NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
	1. *Revised Patient Access Scheme* We will revise our patient access scheme discount. The revised cost of £[redacted] per vial (100 mg) and £[redacted] per vial (200 mg) represents a substantial discount of approximately [redacted] off the published list price. The new PAS discount is included within our revised modelling analyses. 2. *Aflibercept should be evaluated under the provisions of the Supplementary advice to the Appraisal Committees on life-extending, end of life treatments* The Committee noted the mean and median estimates of survival in the placebo group in VELOUR, and with the ERG's preferred estimate from the literature, concluded that patients receiving standard NHS treatment would have an expected survival of less than 24 months; therefore accepting that the first *end-of-life* criterion was met.	
	With regards to the second *end-of-life* criterion – that the treatment offers an extension to life of at least 3 months compared to standard treatment – we believe that the Committee is mistaken in referencing its decision to the median overall survival data "in the absence of a robust estimate of mean overall survival" since both they and the ERG recognise the median is clearly an underestimate of the true benefit. This is illustrated by the fact that even the restricted mean OS is [redacted]% higher than the median and, as acknowledged by the ERG, is also likely to be an underestimate given that 17.2% of patients were alive in the aflibercept arm at the end of trial follow-up.	The Committee agreed that the difference in median overall survival is likely to underestimate the mean survival benefit of aflibercept. However, it considered that the manufacturer's extrapolation of overall survival from a population with very few patients at risk of dying after 30 months follow-up, over a further 12 years, was associated with great uncertainty.
	Furthermore, the Committee's rejection of aflibercept on the second *end-of-life* criterion is inconsistent with its conclusions on the most plausible ICER. The Committee acknowledge that the ERG's analysis which assumed no treatment effect in the follow-up period provides an 'acceptable compromise' and the 'most plausible assumption for extrapolating overall survival'. This preferred extrapolation approach itself produces a mean incremental survival gain of between 3.4 and 3.7 months depending on when the	Having considered model time horizons shorter than 15 years to extrapolate overall survival, the Committee agreed that there was considerable uncertainty around extrapolating overall survival and implementing it in the model. The Committee considered it important to

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	treatment effect is adjusted (e.g. 36m or 30m respectively; Table 1). **Table 1: Mean OS obtained assuming no continued treatment effect after 30 or 36 months** **Extrapolation Function** / **Mean OS (months)** Log-logistic, with HR = 1 after 30 months: 3.4 Log-logistic, with HR = 1 after 36 months: 3.7	take into account what has actually been observed in the trial. In the absence of other evidence (including the lack of data on survival after 07 February 2011 from the VELOUR trial in support of the overall survival claims), the Committee was not satisfied that the estimates produced by the model were sufficiently robust to accept that the 3-month life extension criterion is fulfilled.
	While it is reasonable to expect variation in the values derived from different extrapolation approaches – due to the different mathematical properties of the modelled functions and different modelling time horizons – we note that all the parametric functions assessed produce around three months additional survival, as shown in Table 2. **Table 2: Mean OS obtained with different parametric functions** **Incremental survival (months)** **Function** / **5 year Time horizon** / **10 year Time horizon** / **15 year Time horizon** Log-logistic: 3.0 / 4.2 / 4.7 Weibull: 2.9 / 3.0 / 3.0 Log-normal: 3.4 / 4.8 / 5.3 Exponential: 3.0 / 3.6 / 3.6 Gompertz: 3.0 / 3.1 / 3.1	The Committee was aware that the manufacturer considered the log-logistic function to provide the best fit to the observed data. The Committee agreed that a shorter extrapolation period better reflected the natural history of the disease at this stage, and yet accounted for patients who derived greater benefit from aflibercept than most patients in the VELOUR trial. The Committee was concerned that the log-logistic function had a very 'heavy tail' which may have overestimated the survival benefit of aflibercept.
	Given the consistent demonstration of at least 3 months survival gain, we request that the Committee afford aflibercept the benefit of the doubt as was the case for panitumumab for 2nd line mCRC in TA242[1]. In considering whether panitumumab met the second end-of-life criterion, the Committee concluded that after adjusting for cross-over the mean overall survival gain of panitumumab was estimated to be between 2.7 and 3.2 months. The Committee also took into account – in spite of advice from the clinical experts that gains in progression-free survival cannot reliably translate to gains in overall survival – that panitumumab had demonstrated a progression-free survival gain similar to	The Committee was aware that, in judging whether panitumumab met the criterion for life extension, the Committee for NICE TA242 had taken into consideration the difficulty in accommodating the cross-over in the panitumumab trials and that the mean progression-free survival

