NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer [ID794]

The following documents are made available to the consultees and commentators:

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

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Amgen
   - Merck Serono
   - Beating Bowel Cancer
   - Royal College of Physicians

   The Department of Health, Roche and the Royal College of Nurses informed us that they had no comments on this ACD

3. **Comments on the Appraisal Consultation Document from experts:**
   - Dr Saifee Mullamitha – Clinical Expert, nominated by Roche

4. **Comments on the Appraisal Consultation Document received through the NICE website**

5. **Assessment Group addendum prepared for 6 January meeting**
   - Addendum
   - Response to comments on the ACD

6. **Additional information submitted by the companies** after the 6 January Committee meeting from**:**
   - Amgen
   - Merck Serono

7. **Addendum to the Assessment Report** prepared by the Peninsular Technology Assessment Group for the 7 September Committee meeting**:**

8. **Comments on the Addendum to the Assessment Report** prepared for the 7 September Committee meeting from**:**
   - Amgen
   - Merck Serono
   - Beating Bowel Cancer
   - Bowel Cancer UK
   - The Royal College of Physicians (on behalf of the NCRI-ACP-RCP-RCR)
   - NHS England

- Comments from the clinical experts – Drs Mullamitha and Potter
  Sanofi indicated that they had no comments on the Addendum

9. **Assessment Group addendum prepared on 5 September 2016**

10. **Additional information submitted by the companies** for the January 2017 Committee meeting from:
- Amgen
- Merck

11. **Additional information submitted by consultees** for the January 2017 Committee meeting from:
- Beating Bowel Cancer and Bowel Cancer UK
- Royal College of Physicians on behalf of the NCRI-ACP-RCP-RCR
- NHS England

12. **Addendum from the Assessment** Group for the January 2017 Committee meeting

Any information supplied to NICE which has been marked as confidential has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

Cetuximab and panitumumab for previously untreated metastatic colorectal cancer

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 companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

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 NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Amgen	Executive summary We have carefully reviewed the Appraisal Committee's consideration of the evidence on panitumumab for previously untreated metastatic colorectal cancer (mCRC). We are disappointed by the conclusions reached and the resulting preliminary guidance not to recommend panitumumab. We welcome the opportunity to respond to the Appraisal Consultation Document (ACD). In our response, we address the key issues highlighted in the ACD, specifically regarding robustness of the evidence base and overall survival (OS) data for panitumumab and qualification of panitumumab for End of Life (EoL) criteria. We believe that the evaluation of panitumumab as an EoL therapy, modelled using robust OS data, together with the [redacted] increased patient access scheme (PAS) ([redacted]), would demonstrate panitumumab to be a cost effective treatment; achieving an ICER [redacted] accepted for EoL treatments. Access to panitumumab and cetuximab through the Cancer Drugs Fund (CDF) has delivered critical improvements in outcomes for previously untreated mCRC patients. This appraisal presents an opportunity to move panitumumab into baseline commissioning and provide patients with a vital therapeutic alternative in this life limiting condition.	Thank you for your comment. After considering the comments received in response to the ACD in conjunction with the new evidence submitted by the companies and the assessment group, the committee recommended cetuximab and panitumumab as specified in section 1 of the FAD.
Amgen	1.Strength of the evidence base **Uncertainties regarding the clinical evidence base** The ACD repeatedly noted concerns around the strength of the evidence base for panitumumab:	Thank you for your comment. After considering the comments received in response to the ACD, the committee considered the uncertainties in the clinical evidence as specified in section 4.6 of the FAD.

	"The Assessment Group stated that the clinical evidence was limited because it reflected subgroup analyses. The trials were analysed post-hoc after re-evaluating tumour samples from people with KRAS wild-type exon 2 tumours, and reclassifying them by RAS wild-type status as currently defined. The Assessment Group noted that there were few samples available for re-analysis and missing data further reduced the power of some studies". (Page 9, 4.3) *"The Committee heard that the evidence for cetuximab and panitumumab in people with RAS wild-type colorectal cancer is based on post-hoc subgroup analyses of clinical trial data. The Committee understood that analyses were based on small data sets with missing data, which reduced the chance that these analyses would uncover true differences between treatments. The Committee concluded that, although the current data are more mature than in NICE's technology appraisal guidance on cetuximab for the first-line treatment of metastatic colorectal cancer, there is more uncertainty in the evidence base because it involved smaller populations". (Page 25, 4.30)* *"The Committee concluded that the clinical evidence surrounding the degree to which cetuximab and panitumumab are effective in RAS wild-type metastatic colorectal cancer was subject to considerable uncertainty". (Page 27, 4.32)* We believe that the uncertainties that have been raised around the clinical evidence base in patients with WT RAS tumours do not apply to the comparison of panitumumab plus FOLFOX versus FOLFOX. The clinical evidence for panitumumab plus FOLFOX versus FOLFOX comes from the PRIME study which randomised more than 1000 patients. PRIME included a large number of patients with WT RAS tumours (n=512), the RAS ascertainment rate was high (90% of all randomised patients) and clinically meaningful and statistically significant benefits in PFS and OS in favour of panitumumab plus FOLFOX were demonstrated (Douillard et al, 2013). The PRIME WT RAS evidence was based on a pre-specified subgroup analysis that was accepted by the EMA, with baseline patient characteristics similar to the WT KRAS population and the intent to treat (ITT) population. The size of the WT RAS subgroup (n=512) compares favourably with that of the previously licensed WT KRAS population (n= 656 in PRIME) and the width of confidence intervals around the hazard ratios (HRs) for PFS and OS are similar in the 2 populations, suggesting that loss of precision is not an issue when moving from the WT KRAS population to the WT RAS population (Table 1). It should also be noted that a subgroup analysis was unavoidable since the ability of RAS mutation status to predict response to treatment was unknown when the PRIME trial was designed.	

