							
FOLFIRI	[redacted]	[redacted]	[redacted]	—	—	—	—
Aflibercept + FOLFIRI	[redacted]	[redacted]	[redacted]	10,974	0.4955	0.3601	30,474
ITT excluding patients relapsing on or within 6 months of oxaliplatin-based adjuvant therapy							
FOLFIRI	[redacted]	[redacted]	[redacted]	—	—	—	—
Aflibercept + FOLFIRI	[redacted]	[redacted]	[redacted]	8,573	0.3668	0.2639	32,480

[a]LYG, life years gained; [b]QALY, quality-adjusted life years; [c]Incr., incremental; [d]ICER, incremental cost-effectiveness ratio

ERG critique

6.16 The ERG indicated that the manufacturer's economic evaluation is consistent with the NICE reference case. It noted that the modelled population is based on data from the VELOUR trial, and so reflects the patients in the trial who appear fitter and younger than those seen in clinical practice. The ERG investigated in sensitivity analysis the effect of treating a population that is more representative of patients with metastatic colorectal cancer in the UK than the VELOUR trial by modelling an older population with lower health-related quality of life. The ERG considered that the utility data, along with the assumptions underlying the extrapolation of overall survival, are key drivers of the cost effectiveness, and an area of significant uncertainty.

6.17 To estimate mean overall survival, the manufacturer assumed non-proportional hazards and it modelled each treatment group accordingly. The ERG considered that it is uncertain whether the hazards varied over time. The ERG stated that it could apply the proportional hazards assumption (that is, assuming that hazard ratios remain constant over time) in the manufacturer's model.

Using this alternative extrapolation method, the ERG reported that the ICER increased to £58,784 per QALY gained, with the difference being mainly driven by a [redacted] reduction in incremental QALYs compared with the manufacturer's base case. The ERG considered that even this scenario may be relatively optimistic because the progression-free survival curves separate and then converge at around 12 months.

6.18 In its cost-effectiveness analysis, the manufacturer assumed that the incremental survival benefit of aflibercept plus FOLFIRI initially increases until around 12 months then decreases over the rest of the time horizon, but does not cease at any point during the extrapolation period. The ERG noted that the incremental survival benefit decreases at a relatively slow rate after the initial 12 months and suggests a continuing treatment effect on overall survival during the entire 15-year horizon. The ERG explained that extrapolating overall survival data from the VELOUR trial, in which the median follow-up time was 22 months, over a 15-year time horizon, meant that the assumptions underpinning the extrapolation are central to the analysis and are key factors in explaining the large differences between median and mean overall survivals (that is, the differences between results based on the observed trial data and those from extrapolating the survival curves). The ERG highlighted that the extrapolation of the survival curves beyond the trial period is highly uncertain given that no data were available for more than 36 months follow-up, and particularly that the progression-free survival curves separate and then converge at around 12 months. The ERG stated that the manufacturer did not sufficiently explore this uncertainty by using different assumptions, such as assuming that the survival benefits of aflibercept plus FOLFIRI and FOLFIRI alone become the same beyond the trial period (that is, the treatment effect does not continue beyond the

trial period), or assuming that the survival benefits of aflibercept plus FOLFIRI and FOLFIRI alone converge over the extrapolation period similar to the convergence observed with progression-free survival (figure 2, in this scenario it may be possible that patients receiving aflibercept plus FOLFIRI face a higher risk of death during the extrapolation period than patients receiving FOLFIRI alone). The ERG explored these 2 scenarios in its exploratory analyses.

6.19 Regarding utility estimates in the model, the ERG had concerns about the generalisability of the manufacturer's observational study because the median age of the study population was [redacted] years, and only [redacted] of patients had an ECOG PS of 2, which the ERG did not consider reflective of UK clinical practice. Moreover, the ERG noted that the study was small, and produced counter-intuitive estimates in a subgroup analysis including UK patients only as the mean utility value for patients whose disease progressed was higher than for those who had stable disease and received second-line treatment.