1 Aflibercept for Metastatic Colorectal Cancer ACD Comments Table v2 AE (redacted for WEB)

Consultee	Comment	Response
	cetuximab (5 weeks and 7.8 weeks respectively, in KRAS wild-type patients) and since cetuximab had demonstrated an improvement in survival of over 3 months, panitumumab's survival advantage had been robustly demonstrated. Aflibercept increases progression-free survival by 9.6 weeks. With respect to the third and final *end-of-life* criterion – that the treatment is licensed or otherwise indicated, for small patient populations – we remind the Committee that the population eligible for treatment with aflibercept (Zaltrap) is small; approximately 2600 of the 4000 patients estimated to receive any second line treatment for mCRC. The ACD however, casts doubt on the acceptance of this last criterion in making reference to Eylea, a different formulation of aflibercept that is licensed separately for wet acute macular degeneration. The two medicines are not interchangeable, and aflibercept (Zaltrap) was recognised by the Department of Health as a different medicine and permitted Sanofi to price aflibercept (Zaltrap) as a "New Active Substance". We therefore request that the Committee disregard the other treatment when applying the third *end-of-life* criterion and accept that aflibercept (Zaltrap) meets the 'small populations' test. 3. *Comments on areas of uncertainty in the economic evaluation identified by the ERG and Appraisal Committee.* The ERG performed a number of adjustments to the economic model to address areas of uncertainty which they considered important (see below). From these alternative analyses, the Committee were able to select a "most plausible" ICER, which ranged between £62K to £66K per QALY. The adjustments (on which the "most plausible" ICER was based) included: Correction of AE disutility calculations Adjustment to treatment acquisition costs so they were applied for entire duration patients were in "second-line on treatment" state Incorporation of ageing disutility based on a starting age of 70	benefit for panitumumab was similar to that for cetuximab, and that the latter resulted in an overall survival benefit of 4.7 months. For further details, see sections 4.5–4.7, 4.24 and 4.25. The Committee understood that when one technology is marketed by different companies (for different indications, using different brands), these should not be added for the purpose of establishing the cumulative population to be considered in the context of life-extending treatments at the end of life, and that therefore the criterion for a small population size was fulfilled in this appraisal. For further details, see section 4.23 of the FAD.

Consultee	Comment	Response
	Use of mean, rather than median estimates from the KOL resource-use survey Incorporation of additional administration costs (£15 pharmacy preparation costs) Utility of 0.6 for the Progressive Disease Health state Assumption of no continued treatment effect (i.e. the application of a hazard ratio equal to 1) after the end of trial follow-up. We provide a point-by-point response to these adjustments below. In Appendix B, we present a revised model base-case and results. *3.1. Correction of AE disutility calculations* We accept the correction to the calculation of AE-related disutilities proposed by the ERG and apply this in our revised base-case. *3.2. Use of accurate treatment acquisition costs* Paragraph 4.10 of the ACD states: "It [the Committee] further heard that the acquisition costs of second-line treatments in the model did not depend on the proportion of patients in each state, and that they were calculated outside the model. The Committee agreed that the costs and QALYs in the stable disease health state were not specific to the two sub-states ("on second-line treatment" and "post second line treatment")." We interpret from this statement that the Committee did not reject our approach to the calculation of treatment acquisition costs. We have therefore retained our original approach within our revised base-case, but have provided further justification for this below. We consider that our original approach to calculating treatment costs is the most accurate way of modelling treatment acquisition costs and is more appropriate than the alternative presented by the ERG. Although the overall impact on the ICER is relatively small, the effect of adopting the ERG approach is to inflate the amount of medicine consumed compared to that which was actually used within the VELOUR trial, and thereby bias-upwards the cost of treatment – this has greatest impact on the aflibercept	The Committee noted that the costs and QALYs in the stable-disease health state were not specific to the 2 sub-states ('on second-line treatment' and 'post second-line treatment'). The Committee concluded that overall the model adhered to the NICE reference case for assessing cost effectiveness. For further details, see section 4.12 of the FAD.

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	regimen as will be seen below. In the VELOUR trial, as in normal clinical practice, patients could skip one or more of the individual components of their treatment regimen and/or experience dose delays during any cycle. Reflecting the reality of what treatments were used to achieve the efficacy outcomes observed in VELOUR is important in deriving an unbiased estimate of the cost-effectiveness of aflibercept. In the VELOUR trial, the mean duration of treatment with the aflibercept plus FOLFIRI regimen was [redacted] cycles versus [redacted] cycles in the FOLFIRI plus placebo regimen. The fact that these durations are longer than the mean number of administrations of any one component is due to dose delays and dose skipping. The average administrations derived from using the ERG's alternative modelling approach departs from that observed in the VELOUR trial. Table 3 demonstrates that for all regiment components, the alternative approach overestimates numbers of administrations and the associated costs by 2- 4%. While these appear to be small differences, they nevertheless increase the total treatment costs and this has more impact for the aflibercept plus FOLFIRI arm. **Table 3: Comparison of cost and cycle estimations with ERG calculations**	