Table 1. Comparison of PRIME and OPUS clinical evidence

	PRIME (Panitumumab+FOLFOX vs. FOLFOX)		OPUS (Cetuximab+FOLFOX vs. FOLFOX)	
	WT KRAS	**WT RAS**	**WT KRAS**	**WT RAS**
N	656	512	179	87
RAS ascertainment rate, %	N/A	90	N/A	66
PFS				
HR (95% CI)	0.80 (0.66, 0.97)	0.72 (0.58, 0.90)	0.567 (0.375, 0.856)	0.53 (0.27, 1.04)
Width of 95% CI around HR	0.31	0.32	0.48	0.77
OS				
HR (95% CI)	0.83 (0.70, 0.98)	0.77 (0.64, 0.94)	0.855 (0.599, 1.219)	0.94 (0.56, 1.56)
Width of 95% CI around HR	0.28	0.30	0.62	1.00
Maturity of OS data, n (%) died	535 (82)	422 (82)	126 (70)	63 (72)

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; pmab, panitumumab; N/A, not applicable; OS, overall survival; WT, wild-type.
Source: PRIME (Douillard et al, 2013; Amgen, 2013), OPUS (Bokemeyer et al, 2015; Bokemeyer et al, 2011)

We therefore do not accept the concerns regarding low sample size and missing data, and the consequent lack of power, apply to the evidence base for panitumumab. Instead, the uncertainty in the evidence base relates primarily to the OPUS study comparing cetuximab plus FOLFOX with FOLFOX. OPUS included only 87 patients with WT RAS tumours, had a much lower RAS ascertainment rate (66%) and confidence intervals around HRs were substantially wider than in PRIME, particularly in the WT RAS subgroup (Table 1).

	It is notable that the EMA stated "*although cetuximab data by RAS status are only derived from the randomised phase II study OPUS, the biological rationale supporting the efficacy in patients with RAS wild type tumours only is strong and the conclusions are supported by data related to panitumumab*" (European Medicines Agency, 2013). This underscores the strength of panitumumab data, as it was used to augment the evidence base in patients with RAS WT tumours for cetuximab. Regarding maturity of the OS data, 82% of patients with WT RAS tumours in PRIME had died at the time of the updated analysis of OS compared with 72% of patients in OPUS (Table 1). We would argue that the PRIME data are sufficiently mature and that NICE have been pragmatic and regularly have recommended therapies based on OS data that are not fully mature, e.g. TA319 (National Institute for Health and Care Excellence, 2014a). In summary, we believe that there is robust clinical evidence comparing panitumumab plus FOLFOX versus FOLFOX in WT RAS patients which demonstrates a statistically significant and clinically meaningful median OS gain of 5.6 months. Therefore the uncertainties raised in the ACD, regarding low sample size and missing data relate specifically to the evidence base for cetuximab plus FOLFOX and should not be attributed to panitumumab. **Generalisability of the trial population in PRIME to patients treated in the NHS** The ACD queried the relevance of the trial population in the pivotal phase 3 clinical trial (PRIME) to patients treated in the NHS. *"The Committee heard from clinical experts that the trial populations were younger than patients seen in clinical practice. The Committee concluded that the populations in the clinical trials of cetuximab and panitumumab differed from patients in clinical practice in England, and that this difference was a source of uncertainty in the clinical- and cost-effectiveness results". (Page 25, 4.29)* RCTs are considered the gold standard for assessing new interventions due to control of bias, however it is acknowledged that entry criteria can lead to populations that differ from those seen in routine clinical practice (Ballman et al, 2014). We think it is reasonable to assume that results from PRIME can be generalised to the wider NHS patient population and are not aware of any evidence to suggest otherwise. NICE have	