6.20 The ERG was concerned that the utility estimates used in the model from the manufacturer's utility study ([redacted] and [redacted] for stable and progressed disease respectively), as well as those reported in the literature, were generally high when compared with other 'real world' estimates of utility for colorectal cancer. The ERG was particularly concerned about the utility value in the model attached to patients whose disease had progressed ([redacted]), especially that this value is a key driver of cost effectiveness in the model. The ERG explained that because the model predicts longer overall survival than progression-free survival, [redacted] of absolute QALY increment is accrued after disease progression. Furthermore, the ERG stated that the manufacturer's assumption that utility in the

progressed disease state is independent of time spent in the state is clinically implausible because the patients' health-related quality of life would decrease as disease progresses and the patient ages. The ERG stated that the utility values applied in the model and the assumptions underlying them are likely to favour aflibercept.

6.21 The ERG identified an error in the manufacturer's model regarding how disutilities associated with adverse events were applied, which had the effect of reducing the disutilities in the model. The correction of this error increased the manufacturer's base case ICER from £36,294 to £37,834 per QALY gained, and the ERG applied this change throughout its exploratory analyses.

6.22 The costs of aflibercept plus FOLFIRI and FOLFIRI alone in the model did not depend on the duration of second-line treatment; the manufacturer calculated them separately based on data from the VELOUR trial to reflect the dose delays (for example because of an adverse event) and dose modifications observed in the trial. The ERG, however, stated that any dose reductions and delays would have been more accurately reflected in the cost estimates if drug cost per administration (including acquisition and administration costs) had been applied directly to the proportion of patients in each health state, in line with how utility values were applied in the model. Adjusting this increased the manufacturer's base case ICER from £36,294 to £37,539 per QALY gained, and the ERG applied this change throughout its exploratory analyses.

6.23 The manufacturer assumed that, because aflibercept is administered over 1 hour at the same time as FOLFIRI, no extra administration costs in terms of additional staff or inpatient admissions (and associated facilities) would be needed to administer aflibercept. The ERG indicated that administering

aflibercept involves preparing an additional infusion, which incurs an extra cost compared with FOLFIRI alone. The ERG highlighted that in Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy (NICE technology appraisal guidance 242), the pharmacy preparation of cetuximab and bevacizumab was estimated to be £15 per infusion. In addition, the ERG stated that if aflibercept is given before or after FOLFIRI, instead of at the same time, administering aflibercept will include an additional hour of infusion time compared with administering FOLFIRI alone. The ERG noted that the model is sensitive to the assumptions underlying the administration costs of aflibercept plus FOLFIRI, and it explored these assumptions in sensitivity analyses.

6.24 For resource use for community and personal and social care, the manufacturer used in the model the median estimate from its survey of clinical oncologists, instead of the mean. The ERG indicated that mean values are most commonly used in cost-effectiveness analyses, and that the use of medians may underestimate expected costs. The ERG noted that when the manufacturer used the mean value in a sensitivity analysis, the base-case ICER increased from £36,294 to £41,222 per QALY. The ERG stated that it is unclear in this case whether the median is a better estimate than the mean, as there was a small number of survey responders (n=6), and the data were considerably skewed. The ERG noted that the model is sensitive to this parameter and it further explored this in sensitivity analyses.

6.25 The ERG advised that the results of the analysis of the liver metastasis only subgroup should be interpreted cautiously. Because overall survival and progression-free survival data for each treatment group were fitted to the respective Kaplan-Meier

curves for this subgroup from the VELOUR trial, and the subgroup corresponds to approximately 25% of the trial population, the ERG highlighted that this subgroup analysis may not be powered to demonstrate the treatment effect associated with this subgroup. For the analysis of the subgroup which excluded adjuvant chemotherapy, the ERG indicated that this analysis was performed post-hoc, and so its results may be biased. The ERG's clinical advisors also stated that those who received adjuvant chemotherapy and relapsed quickly afterwards would not be treated differently to other patients in UK clinical practice.

ERG exploratory analyses

6.26 The ERG investigated the uncertainty around how the manufacturer had chosen to extrapolate overall survival by considering alternative scenarios for the magnitude and duration of the overall survival benefit. In this, the ERG modelled the following scenarios:

- Assuming that the survival benefits of aflibercept plus FOLFIRI and FOLFIRI alone become the same after 30 or after 36 months of treatment (2 scenarios).
- Assuming that any survival benefits for aflibercept plus FOLFIRI and FOLFIRI alone converge after 30 or after 36 months of treatment over a period of 12 or 18 months, after which the survival benefits of aflibercept plus FOLFIRI and FOLFIRI alone become the same (4 scenarios).