		Number of cycles			Costs		
		Actual data from VELOUR	Estimated from time in 2nd-line health state	Difference	Costing based on actual data from VELOUR	ERG costs based on time in 2nd-line health state	Difference
Aflibercept plus FOLFIRI	Aflibercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Irinotecan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Leucovorin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-FU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLFIRI							
	Irinotecan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Leucovorin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5-FU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Consultee	Comment	Response
	*- based on original PAS price As our original approach more accurately reflects the treatment administered in VELOUR trial we maintain that this is a better approach to modelling this complex interplay of regimen components and we therefore maintain this as part of our revised base-case. *3.3. Application of age-related disutility with a correction for the age of the starting cohort* In our revised base-case we have incorporated the age-related disutility as applied by the ERG. However, based on the available evidence and the feedback of experts, we consider the age of the population who are likely to receive aflibercept plus FOLFIRI in UK practice is similar to that observed in VELOUR; we therefore apply a starting age of 60 in our revised base-case. The ERG considered the starting age should be 70, as they believe the VELOUR trial population is younger and fitter than patients with mCRC seen in UK clinical practice. The ERG report originally cited information on the CRC population as a whole in support of their conclusions on the generalisability of the VELOUR population; they subsequently retracted this, and their erratum document acknowledges their conclusions are based on the feedback of one clinical expert. The subpopulation of patients who will be suitable to receive and benefit from multiple lines of combination chemotherapy (and therefore to be eligible for aflibercept) is not the same as the mCRC or CRC population as a whole. Our recollection of responses provided to Committee's questions by the clinical experts at the first Committee meeting were that the VELOUR population does indeed reflect those patients in UK clinical practice likely to receive treatment with aflibercept in combination with FOLFIRI. Both these experts and others that we have heard from, have reflected that age is not a selection criterion for treatment, however to be suitable for second-line combination chemotherapy patients must be fit and with relatively few comorbidities; such patients are therefore likely to be younger than the mCRC population as a whole. We provide below empirical data collected from UK observational studies of patients with mCRC receiving second-line chemotherapy. These indicate that the average age of patients likely to receive aflibercept plus FOLFIRI in UK clinical practice is indeed	Having considered the data from the observational studies, the Committee agreed that the 70-year age of starting treatment, as initially assumed by the ERG in its base case, was too high. It concluded that an age between 60 and 65 years is more appropriate. For further details, see section 4.18 of the FAD.

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	consistent with the average age of patients in the VELOUR trial (Table 4). We therefore question the accuracy of the references made to this discussion in the consultation document, and importantly the application of ageing disutilities to a modelled population with the starting age of 70, and use the starting age of 60 in our revised base-case. **Table 4: Age from UK real-world studies**	

Study	Methodology	Inclusion criteria	Mean age
Observational RU study (described previously in Sanofi submission)	Service evaluation in 4 NHS hospitals	All mCRC patients who had received an irinotecan-based chemotherapy regimen following prior treatment with an oxaliplatin-based regimen including patients relapsing within 6 months of completion of oxaliplatin adjuvant chemotherapy (i.e. all patients within the licensed indication for aflibercept) (commenced irinotecan from 1st Jan 2008)	63
Kantar health chart review[2]	Prospective study - physician documented every patient with mCRC seen over 2-3 weeks	All mCRC patients seen by included physicians	60 (active 2nd line therapy) 71 (supportive care only)
IMS OncoAnalyzer databse [3, 4]	Largest commercially available oncology patient record database	UK patients receiving 2nd line chemotherapy for mCRC (and not enrolled in clinical trials)	63; Median age category 61 – 65
mCRC utilities study (described previously in Sanofi submission)	Cross-sectional study in 2 key UK centres (and 3 Dutch centres)	On 2nd or subsequent lines of treatment or best supportive care , received prior oxaliplatin in 1st line and had Eastern Cooperative Oncology Group (ECOG) performance status scores of 0-2 at 2nd line initiation	63

	3.4. Median values from survey data – why this was an appropriate approach to	Although the Committee agreed that

Consultee	Comment	Response
	take In our original submission we applied median values from a key opinion leader survey to estimate resource-use components associated with community and social care. The clinicians surveyed came from similar, large UK centres, and could be expected to be familiar with secondary care resource use. As commented in the consultation document, if the sample of clinicians were appropriately homogenous, then the distribution of the data collected would be largely uniform, and it would be more appropriate to use mean estimates than median. Whilst we agree with the Committee's opinion on this point, the evidence of significant variation (skew) in a number of the reported resource-use values is indicative of a lack of homogeneity in the survey respondents rather than a representation of the natural variation in the resource-use they are reporting on. It is reasonable to expect the experts' experience and knowledge of care in the community and hospice setting would be more variable as they would be less familiar with day-to-day activities in these settings. To demonstrate this, we examine the responses to estimate of the number of visits (per two week period) from a palliative care team to support patients in the progressed disease state; the responses were: 0.6; 1; 1; 1.3; 2; 8. The estimate of 8 is clearly an outlier in this series and its impact is significant – the ICER based on the mean (2.32) of these values is approximately £4000 higher than when using the median (1.17). We considered it very unlikely that differences of this nature between one or two experts really reflects the real distribution of resources used in these settings and considered that the median value in this set of skewed data would provide a better and more consistent estimate of resource use for the costing of community and social care. Our approach is further supported when we compare the results of using the median values with the estimates used in other mCRC appraisals. In TA242 the per-cycle management costs for the progressed disease state in the Assessment Group model were £1039 per month[5]. This is reasonably close to the £[redacted] per month we obtain using the median of survey responses. Using the mean of responses from the survey generates a substantially higher monthly cost of £1757. Using the mean, rather than the median values, results in an increase of only ~£200 in	mean values should normally be used to estimate resource use and costs, it concluded that, in this instance, the survey responses on 1 parameter appear to contain an outlier, and so using the mean after excluding the outlier could be considered appropriate. For further details, see section 4.19 of the FAD.