	taken a pragmatic stance on this in other appraisals, e.g. TA221 (National Institute for Health and Care Excellence, 2011).	
Amgen	2. Robustness of the OS gain for panitumamab The ACD noted concerns regarding the robustness of the OS gain for panitumumab *"The Assessment Group assumed in its base-case analysis that the duration of survival after first-line treatment was independent of first-line treatment (that is, any treatment effect from first-line drugs stopped when disease progressed). By contrast, in the randomised controlled trials, overall survival reflected response to both first and subsequent lines of treatment. However, the Assessment Group considered it inappropriate to assume this in its model because the trials included second-line drugs that are not commonly used in the NHS (including second-line panitumumab, cetuximab and bevacizumab) and may prolong survival. It also noted that second-line treatments were imbalanced across the trial arms. In addition, it considered that the survival data from trials were not mature enough. Therefore the Assessment Group modelled only progression-free survival from the randomised controlled trials, not overall survival". (Page 14, 3.13)* We believe that the economic model should be based on OS which is widely recognised as the "gold standard" endpoint in oncology trials from a clinical and patient perspective (Driscoll et al, 2009). It is common for patients to move on to subsequent lines of treatment (which may prolong survival) post-progression in oncology trials and we note that NICE has previously accepted economic models based on OS in this situation, e.g. TA319, TA268 and TA269 (National Institute for Health and Care Excellence, 2014a; National Institute for Health and Care Excellence, 2012a; National Institute for Health and Care Excellence, 2012b). We acknowledge that subsequent treatments may prolong survival (in particular second-line anti-EGFR therapy and bevacizumab which are not commonly used in the NHS) and that these were not balanced across treatment arms in PRIME. It should be noted that the proportion of WT RAS patients receiving any subsequent anti-tumour therapy was slightly higher in the FOLFOX arm compared with the panitumumab arm (67% vs 58%): Use of traditional chemotherapy agents was slightly higher in the FOLFOX arm (64% vs 54%),	Thank you for your comment. After considering the comments received in response to the ACD, the committee considered the uncertainties in the clinical evidence as specified in sections 4.6 and 4.14.

whilst use of bevacizumab was broadly similar for the FOLFOX and panitumumab plus FOLFOX arms respectively (13% vs 16%). However subsequent anti-EGFR therapy was more commonly received in the FOLFOX arm than in the panitumumab plus FOLFOX arm (19% vs 7%).

In our response to the Assessment Report, we presented analysis which used a variety of recognised statistical methods to explore the impact of subsequent anti-EGFR therapy on the OS benefit in PRIME in WT KRAS patients (Douillard et al, 2012). We now present further analysis in the WT RAS population of interest, using the inverse probability of censoring weighted (IPCW) method; the OS HR for panitumumab plus FOLFOX versus FOLFOX is 0.69 (95% CI 0.50 to 0.95) compared with the ITT analysis HR of 0.77 (95% CI 0.64 to 0.94) (Table 2).

The results from the WT RAS analysis confirms those presented for KRAS and suggest that the true OS benefit for panitumumab plus FOLFOX versus FOLFOX is larger than that observed in the PRIME trial (Table 2). The Assessment Group acknowledged this during the first Appraisal Committee meeting and stated likewise in their response to consultee comments that the ICER for panitumumab plus FOLFOX versus FOLFOX can be considered an upper bound (in OS scenario analysis).

In addition, the ACD concerns about the use of second-line drugs that are not commonly used in the NHS are only relevant if they serve to prolong the OS gain for panitumumab. The results presented in the table below show that these concerns are unfounded, as they do not inflate the OS gain for panitumumab.

Table 2. Impact of subsequent anti-EGFR therapy on OS in PRIME

	OS HR (95% CI) Panitumumab plus FOLFOX vs FOLFOX	
	WT KRAS[a]	**WT RAS[b]**
Intent to treat analysis	0.88 (0.73, 1.06)	0.77 (0.64, 0.94)
Statistical model for influence of subsequent anti-EGFR therapy		
Branson & Whitehead, 2002	0.84 (0.68, 1.05)	
Robins & Tsiatis, 1992	0.83 (0.66, 1.04)	
Allison, 1995	0.68 (0.55, 0.83)	

	Inverse probability of censoring weighted (IPCW) | 0.74 (0.56, 0.97) | 0.69 (0.50, 0.95) CI, confidence interval; HR, hazard ratio; OS, overall survival; WT, wild-type. [a] Based on final analysis (data cut-off 02 August 2010). [b] Based on OS update analysis (data cut-off 24 January 2013). Source: WT KRAS: (Douillard et al, 2012); WT RAS: (Peeters et al, 2013). The validity of a PFS-based model for the base case is questionable given that OS results generated from the model are not consistent with results from the PRIME and OPUS trials: In Table 3 of the ACD the base case model mean OS gain for panitumumab plus FOLFOX versus FOLFOX is 2.6 months, which is substantially lower than the mean OS gain of 5.7 months in PRIME. Similarly, the base case model mean OS gain for cetuximab plus FOLFOX versus FOLFOX is 6.6 months, which is much higher than the mean OS gain of 0.5 months in OPUS. In summary, we do not accept that an OS model is inappropriate and indeed the Assessment Group have stated that OS is an important scenario analysis in their response to consultee comments. Analysis of the impact of subsequent therapies on OS suggests that the OS benefit observed is an underestimate of the true benefit of panitumumab plus FOLFOX compared with FOLFOX. This also addresses ACD concerns regarding second-line therapies not commonly used in the NHS, by demonstrating that they do not prolong OS gain for panitumumab. Therefore we consider OS data in PRIME is robust and should be used in the economic model, in preference to PFS data, to inform the base case ICER.	
Amgen	<u>3. Consideration of the EoL criteria for panitumumab</u> The Appraisal Committee considered the evidence presented on the EoL criteria and concluded that the while panitumumab fulfilled the criteria of short life expectancy and extension to life, there was uncertainty around the criterion of small patient population (< 7000 people) and therefore it deemed that EoL status was “probably not met” for panitumumab. The Assessment Report included three population estimates for the RAS WT mCRC population: 5,968, 4,728 and 8,511, the first two being Merck Serono estimates and the last the Assessment Group’s estimate of the population. The decision that panitumumab does not meet EoL criteria was based solely on the one estimate that exceeded 7,000 and consequently is unbalanced. More importantly, the Assessment	Comment noted. The population size is no longer a consideration for end-of-life. Please see the Final CDF Technology Appraisal process and methods (addendum to the Guide to the Processes of Technology Appraisal and addendum to the Guide to the Methods of Technology Appraisal for further information. The committee’s end-of-life considerations are outlined in section 4.20 of the FAD.