In all the above scenarios, the ERG assumed that the incremental survival benefit of aflibercept plus FOLFIRI continues until either 30 or 36 months (results are presented in table 6). The ERG chose these time points because it identified them as particularly uncertain from the hazard ratios for overall survival by 6-month

periods presented by the manufacturer. In the scenario in which the ERG assumed that the survival curves of aflibercept plus FOLFIRI and FOLFIRI alone converge over 12 or 18 months, the ERG explained that when the curves converge over 12 months, the magnitude of the treatment effect of aflibercept plus FOLFIRI is assumed to decline at a higher rate than when the curves converge over 18 months, and so the convergence over 12 months results in higher ICERs.

Table 6 Cost-effectiveness results for the ERG's scenarios for treatment duration

Scenario	Inc.[a] Costs (£)	Inc.[a] QALYs[b]	ICER[c] (£/QALY[b])
Manufacturer's base case	8,816	0.2429	36,294
No continued effect after 30 months	8,358	0.1834	45,570
No continued effect after 36 months	8,473	0.1984	42,718
OS[d] curves converge from month 30 over 12 months	7,858	0.1184	66,377
OS[d] curves converge from month 30 over 18 months	7,980	0.1343	59,428
OS[d] curves converge from month 36 over 12 months	7,976	0.1337	59,666
OS[d] curves converge from month 36 over 18 months	8,067	0.1456	55,424

[a]Inc., incremental; [b]QALY, quality-adjusted life years; [c]ICER, incremental cost-effectiveness ratio; [d]OS, overall survival

6.27 To address its concerns about some of the parameters used in the manufacturer's base-case model, the ERG undertook the following sensitivity analyses, varying 1 parameter at a time:

- Applying alternative utility values from the literature for patients whose disease had progressed using 2 sources: the 0.21 from Best et al. (2010) and 0.60 from Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer (NICE technology appraisal guidance 118). The ERG stated that the later may reflect more closely the range of values reported in the literature.
- Applying a cost for preparing an additional infusion of aflibercept, and a cost for an additional hour of infusion time for aflibercept plus FOLFIRI compared with administering FOLFIRI alone. For the preparation cost, the ERG applied a cost of £15, in line with NICE technology appraisal guidance 242, and it applied £45 as the cost of extra time of infusion based on NHS reference costs. The ERG explored the impact of these 2 assumptions separately and jointly.

The results of this analysis are presented in table 7.

Table 7 The ERG's cost-effectiveness results of the one-way sensitivity analyses

Scenario	Inc.[a] Costs (£)	Inc.[a] QALYs[b]	ICER[c] (£/QALY[b])
Manufacturer's base case PD[d] utility = [redacted], aflibercept preparation cost = £0, aflibercept extra hour cost = £0	8,816	0.2429	36,294
PD[d] utility = 0.21	8,816	0.1239	71,143
PD[d] utility = 0.60	8,816	0.2171	40,608
Aflibercept preparation cost = £15 Aflibercept extra hour cost = £0	8,996	0.2429	37,035
Aflibercept preparation cost = £0 Aflibercept extra hour cost = £45	9,356	0.2429	38,517
Aflibercept preparation cost = £15 Aflibercept extra hour cost = £45	9,536	0.2429	39,258

[a]Inc., incremental; [b]QALY, quality-adjusted life years; [c]ICER, incremental cost-effectiveness ratio; [d]PD, progressed disease

6.28 The ERG applied simultaneously in the manufacturer's base-case model its preferred adjustments and model inputs (hereafter the 'ERG base case'). The ERG first corrected the error it identified in the manufacturer's model (sections 6.21) and applied the acquisition and administration costs to all patients in the second-line treatment health state of the model (section 6.22). In addition, it assumed that patients entered the model at the age of 70 years and accounted for the impact of age on health-related quality of life by applying a utility decrement for aging (this adjustment alone increased the manufacturer's base case ICER from £36,294 to £38,500 per QALY gained). The correction of the errors combined with the adjustment for aging gave an ICER of £41,653 per QALY

gained. The ERG then applied its preferred model inputs for the parameters it changed in one-way sensitivity analyses:

- An additional administration cost for aflibercept of £15
- Mean instead of median resource use estimates from the manufacturer's survey of UK oncologists.

The ERG applied the above with or without

- a utility value of 0.60 for patients whose disease had progressed.