Consultee	Comment	Response
	the incremental costs for stable disease, whereas for progressive disease, the incremental costs are increased by ~£1000. As costs are applied on a per cycle basis, costs are increased more in the aflibercept arm due to the longer post-progression survival. Thus the impact is to penalise aflibercept for increasing survival. Therefore, overall we consider that the median is still the most appropriate way to account for the skewed data in this particular survey, and generates progressive disease costs that are consistent with those in previous appraisals. We apply this in our base-case, but also explore in scenario analyses the impact of using the mean values from the survey data in general, but excluding the outlier for the parameter of the number of visits from the palliative care team (the parameter described above). We also provide an analysis using per cycle management costs based on TA242. *3.5. Administration costings to reflect increased cost of delivery* In our original submission we used HRG codes to estimate the overall costs to the NHS of chemotherapy administration. Healthcare Resource Groups are: "standard groupings of clinically similar treatments which use common levels of healthcare resource" and are considered the most relevant cost sources when considering the overall cost to the NHS (http://www.hscic.gov.uk/hrg). We considered that the code SB14Z would be relevant to both FOLFIRI alone and FOLFIRI in combination with aflibercept; this is the most costly of the published HRG codes and may indeed overstate the actual costs of delivering the standard chemotherapy regimen, particularly after the first cycle. The ERG and Committee considered additional costs may be incurred for the administration of aflibercept in addition to FOLFIRI. As noted by the ERG it is difficult to accurately estimate these additional costs. They estimated a cost of an additional £15 for pharmacy preparation time, based on that previously estimated for bevacizumab and cetuximab. This was estimated by the Assessment Group in TA242 based on expert input from a pharmacist and applied in their model[5]. This additional cost was incorporated into the analysis that generated the "most plausible ICERs" (£62K – £66K per QALY). The ERG also estimated a figure of £45 per cycle for the additional administration time related to aflibercept treatment. This was not included within the £62 – 66k ICER estimates, and the ACD reports that the Committee considered the ICER could be higher	The Committee acknowledged that the manufacturer's revised base case accounted for the extra preparation cost and the cost for an additional infusion time for aflibercept. For further details, see section 4.17 of the FAD.

Consultee	Comment	Response
	if these costs were considered. The Committee also considered that the pharmacy preparation costs for aflibercept could be higher than the £15 estimated by the ERG. We do not consider this to be the case - the preparation costs for aflibercept will be similar to bevacizumab and cetuximab, which are both biologic drugs requiring similar preparation methods and times. There is no reason to suppose aflibercept would require higher preparation costs than these other biologics. We therefore consider the £15 cost applied in TA242 to be the most appropriate cost estimate available. We acknowledge the ERG's and Committee's concerns that aflibercept may incur additional costs for pharmacy preparation and administration above those accounted for within the HRG code used in our original model, and address these within our revised base-case. We use the ERG's cost estimates and incorporate the addition of both an additional £15 pharmacy preparation cost and a cost of £45 for additional administration time (i.e. an additional £60 per aflibercept cycle). These were applied in line with the average number of cycles of aflibercept received in the model. *3.6. Why utilities for stable and progressive disease health states should be based on values reported directly from patients, as per the NICE reference case* The utility values in our submission come from an observational real-world study in patients with mCRC undergoing second-line treatment. These data were collected in the UK and Netherlands in 2012/13 and meet the exact requirements of the NICE reference case; i.e. EQ-5D values reported directly from relevant patients and valued using the UK value-set. In considering the face validity of the utility values presented in our submission, the ERG and Committee made reference to population 'norm' data for the corresponding age-group indicating that both stable and progressive disease health state valuations appear too high. This, we suggest, is a mistaken comparison because it is prefaced on the notion that without their cancer, the individuals should report values reflecting the population 'norm' data, and that the presence of their cancer should impose a further burden upon them and naturally reduce this utility valuation. This is mistaken because the population 'norm' data represents an average value and includes patients with good and moderate health, along with those with poor health including significant comorbidities that would	The Committee, having noted the mean and median time to disease progression in the manufacturer's utility study, considered that the utility value chosen by the manufacturer for the progressed-disease state did not reflect the entire duration of progressed disease but only early progressed disease, and so was likely to be an overestimate. The Committee was aware that, in its base case, the ERG used an alternative lower value of 0.60, which had been used in TA118. The Committee agreed that no utility values for progressed disease were universally accepted as valid, but that it would be important that the utility value reflected the entire progressed-