	Group's estimate of 8,511 is an overestimate as it is based on a population that is broader than the population licensed for treatment with panitumumab: The license for panitumumab is limited to WT RAS patients who are eligible for certain chemotherapy regimens (FOLFOX or FOLFIRI in the first-line setting and FOLFIRI in the second-line setting for patients who have received first-line fluoropyrimidine-based chemotherapy excluding irinotecan) The estimate of 8,511 is based on the total (instead of the licensed) wild type RAS population, regardless of the type of chemotherapy regimen these patients would be eligible for. Using the IMS Oncology Analyser (an oncology patient-record database based on clinician-reported case histories from UK patients and considered the most established and robust data source of market share data) we demonstrate that the population size falls well below the criterion of 7,000 when considering the patients eligible for panitumumab as per its license indication in different lines of therapy. • The number of patients treated with FOLFOX or FOLFIRI in the first- line setting who would be eligible for panitumumab first-line therapy, in accordance with its license, was estimated to be 3,250 (**Error! Reference source not found.**). • The number of patients eligible for panitumumab second-line therapy, in accordance with its license, was estimated to be 1,693 (**Error! Reference source not found.**). • The number of patients eligible for panitumumab third-line monotherapy (after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens), in accordance with its license, was estimated to be 180 (**Error! Reference source not found.**). This was based on the Tappenden algorithm (Tappenden et al, 2007), where 5% of the total second-line chemotherapy population goes on to receive third line chemotherapy. Therefore a total of 5,123 patients are eligible for panitumumab across the first, second and third-line settings, which is well below the suggested population limit for EoL criteria. It is highly likely that this estimate of population size is an overestimate. In the first-line setting, the market share of patients previously treated with FOLFOX/FOLFIRI regimens (45.2%, **Error! Reference source not found.**) also included regimens in combination with a biologic. In the second-line setting, the market share of patients	

	previously treated with fluoropyrimidine combination therapy without irinotecan (47.1%, **Error! Reference source not found.**), included cetuximab treatment (although in practice retreatment with an anti-EGFR inhibitor would be highly unlikely). It is also noteworthy that in the previous NICE assessment of aflibercept in TA307 (National Institute for Health and Care Excellence, 2014b), the total second-line chemotherapy population in mCRC accepted by the Committee was 4,000 patients (Wade et al, 2013). This is again much smaller than the estimate of total second-line chemotherapy population of 7,190 in **Error! Reference source not found.**. The Appraisal Committee's conclusion that panitumumab does not meet the population size EoL criterion is also inconsistent with previous EoL determinations where NICE have placed less importance on this criterion and accepted treatments whose estimates of patient numbers were less certain and exceeded the threshold (<7000). Examples include TA309 (National Institute for Health and Care Excellence, 2014c) and TA208 (National institute for Health and Care Excellence, 2010). The ongoing consultation jointly published by NHS England and NICE for the future of the CDF proposes the removal of the restriction of cumulative patient population from the current EoL criteria, recognising that ***"this criterion has rarely been engaged"***. Although the NHS England / CDF consultation is ongoing and is expected to be published in April 2016, it is important for the Committee to be aware of the impending changes to the EoL criteria, since panitumumab would certainly qualify for EoL under the new proposals. Importantly, the current considerations of the Committee that panitumumab does not meet EoL criteria would no longer be relevant when guidance on this appraisal (ID794) comes to be published in April next year. We have demonstrated that when using the current EoL criteria (which include the criterion on small patient population size), the panitumumab licensed population falls well within the upper bound of 7,000 patients and should therefore qualify as an EoL treatment. In addition, panitumumab will also meet the revised changes to the EoL criteria proposed under the ongoing CDF consultation, with the removal of the criterion for small patient population size.	
Amgen	4. <u>Assessment of the ICER for panitumumab using the robust OS data and assuming the EoL life criteria are met</u> The Committee state in the ACD that *"even if the end-of-life criteria were met, an unacceptably large weighting would need to be put on the QALY to bring the ICERs*	Comment noted. After considering the comments received in response to the ACD in conjunction with the new evidence submitted by the companies and the assessment group, the committee