When the ERG applied the 0.60 utility value, the analysis gave an ICER of £54,368 per QALY gained for aflibercept plus FOLFIRI compared with FOLFIRI alone (incremental costs 10,509, incremental QALYs 0.1933). Without this modification (that is, using the same value in the manufacturer's base case), the ICER was £47,965 per QALY gained (incremental costs 10,509, incremental QALYs 0.2191).

6.29 The ERG presented deterministic results for the scenario analyses (section 6.27) within its base case. It presented results for the overall population (table 8), and separately for each subgroup the manufacturer identified (table 10). For further results see pages 118-122 in ERG report.

Table 8 The ERG's cost-effectiveness results for the scenario analyses within the ERG' alternative base case – overall population

Model	Extrapolation Scenario	PD[a] utility	Inc.[b] Costs (£)	Inc.[b] QALYs[c]	ICER[d] (£/QALY[c])
MS[e] Base case	-	[redacted]	8,816	0.2429	36,294
ERG base case	-	[redacted]	10,509	0.2191	47,965
		0.600	10,509	0.1933	54,368
ERG base case	No continued effect after 30 months	[redacted]	9,829	0.1645	59,743
		0.600	9,829	0.1478	66,506
	No continued effect after 36 months	[redacted]	10,033	0.1785	56,197
		0.600	10,033	0.1595	62,894
	OS[f] curves converge from month 30 over 12 months	[redacted]	8,944	0.1039	86,056
		0.600	8,944	0.0971	92,089
	OS[f] curves converge from month 30 over 18 months	[redacted]	9,155	0.1188	77,056
		0.600	9,155	0.1096	83,503
	OS[f] curves converge from month 36 over 12 months	[redacted]	9,152	0.1186	77,161
		0.600	9,152	0.1095	83,605
	OS[f] curves converge from month 36 over 18 months	[redacted]	9,314	0.1300	71,635
		0.600	9,314	0.1191	78,226

[a]PD, progressed disease; [b]Inc., incremental; [c]QALY, quality-adjusted life years; [d]ICER, incremental cost-effectiveness ratio; [e]MS, manufacturer submission; [f]OS, overall survival

The ERG found that using median resource use estimates from the manufacturer's survey of UK oncologists, instead of mean, (that is, as per the manufacturer's base case) consistently decreased the ICERs for the scenario analyses within the ERG base case by approximately £5,000 per QALY gained.

6.30 The ERG also presented results based on the probabilistic sensitivity analysis for selected scenario analyses (table 9).

Table 9 The ERG's probabilistic cost-effectiveness results for the scenario analyses within the ERG' alternative base case – overall population

	Scenario	Inc.[a] Costs (£)	Inc. QALYs[b]	ICER[c] (£/QALY[b])
Manufacturer's base case	-	8,816	0.2429	36,294
ERG base case[*]	-	11,821	0.19	61,446
Treatment effect duration	No continued effect after 30 months	11,387	0.16	71,732
	No continued effect after 36 months	11,387	0.16	71,732
	OS[d] curves converge from month 30 over 12 months	10,286	0.10	106,945
	OS[d] curves converge from month 36 over 18 months	10,702	0.12	90,824

[*]progressed disease utility = 0.60, mean resource use from oncologist survey; [a]Inc., incremental; [b]QALY, quality-adjusted life years; [c]ICER, incremental cost-effectiveness ratio; [d]OS, overall survival

6.31 For the subgroup analyses combining the ERG's assumptions of overall survival and the ERG's alternative base case, the ICER for aflibercept plus FOLFIRI compared with FOLFIRI ranged from £46,576 to £58,257 per QALY gained for the liver metastases only subgroup, and from £57,224 to £80,187 per QALY gained for the subgroup which excluded patients who had received adjuvant oxaliplatin-based therapy and relapsed within the following 6 months. The ICERs from this analysis are presented in table 10; for further details see pages 124-127 of the ERG report.