Consultee	Comment	Response
	preclude them from consideration for second-line chemotherapy. What this means is that, by judging the actual, measured EQ-5D scores from fit mCRC patients selected as suitable for second-line chemotherapy, against population norms that are assumed to reflect healthy individuals, but in fact include significant variations due to other major comorbidities, risks inappropriately prejudicing opinion against the real – directly measured – EQ-5D data from the relevant patient cohort. We therefore suggest that the EQ-5D values reported from a directly relevant patient population should not be dismissed as unreasonably high based on an oversimplified benchmarking process with population norm data. In considering the value attributed to progressive disease, the ERG has selected, and the Committee subsequently accepted, a value of 0.6 that does not appear to be based on data, but rather on a 'sense' of appropriateness. We would reiterate that the data from our utility study is measured (as per the NICE reference case) in real patients who had progressed following second-line chemotherapy. The mean time to progression was [redacted] months therefore these are not values from patients who had recently progressed and therefore should be considered reasonably representative of the progressive disease state as a whole. A key consideration raised by the Committee is that progressive disease utility is likely to decline through the course of the progressive disease and therefore a higher value (e.g. 0.71) may not be applicable over the entire course of the progressive disease state. Our understanding from the clinical experts is that patients' HRQoL does not continuously worsen in the progressive disease-state but in most cases does so sharply only towards the end of life. To address this alongside our revised base case we have explored through a scenario analysis the application of a much lower utility for the end of life period. In this scenario we apply a decrement equivalent to applying a utility of 0.3 during the last two months of life. This is described in Appendix A. *3.6.1. Update to the aflibercept safety and utility study - ASQoP* The VELOUR study did not include QoL data but to remedy this we have collected EQ-5D data through a Phase IIIb trial (the ASQoP trial). In our submission we provided baseline data from an interim analysis of this study, which is collecting EQ-5D data from	disease state. For further details, see section 4.16 of the FAD. The Committee was aware that the manufacturer got the utility value for the stable-disease state from the 'mCRC utilities study' and revised it after consultation to a value derived from the ASQoP study. The

Consultee	Comment	Response
	patients receiving aflibercept in combination with FOLFIRI (details of this study were provided in our original submission). Here we present a second interim analysis. This analysis provides data from patients receiving aflibercept in combination with FOLFIRI following progression on an oxaliplatin-based regimen and is therefore highly relevant to the decision problem. Further baseline data have been added at this update for more recently recruited patients, and data for patients recruited earlier who have since received their first few cycles of treatment are now available. The earliest patients into the study have received further cycles but due to limited numbers, data for the later cycles are not presented here. At the data cut-off date for this interim analysis, 149 patients were screened and 116 had received at least 1 cycle. The mean age was 61. Currently available EQ-5D results are shown in Table 5. **Table 5: EQ-5D data from ASQoP interim analysis (full Global interim population)** **Visit** / **N** / **Mean EQ-5D (SD)** **Baseline visit** / 67 / 0.77 (0.22) **Cycle 3** / 63 / 0.78 (0.24) **Change from baseline** / 63 / 0.01 (0.24) **Cycle 5** / 30 / 0.79 (0.18) **Change from baseline** / 30 / -0.02 (0.25) We incorporate the ASQoP data presented above in our revised base-case for the stable disease state, using a weighted average of cycle 3 and 5 (i.e. patients on treatment). This gives a value of 0.78, which is similar to the value obtained from our observational utility study ([redacted]) used for the stable disease state in our original model. As there are not yet data available from ASQoP for patients in the progressed disease state we use the same data as in our original submission for this (i.e. the value of 0.71 from the observational utility study).	Committee noted that the ERG preferred another value from the ASQoP study for the stable-disease state but, because the difference between the manufacturer's value and the ERG's preferred value was small and likely to have a negligible impact on the ICER, the Committee concluded that either value could be considered appropriate. For further details, see section 4.15 of the FAD.