	for cetuximab and panitumumab into the range representing a cost-effective treatment". (Page 35, 4.41) This conclusion is misleading for panitumumab. Whilst this may be true for a base case using suboptimal survival data, i.e. PFS data, it is incorrect when using OS data from the PRIME study to inform the base case model. Indeed, the Assessment Group estimated the ICER for panitumumab based on OS data and including the previous [redacted] confidential PAS to be [redacted], which although is not within the threshold considered when appraising EoL treatments, is close to it. It is also noteworthy that the ICER is expected to decrease further when a resection rate of 15%, as advised by experts, is applied instead of the current lower resection rate of 12.6% for panitumumab.	recommended cetuximab and panitumumab as specified in section 1 of the FAD. The committee's end-of-life consideration and conclusions are outlined in sections 4.0 of the FAD.
Amgen	5. <u>Consideration of a revised base case ICER for panitumumab using robust OS data, assuming EoL criteria are fulfilled, and applying the increased confidential PAS for panitumumab</u> Colorectal cancer is the third most common cancer in England and prognosis is poor in patients with metastatic disease. It is for these patients with a clear unmet need for whom there are no NICE-approved targeted therapies for the first line treatment of mCRC. Panitumumab in this setting offers a chance of providing significant patient benefit and would be a valuable option for these patients. If the Appraisal Committee's draft guidance is published as final guidance, there will no first-line targeted treatment options available to NHS patients with mCRC. Although the panitumumab OS data were considered strong for the purpose of regulatory approval in the RAS WT patient population, the ACD raises questions around the strength of the clinical evidence base and the robustness of OS data in this setting. We have addressed these concerns in our response and are now offering what we believe to be [redacted] increased PAS ([redacted]) in order to mitigate the risk to the NHS resulting from any residual uncertainties in the evidence base and to demonstrate the cost effectiveness of panitumumab (when OS data is used and when panitumumab is deemed to meet the EoL criteria). We would strongly recommend that the Committee consider a more plausible revised base case analysis based on the use of robust and highly plausible OS data and the	Comment noted. After considering the comments received in response to the ACD in conjunction with the new evidence submitted by the companies and the assessment group, the committee recommended cetuximab and panitumumab as specified in section 1 of the FAD. The committee's end-of-life consideration and conclusions are outlined in section 4.240of the FAD.

<table>
<tr>
<td></td>
<td>fulfilment of current EoL considerations (including policy considerations around the removal of the EoL criterion on small patient population size), specifically:
• Use a model structure based on OS
• Apply EoL considerations to panitumumab
• Apply the increased confidential discount of [redacted] to the drug cost of panitumumab
• Assume a resection rate of 15% as advised by experts
We believe this more plausible revised base case, considering all the factors above, would bring the ICER for panitumumab into a range representing a cost-effective treatment.</td>
<td></td>
</tr>
<tr>
<td>Amgen</td>
<td>6. Factual Inaccuracies
We wish to highlight two factual inaccuracies within the ACD and propose the recommended corrections as described in Table 3 below.

Table 3. Factual inaccuracies in the ACD
<table>
<tr><th>ACD Section</th><th>Factual Inaccuracy</th><th>Recommended Correction</th></tr>
<tr><td>2.1</td><td>The 5-year survival rate for mCRC is stated as ‘under 60%’</td><td>The value stated in the NICE final scope document is 6.6% so this should be corrected to ‘under 10%’</td></tr>
<tr><td>4.39</td><td>The ACD states ‘The Committee understood from the clinical experts that the Assessment Group had overestimated resection rates. The Assessment Group had not presented ICERs using lower resection rates, but informed the Committee that lower resection rates would increase the ICERs and worsen cost effectiveness’</td><td>This statement is not correct for panitumumab. The resection rate used in the model for panitumumab is 12.6% which is below the 15% rate recommended by the clinical experts (section 4.36 of ACD) and therefore is not an overestimate. Using the 15% rate advised would decrease the ICER for panitumumab and improve cost effectiveness.</td></tr>
</table></td>
<td>Comment noted. The FAD has been revised and the highlighted factual inaccuracies are no longer included in the document.</td>
</tr>
</table>

Merck Serono	Merck Serono's comments on Appraisal Consultation Document Merck is disappointed by the committee's preliminary decision to not recommend cetuximab for treatment of patients with mCRC and believe a number of key areas in the Appraisal Consultation Document (ACD) should be revised which are outlined here in our response. The Appraisal Committee have requested feedback on a number of questions including those noted here. • **Has all of the relevant evidence been taken into account?** Merck does not agree that all the relevant evidence has been taken into account. Namely, there is a wealth of clinical evidence and clinical usage that supports the efficacy of cetuximab in combination with chemotherapy, both FOLFOX and FOLFIRI; this should be taken into account and the equivalence of benefit seen with cetuximab/FOLFIRI with cetuximab/FOLFOX be acknowledged. • **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** No, the clinical and cost effectiveness analyses conducted are based upon inaccurate treatment durations, treatment schedule and administration costs and therefore do not reflect a true representation of the clinical environment nor the appropriate costs to the NHS. • **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** No, these recommendations would mean that cetuximab, which has been available for treatment of patients with metastatic colorectal cancer (mCRC) since 2011 would no longer be widely available via the NHS and that the majority of mCRC patients would only have access to chemotherapy, without any personalised medicines, for treatment of their metastatic disease and therefore represents a step backwards for patient care. **General issues with the ACD findings**	Thank you for your comment. After considering the comments received in response to the ACD in conjunction with the new evidence submitted by the companies and the assessment group, the committee recommended cetuximab and panitumumab as specified in section 1 of the FAD. Specific comments are addressed in the sections below.