Table 10 The ERG's ICERs for the scenario analyses within the ERG' alternative base case – subgroups

	Scenario	PD[a] utility	ICER[b] (£/QALY[c])	
			Subgroup 1[*]	*Subgroup 2*[†]
Base case		[redacted]	30,474	32,480
Treatment effect duration	No continued effect after 30months	[redacted]	44,168	54,072
		0.600	47,764	60,076
	No continued effect after 36 months	[redacted]	42,895	51,249
		0.600	46,576	57,224
	OS[d] curves converge from month 30 over 12 months	[redacted]	55,909	74,863
		0.600	58,257	80,187
	OS[d] curves converge from month 30 over 18 months	[redacted]	52,383	67,943
		0.600	55,159	73,607
	OS[d] curves converge from month 36 over 12 months	[redacted]	52,368	67,935
		0.600	55,145	73,599
	OS[d] curves converge from month 36 over 18 months	[redacted]	50,120	63,633
		0.600	53,136	69,431

[*]liver metastases only subgroup; [†]overall population excluding adjuvant subgroup; [a]PD, progressed disease; [b]ICER, incremental cost-effectiveness ratio; [c]QALY, quality-adjusted life years; [d]OS, overall survival

7 End-of-life considerations

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Overall population: The average life expectancy of patients with metastatic colorectal cancer is less than 24 months. The manufacturer's submission states that the observed median overall survival ranges between 10.5 months and 18 months. The ERG indicated that 1 study (Seymour et al., 2011) was conducted in the UK so is likely to be the most reflective of the UK population; this study reported a median overall survival of 10.5 months. Liver metastasis only subgroup: No estimate was provided; the life expectancy is likely to be longer than for the overall population.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Overall population: Estimates ranged from 1.9 (restricted mean overall survival) to 6.6 (mean overall survival without the truncation of the survival curves). In the ERG's alternative scenario assuming no continued treatment effect after 30 or 36 months, mean overall survival ranged from 3.4 to 3.7 months. Scenarios assuming that the overall survival curves converged gave a mean survival gain for aflibercept ranging from 2.1 to 2.6 months. Liver metastasis only subgroup: Median overall survival [redacted], restricted mean overall survival [redacted] For further details on estimates of overall survival see table 3.

The treatment is licensed or otherwise indicated for small patient populations	Overall population: The manufacturer stated that the population that would be eligible for treatment with aflibercept plus FOLFIRI in the UK as per the marketing authorisation is small; it estimated the size of this population to be approximately 2,578 patients in England and Wales in 2013. The manufacturer stated this figure is likely to be an overestimate given that some patients who received prior oxaliplatin chemotherapy may not be fit enough to receive FOLFIRI. Liver metastasis only subgroup: 619 patients (manufacturer submission).

8 Equalities issues

8.1 No potential equality issues were raised during the scoping consultation or workshop. The manufacturer did not identify any equality issues in its evidence submission.

9 Innovation

9.1 The manufacturer stated that aflibercept is a novel recombinant fusion protein that was specifically designed to bind to all human isoforms of VEGF-A, VEGF-B and PlGF, thereby creating a VEGF-signalling blockade. It indicated that aflibercept is the first anti-angiogenic agent to bind all of these factors, which are believed to play important roles in pathologic angiogenesis. The manufacturer further indicated that, in binding VEGF-A, VEGF-B and PlGF, aflibercept covers a wider spectrum of angiogenic factors than any other agent currently being used in metastatic colorectal cancer therapy, which may make aflibercept less susceptible to the development of drug resistance than agents that target only one ligand.

9.2 The manufacturer highlighted that aflibercept is the first anti-angiogenic therapy to show an overall survival benefit in patients with metastatic colorectal cancer who have been treated with an oxaliplatin-based therapy, and the only drug to demonstrate a statistically significant overall survival benefit in combination with FOLFIRI in such patients. It also stated that aflibercept is the first anti-angiogenic therapy to show benefit in patients with metastatic colorectal cancer previously treated with another anti-angiogenic therapy.

10 Authors

Ahmed Elsada
Technical Lead(s)

Joanna Richardson
Technical Adviser

with input from the Lead Team Daniel Hochhauser, John Cairns and Cliff Snelling

Appendix A: Supporting evidence

Related NICE guidance

Published

- Colorectal cancer, the diagnosis and management of colorectal cancer. NICE clinical guideline 131(2011). Available from www.nice.org.uk/guidance/CG131
- Cetuximab (monotherapy or combination chemotherapy), bevacizumab (in combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy (review of TA150 and part review of TA118). NICE technology appraisal guidance 242 (2012). Available from www.nice.org.uk/guidance/TA242
- Panitumumab in combination with chemotherapy for the treatment of metastatic colorectal cancer. NICE technology appraisal guidance 240 (2011). Available from www.nice.org.uk/guidance/TA240

NICE pathways

- There is a NICE pathway on colorectal cancer, which is available from http://pathways.nice.org.uk/pathways/colorectal-cancer