Consultee	Comment	Response
	3.7. Overall survival The Committee and the ERG have reflected that the estimate of mean overall survival is a major driver of cost-effectiveness in the model. This is to be expected in an oncology model, and by following the Decision Support Unit's best practice guide for extrapolating survival data, we presented in our submission the results of multiple curve fit analyses and performed the recommended interpretive steps before settling on the base-case estimate for our economic evaluation. The variation in the predicted mean survival results seen with the fitting of multiple curves to the data is not unexpected – these different functions have different underlying mathematical formulae and therefore generate different results. This is the reason for testing different functions and analysing both statistical and visual fit to the raw data. We recognise the Committee is concerned that the extrapolation of mean OS is however a source of uncertainty in the cost-effectiveness estimates. The NICE Methods Guide (2008, Section 5.7.3) states that "alternative scenarios should be considered to compare the implications of different assumptions around extrapolation for the results. For example, for the duration of treatment effects scenarios might include when the treatment benefit in the extrapolated phase is: (i) nil; (ii) the same as during the treatment phase and continues at the same level; or (iii) diminishes in the long term". The first scenario is the most pessimistic of these. This is represented by the analysis conducted by the ERG that assumes a hazard ratio of 1 after the end of trial follow-up (30 or 36 months), and is that presented in the analyses generating the Committee's "most plausible" ICER. The second scenario is more positive than our original submitted base-case assumption and therefore we have not considered this further. The third scenario is consistent with our base-case in which the HR gradually increases back to 1. However, we recognise the concerns of the Committee and the ERG that in this analysis the increase in the HR is slow and the HR does not reach 1 during the time horizon of the model. We therefore explore a more conservative assumption in our revised base-case. We consider that, rather than assuming the HR reverts to 1 after the end of the observed	The Committee agreed that the ERG's scenario, which assumes equal risk of death for all patients beyond the trial period (hazard ratio equals 1.0), represents an acceptable compromise between the 2 extremes of assuming continuing treatment effect (manufacturer's base case) and allowing for a reversed treatment effect (ERG's other scenario). The Committee acknowledged the new scenario implemented in the manufacturer's revised base case. The Committee agreed that all scenarios to extrapolate overall survival were associated with some degree of uncertainty. As the manufacturer had not provided the follow-up data from the trial on which to validate its new approach, the Committee chose the ERG's scenario. For further details, see section 4.14 of the FAD.

Consultee	Comment	Response
	period, it is more clinically plausible to assume the HR will increase to 1 gradually over a short period of time. We have therefore performed an analysis in which the HR is gradually increased (tapered) back to 1 over a period of 12 months, following the end of trial follow-up. Further details of how this was applied in the model are provided in the Appendix A. We incorporate this in our revised base-case, starting the taper at 36 months. We have explored in scenario analyses the impact of starting this tapering at 30 or 24 months. *3.8 Impact of addressing the points raised on the economic model* In Appendix B we present a revised economic model base-case that addresses the points above and present deterministic and probabilistic results and scenario analyses. The base-case ICER in this was £42,242 (incorporating the revised PAS).	The Committee concluded that the most plausible ICER was higher than the normally acceptable maximum ICER range of £20,000–30,000 per QALY gained, and that aflibercept could not be considered a cost-effective use of NHS resources for patients with metastatic colorectal cancer. For further details, see section 4.26 of the FAD.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
	Thank you for the opportunity to respond to the recent STA provisional guidance ID514. Please consider this letter as expressing the views of the Colorectal cancer Oncologists in Wales as per listed names below. Whilst appreciating the provisional guidance and the detail that has been examined in developing this guidance, we wished to raise and emphasise a number of issues, for consideration by the expert panel: 1. Clinically this drug is effective in this cohort of patients.	The Committee agreed that the difference in median overall survival of 1.44 months reflects a statistically significant but clinically small benefit. It also agreed that, given the data from the VELOUR trial, the true mean overall survival benefit is likely to be closer to the median estimate of 1.44 months than the manufacturer's mean estimate of 4.7 months. For further details, see sections 4.5 and 4.6 of the FAD.

Nominating organisation	Comment	Response
	2. The number of patients who would be appropriate to receive this therapy within England and Wales is relatively small and perceived by this group to come beneath the threshold of guidance for rare indications. Thus, as an end of life therapy this treatment would have relatively insignificant economic impact. 3. Aflibercept is available through the “Cancer Drug Fund” throughout England and will remain so after full guidance is issued. 4. Wales is currently the only contributing country under which NICE guidance is of significant impact, thus as a group of oncologists with responsibility for patients in Wales, we feel that our voice should have significant bearing upon final decisions. 5. It is now evident that there is an economic impact which to date has not been fully assessed or debated; in terms of an institution or nations inability to offer patients “standard of care “. Such a phenomenon impacts upon inward investment by pharma and technology companies and dis-enfranchises patients from the opportunity of being recruited to clinical trials. 6. Whilst we as a group do not profess to be health economists it strikes us that the overriding deciding factor over the guidance for this therapy is a health economics issue. When differing models are used a huge variety in terms of cost per QALY is achieved. We would argue that when a decisions is being made in terms of a therapy that undeniably offers physical benefit to patients and their families and such uncertainty exists, that the benefit of the doubt should side toward the patient benefit rather than the uncertainty of an economic argument for a small sub group of patients with a terminal diagnosis. Your deliberation of these points is much appreciated.	The Committee agreed that the criterion for a small population size was fulfilled in this appraisal. However, it did not agree that aflibercept offered an extension to life of at least an additional 3 months. The Committee therefore concluded that aflibercept did not meet the criteria for an end-of-life therapy as defined by NICE. For further details see section 4.23 and 4.24 of the FAD. The Committee noted that 50% of patients who received aflibercept in the AFFIRM trial lived for up to 1.44 months longer than people who received placebo, and acknowledged the difficulty in finding robust mean overall survival data considering the issues with the extrapolation carried out. In considering those issues, the Committee discussed which extrapolation period could be considered appropriate to estimate mean overall survival, in view of the life expectancy of patients with metastatic colorectal cancer in clinical practice. For further details, see sections 4.7 and 4.24 of the FAD.