	1) **Assessment group drug administration Costs.** There are serious and substantive errors with the administration costs ascribed in the ERG model, which render its estimation of administration cost non-credible. This has been confirmed by Department of Health, Reference Costs Team (Appendix 1 & 2) and the revised cost should be applied to future modelling. The appropriate administration costs are £830 per month for chemotherapy administration, and £849 per month for cetuximab plus chemotherapy administration, assuming the fortnightly administration routinely used in clinical practice. 2) **Weekly dosing regimen used by NICE.** The provisional recommendations in the ACD are not a suitable basis for guidance to the NHS as NICE has ignored the fact that cetuximab is predominantly administered in the NHS as a fortnightly dose and instead has applied weekly administration costs in the model. NICE should seek to model those costs which most closely reflect current UK practice, while remaining mindful of the licenced indication. 3) **Applicability of clinical data to the UK population was questioned.** Merck contests this. The clinical data underpinning this submission are relevant to the UK population; those patients treated in the clinical trials with cetuximab/chemotherapy represent the patient population that would be considered fit for treatment with cetuximab/chemotherapy in UK clinical practice. **The broad first line metastatic colorectal cancer population** **1) Limitation of post-hoc analyses.** The post hoc RAS analyses presented in this submission represent the advances in the scientific understanding of personalised medicine over the last 10 years. These RAS data were robust enough to be accepted by EMA for a license change in 2013. In addition, with the advancement seen in personalised medicine, it would be unethical to conduct a clinical trial in RAS wild-type patients fit for triplet treatment (cetuximab/chemotherapy) and offer them chemotherapy alone, denying them the additional survival benefit obtained from cetuximab combined with chemotherapy.	

	2) **Questions regarding cetuximab/FOLFOX efficacy.** There are a number of clinical trials in addition to OPUS as well as clinical usage that supports the efficacy of cetuximab in combination with chemotherapy, both FOLFOX and FOLFIRI; this should be taken into account and the equivalence of benefit seen with cetuximab/FOLFIRI with cetuximab/FOLFOX be acknowledged. The OPUS RAS wild-type analysis is affected by the limited number of samples available in the post-hoc analysis but it does not represent the overall clinical efficacy dataset supporting cetuximab/FOLFOX. 3) **Assessment group overestimation of treatment duration.** The modelled treatment duration from the ERG grossly overstates reality and in turn inflates the ICER. The actual mean treatment durations from the clinical trials have been supplied and it was confirmed by clinical experts at the committee meeting that these are more representative than the modelled treatment durations from the ERG. Real world data suggests a mean treatment duration for cetuximab plus chemotherapy of 23.7 weeks. 4) **End of Life criteria.** Merck disputes that the cetuximab patient population exceeds 7,000. Cetuximab is a well-established drug in the UK, not a new treatment and meets end of life criteria based on the number of patients that are actually treated , reflecting the true potential population and therefore should be granted a fully extended QALY threshold. **The liver limited disease (LLD) sub-population** 1) **Confusion around patient populations in the ACD.** There seemed to be some confusion regarding differentiating between the broad mCRC population and the LLD mCRC population. The LLD population is a specific subset of patients with initially unresectable liver-only metastasis that could be downsized with cetuximab, allowing for potentially curative resection. Approximately 15-20% of the mCRC population will have metastases that are confined to the liver upon presentation with metastatic disease. Compared to the general mCRC population, the LLD population have a better prognosis and are treated with curative intent as opposed to palliative treatment. The scope	

	of this MTA is for patients with previously untreated mCRC, therefore the total population, not just the LLD sub-population, therefore the focus of the Merck submission was the total population. 2) **Cost effective in NICE TA176 but not in current analysis.** Cetuximab in combination with chemotherapy has previously been evaluated as cost effective in this patient population. A smaller restricted patient population (all RAS wild-type instead of KRAS wild-type) which has the potential to enhance outcomes, would be expected to increase, not decrease this cost effectiveness but this is what has been seen in the ERG model. Therefore, Merck contests that with a refinement of the patient population cetuximab plus chemotherapy remains cost effective when moving from the KRAS to the RAS wild-type LLD mCRC patient population. Therefore, Merck feel that there are a number of outstanding issues that need to be addressed in order for an accurate assessment to be completed and will continue to work constructively with the NICE committee and the clinical experts to address and understand potential areas of methodological differences, to make a fully informed and appropriate decision with regards to this appraisal.	
Merck Serono	Introduction Merck is disappointed with the preliminary NICE conclusion not to recommend NHS funding for cetuximab in combination with chemotherapy, for RAS wild-type metastatic colorectal cancer as outlined in the ACD. Colorectal cancer is the second biggest cancer killer in the UK1. The 5 year survival rate for patients diagnosed with colorectal cancer is 58%2, whereas for those patients with metastatic colorectal cancer (mCRC) the 5 year survival rate is only 6.6%3. highlighting the unmet need for these patients. A number of studies have shown that colorectal cancer survival in England is still behind comparably wealthy countries4,5. For patients with advanced disease, appropriate drug therapy is crucial to extending the length and quality of life that colorectal cancer patients have left at the end of their lives. It is in this context that the use of 1st line cetuximab combined	Thank you for your comment. After considering the comments received in response to the ACD in conjunction with the new evidence submitted by the companies and the assessment group, the committee recommended cetuximab and panitumumab as specified in section 1 of the FAD. Specific comments are addressed in the sections below.