Comments received from members of the public

Role*	Section	Comment	Response
NHS Professional	1	I do not agree with this recommendation.	Comment noted. The Committee concluded that the most plausible ICER was higher than the normally acceptable maximum ICER range of £20,000–30,000 per QALY gained. For further details see section 4.26 of the FAD.
	2	This is a novel treatment technology.	Comment noted. The Committee acknowledged that aflibercept represented a novel recombinant fusion protein. However, the Committee concluded that all benefits of a substantial nature relating to treatment with aflibercept plus FOLFIRI had been captured in the QALY calculation. For further details see section 4.20 of the FAD.
	4	There is good evidence from a well designed phase 3 clinical trial to support the use of the drug for patients with metastatic colorectal cancer with FOLFIRI chemotherapy as second line treatment after Oxaliplatin based chemotherapy.	Comment noted. The Committee agreed that the difference in median overall survival of 1.44 months reflects a statistically significant but clinically small benefit. The Committee also agreed that, given the data from the VELOUR trial, the true mean overall survival benefit is likely to be closer to the median estimate of 1.44 months than the manufacturer's mean estimate of 4.7 months. For further details see section 4.5 and 4.6 of the FAD.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
NHS Professional	1	The concept of continuing anti VEGF blockade has been proven to extend overall survival in patients with metastatic colo-rectal cancer in the TML study (Treatment througt mulitiple lines) using a different agent Bevacizumab. Aflibercept has extended survival for the same group of patients in 2nd line in combination with Irinotecan and 5FU. This group had a patients who recieved avastin and who did not in first line setting. This offers a valuble option of colo-rectal cancer patients who had progressed on first line agent in combination with Bevacizumab/or without, especially the patients harboring the K-ras mutation. This particular group have no other biological option available. I believe using Aflibercept give our patients and clinicians muliple options to maximise the benefit from therapy and extend their lives.	Comment noted. The Committee heard that, because the overall survival curves continued to separate for both patients who had or had not stopped treatment, the survival curves might reflect a disease modifying effect in that aflibercept might have altered the natural course of the disease whereby, despite the disease progressing, patients lived longer even after treatment stopped. The Committee agreed that there was no robust evidence to make firm conclusions about the likely cause of the different shapes of the overall survival and progression-free survival curves. For further details see section 4.8 of the FAD. The Committee was aware that there is currently no established method in clinical practice to identify patients with metastatic colorectal cancer who could particularly benefit from treatment, and it was not presented with evidence on how these patients could be selected for treatment with aflibercept. The Committee was aware that, as a post-authorisation commitment to the European Medicines Agency, the manufacturer initiated a biomarker program encompassing 3 studies to help select patients who may be more likely to benefit. The Committee agreed that the results of these studies would be useful for a future review of this appraisal. For further details see section 4.27 of the FAD.
	2	This combination accentuates the toxicity of chemotherapy, so patients selection is vital.	
	3	The Velour study was a well conducted study which met it's primary endpoint. I agree that patient selection is vital with this combination, but it offers a real choice for patients	

Role*	Section	Comment	Response
NHS Professional	1	I would like to support availability of aflibercept for selected group of patients	Comment noted. The Committee was aware that there is currently no established method in clinical practice to identify patients with metastatic colorectal cancer who could particularly benefit from treatment, and it was not presented with evidence on how these patients could be selected for treatment with aflibercept. The Committee was aware that, as a post-authorisation commitment to the European Medicines Agency, the manufacturer initiated a biomarker program encompassing 3 studies to help select patients who may be more likely to benefit. The Committee agreed that the results of these studies would be useful for a future review of this appraisal. For further details see section 4.27 of the FAD.
NHS Professional	1	The decision not to recommend aflibercept is obtuse. Aflibercept is a unique technology in a sense that it is a not a monoclonal antibody, but a genetically engineered fusion molecule incorporating VEGF receptors 1 and 2 leading to a VEGF 'trap'. It binds VEF-A but unlike bevacizumab also VEGF-b and placental growth factor. Alflibercept incombination with FOLFIRI produces a prolonged survival because the survival curve is biphasic and a group of around 20% have survival of over 2 years. This is not seen with bevacizumab. It is reminiscent of ipilimumab where some patients get substantial benefit and this has not been taken account of.	Comment noted. The Committee acknowledged that aflibercept represented a novel recombinant fusion protein. However, the Committee concluded that all benefits of a substantial nature relating to treatment with aflibercept plus FOLFIRI had been captured in the QALY calculation. For further details see section 4.20 of the FAD. The Committee was aware that there is currently no established method in clinical practice to identify patients with metastatic colorectal cancer who could particularly benefit from treatment, and it was
	2	Aflibercept is unique technology, it is a soluble fusion molecule and represents a new chapter in applied genetically engineered targeted medicines	