	with chemotherapy (FOLFIRI or FOLFOX) can be part of the treatment plan for appropriate patients. Improvements in understanding the importance of the RAS biomarker in mCRC has allowed for significant improvements in identifying appropriate patients who may be considered for treatment with cetuximab which would be expected to also show improvements in the cost-effectiveness to the NHS. Cetuximab has had an EU marketing authorisation since 2004 and is a well-established medicine that has been used worldwide in nearly 600,000 patients and recommended in both NCCN6 and ESMO7 guidelines for colorectal cancer. Since the inception of the Cancer Drugs Fund (CDF) in April 2011, over 5,500 patients have been treated with cetuximab and it has been maintained on the CDF list while other drugs for mCRC have been removed, highlighting both the strength of clinical data and the value clinicians place on its availability. Without access to cetuximab the lives of patients and families suffering from mCRC will be significantly impacted. There are considerable areas of confusion within the ACD document that warrant attention and these areas are addressed below. Although in the ACD the committee's preliminary guidance is not to recommend cetuximab, the Committee concluded that adding cetuximab to chemotherapy provides benefits to patients with RAS wild-type metastatic colorectal cancer. Merck will continue to work constructively with NICE to address and understand potential areas of methodological differences that should be addressed, to make a fully informed and appropriate decision with regards to this appraisal.	
Merck Serono	<u>Drug Administration Costs</u> The drug administration costs used by the Assessment Group remain unfeasibly high. Merck has uncovered that the Assessment group have indeed made errors regarding administration costs and included costs in the model that are already included in the HRG, thereby double-counting costs. This has been confirmed by Department of Health, Reference Costs Team as outlined in the attached letter (Appendix 2). Alongside the length of treatment, the cost of administration has the largest impact on model results and therefore it is important to highlight the errors made by the Assessment Group in estimating these costs. These erroneous costs are a key factor	Comment noted. Comment noted. The committee considered the ICERs including fortnightly dosing. Please see section 4.5 of the FAD.

	driving divergence between the ERG model and the reality of colorectal cancer treatment costs in England and Wales. The Assessment Group have overestimated costs through both duplication of costs and the unnecessary addition of costs which are in fact fully absorbed by the HRG. Based on the actual costs confirmed by NHSE, Merck have recalculated the administration costs involved. The model should be corrected, with chemotherapy administration cost at £830 per month, and cetuximab plus chemotherapy administration cost at £849 per month when using fortnightly dosing (or £1,505 per month if administered weekly). These costs are robust and are in line with other assessments in this therapy area, including one by the same Assessment group[8], and should be the costs utilised for modelling going forward within this assessment. A full analysis of the errors identified, corrections applied, and NHS reference costs confirmation can be found in appendices 1 & 2. Fortnightly cetuximab administration Cetuximab is typically administered intravenously every two weeks in combination with chemotherapy in first line mCRC in England. This dosing schedule is a doubling of the weekly cetuximab dose administered every 2 weeks. This treatment schedule, whilst differing from that in the Summary of Product Characteristics (SmPC), does not alter the total dose of cetuximab administered but rather the administration schedule and has become common treatment practice. As the committee heard from one of the clinical experts from The Christie Hospital, they have not administered cetuximab on a weekly schedule for the last 8 years at the Christie. The National Cancer Drugs Fund (CDF) in England recommended this dosing regimen (NHS England website[9]) in February 2014. Fortnightly administration is the standard of care in many territories, including in the UK via the CDF and this dosing regimen is also supported by the NCCN guidelines[6], which oncologists voted to be the most influential oncology guidelines at a guidelines update session at the most recent European Cancer Conference (ECC) meeting and the British Columbia guidelines.	

	There are a number of studies where cetuximab has been used on a fortnightly basis. The randomised CECOG-CORE II phase II study evaluated cetuximab/FOLFOX administered weekly or every two weeks in 152 patients[12]. The authors concluded that cetuximab administered every two weeks has comparable activity and a comparable safety profile as weekly dosing in combination with FOLFOX. In the APEC study in RAS wild-type patients, outcomes for cetuximab/FOLFOX vs cetuximab/FOLFIRI on a 2-weekly schedule were comparable; PFS 13.3 vs 12.8 months and OS 27.8 vs 28.7 months respectively[10]. These clinical results are similar to those from studies carried out with weekly dosing regimens such as CRYSTAL and OPUS, which underpin this NICE assessment. In addition, Hubbard and colleagues[11] carried out a review of several studies assessing weekly vs. every two weeks cetuximab dosing and found that the results of dosing cetuximab every 2 weeks were comparable to those obtained from weekly dosing. Fortnightly administration also means that cetuximab can be given on the same day as chemotherapy once every 2 weeks reducing clinic visits by half, which results in more convenience and better quality of life for the patient[11,12] and is also therefore more economical to the NHS. The following statement is taken from the PenTAG report: *"In the CRYSTAL and OPUS RCTs, cetuximab was given weekly. However, in our economic analysis, in common with Merck Serono, we assumed that cetuximab is administered fortnightly, to coincide with FOLFOX/FOLFIRI administration. Fortnightly administration is common clinical practice in the NHS. Further, Merck Serono argue on the basis of an open-label RCT and a literature review that 500mg/m² fortnightly administration is as effective as induction 400 mg/m² followed by weekly 250 mg/m² administration. We consider that this is justified by the clinical evidence."* Merck contends that although the dosing schedule as outlined in the cetuximab SPC is weekly, common clinical practice in England is 2-weekly administration. There is no change in the total dose of cetuximab administered, just the schedule of administration.	