Role*	Section	Comment	Response
	3	The manufacturers submission is well written. The time line of 15 years for survival projection is probably not reasonable. However the survival curve for VELOUR is biphasic and around 20% of patients get substantial benefit. The modelling of these curves needs to take into account this phenomenon.	not presented with evidence on how these patients could be selected for treatment with aflibercept. The Committee was aware that, as a post-authorisation commitment to the European Medicines Agency, the manufacturer initiated a biomarker program encompassing 3 studies to help select patients who may be more likely to benefit. The Committee agreed that the results of these studies would be useful for a future review of this appraisal. For further details see section 4.27 of the FAD.
	4	This is by and large reasonable but you must react to new evidence. Here because those patients progressing within 6 months of completing adjuvant therapy did so badly (actually harmed) I would not treat this group of patients. We have known that this group do badly since the ACCENT group published a retrospective analysis of around 10 000 patients relapsing at different periods after completing adjuvant therapy and this trial VELOUR, provides new evidence on this point. Doing this does improve the utility of aflibercept considerably. The other point is single agent irinotecan is really not used ay all in the NHS, is nearly always FOLFIRI	Comment noted. The Committee heard from the clinical specialists that, in clinical practice, patients who had received oxaliplatin-based therapy in the adjuvant setting and relapsed within the following 6 months would not be treated differently to the overall trial population. In addition, the Committee noted that the analysis for this subgroup was planned after the trial results had been compiled, and that the test for interaction did not show that the treatment effect in this subgroup differed from the effect in the rest of the trial population. The Committee therefore concluded that it did not need to consider further the subgroup that excluded patients whose disease had relapsed 6 months or less after starting oxaliplatin-based adjuvant therapy. For further details see section 4.10 of the FAD.
	6	TA 242 was very flawed because it really didn't review all the available RCT evidence for bevacizumab or the EGFR monoclonals. NICE technology and methods unravel when multiple trials need analysis.	Comment noted.

Role*	Section	Comment	Response
NHS Professional	1	I don't understand the logic. FOLFIRI-Aflibercept is an effective and well tolerated regimen. It's at the very least non inferior to similar studies using Bevacizumab.	Comment noted. The Committee agreed that the difference in median overall survival of 1.44 months reflects a statistically significant but clinically small benefit. The Committee also agreed that, given the data from the VELOUR trial, the true mean overall survival benefit is likely to be closer to the median estimate of 1.44 months than the manufacturer's mean estimate of 4.7 months. For further details see section 4.5 and 4.6 of the FAD. Bevacizumab is not recommended by NICE in TA242 at this stage in the treatment pathway. It was therefore not considered a relevant comparator for aflibercept in this appraisal.
	2	I believe this makes the drug slightly cheaper than Bevacizumab	Comment noted. Bevacizumab is not recommended by NICE in TA242 at this stage in the treatment pathway. It was therefore not considered a relevant comparator for aflibercept in this appraisal.
	3	I think the clinical data speaks for itself. It is in my understanding cost beneficial over bevacizumab. I cannot follow the logic in the QALY or ICER calculations at all. For CDF purposes it is unlikely that maintenance therapy will be approved, what is the QALY / ICER using 12 cycles FOLFIRI-Af with no maintenance?	Comment noted. Bevacizumab is not recommended by NICE in TA242 at this stage in the treatment pathway. It was therefore not considered a relevant comparator for aflibercept in this appraisal. NICE recommendations are independent of how the Cancer Drugs Fund is likely to approve funding for health technologies.

Role*	Section	Comment	Response
	4	There are defined groups of patients for whom a 3 month improvement in survival is possible, I am disappointed at the negative guidance. This drug, for certain patient groups, should be available via the NHS. We can discuss the patient groups I feel would benefit most	Comment noted. The Committee was aware that there is currently no established method in clinical practice to identify patients with metastatic colorectal cancer who could particularly benefit from treatment, and it was not presented with evidence on how these patients could be selected for treatment with aflibercept. The Committee was aware that, as a post-authorisation commitment to the European Medicines Agency, the manufacturer initiated a biomarker program encompassing 3 studies to help select patients who may be more likely to benefit. The Committee agreed that the results of these studies would be useful for a future review of this appraisal. For further details see section 4.27 of the FAD.