	Therefore, to model actual costs, 2 weekly administration is a more accurate reflection of the cost burden to the NHS, whereas weekly administration would artificially inflate these figures. Merck is not suggesting NICE make a recommendation for cetuximab which is outside of its license, but rather that NICE models its calculations based on the most accurate reflection of the costs in order to determine the true QALY.	
Merck Serono	Applicability of clinical trial data to the UK population The committee expressed reservations regarding the applicability to the UK population of the clinical trial data used to support this submission. Clinical experts discussed that in practice cetuximab is reserved for a subgroup of mCRC patients who are fit enough to tolerate triple therapy (cetuximab/chemo) treatment and that the patients in the supportive studies were younger, had better performance status and fewer co-morbidities than the broad metastatic CRC population. Merck agrees that the patient population represented in clinical studies indeed represents a subset of the entire mCRC patient population, and that subset corresponds with those selected for cetuximab treatment in clinical practice, namely those of better performance status, who can tolerate and benefit from triple therapy (cetuximab plus FOLFOX or FOLFIRI). Therefore the clinical data findings should be considered relevant to UK practice.	Comment noted. The committee concluded that, for the purpose of this appraisal, the populations in the clinical trials of cetuximab and panitumumab were broadly generalisable to clinical practice in the NHS. Please see section 4.6 of the FAD.
Merck Serono	RAS wt analysis of cetuximab in combination with chemotherapy in the broad metastatic disease CRC population Concern has been expressed by the NICE committee that the RAS wild-type data under consideration to represent the clinical evidence for both cetuximab and panitumumab have limitations due to being post-hoc sub-group analyses. Merck do not contest this, and acknowledge that it increases uncertainty around results. However, it should be noted that modern science moves faster than clinical trials. Much research has been undertaken to understand the molecular and genetic pathways that play a role in identifying those patients that are likely to benefit from personalised medicines such as cetuximab and to exclude those patients that do not benefit. These data were considered robust enough to have warranted amendment of the marketing authorisation from the European Medicines Agency (EMA) in 2013 and have been	Comment noted. The committee concluded that The committee concluded that, for the purpose of this appraisal, the populations in the clinical trials of cetuximab and panitumumab were broadly generalisable to clinical practice in the NHS. Please see section 4.6 of the FAD.

	accepted by the clinical panel of the CDF and the Scottish Medicines Consortium in their appraisal of first-line cetuximab (guidance 1012/14). In situations such as these, where biomarkers are identified subsequent to the completion of a clinical trial, conducting analysis of archived samples is the only viable option. Increased understanding of these biological pathways and improved personalisation of medicines such as cetuximab, means that patients who gain no clinical benefit are not exposed to unnecessary side-effects for no treatment gain. With the increased focus on personalised medicines in the advancement of oncology treatments, this phenomenon is likely to be more frequently observed with emerging new therapies which will continue to be a challenge for NICE in the future. Notably the treated population has been successively restricted, first from all patients (the original intent to treat (ITT) population) to KRAS wild-type patients only, then from KRAS wild-type patients to All RAS (KRAS and NRAS wild-type patients). As the targeted population was restricted, so the hazard ratio improved ***Figure 1 removed, please see Merck Serono's complete ACD response in the committee papers.*** Merck contends that the clinical data presented supports the efficacy of cetuximab in combination with either FOLFOX or FOLFIRI chemotherapy backbones. In the large CRYSTAL study, superiority of cetuximab plus FOLFIRI compared to FOLFIRI alone was demonstrated across endpoints. The smaller phase 2 OPUS study was affected by the limited number of RAS wild-type samples available for analysis. Despite this, in the OPUS study the PFS improved when the population was refined from KRAS wild-type to RAS wild-type. The overall survival data demonstrated in the KRAS wild-type population became non-significant in the RAS wild-type patient population due to limited patient numbers, but as discussed earlier, the economic models developed by Merck and the Assessment Group are based on PFS. In this context, the ERG approach of modelling data seems the most appropriate way to address these uncertainties. Moreover these studies may underestimate the magnitude of impact on survival. [redacted]	

	[redacted] The confounding effect of later line anti-EGFR therapy is likely to have led to understatement of the true survival benefit of 1st line cetuximab. Examination of first line studies beyond that under consideration in this appraisal suggests that cetuximab in combination with FOLFOX or FOLFIRI can extend median overall survival to in excess of 30 months (FIRE3 – 33.1 months14, CALGB-80405 - 32 months15, CECOG/CORE2 – 28.5 months12). Assuming chemotherapy only provides approximately 20 months OS, which is what has been shown in numerous clinical trials and is reinforced by expert clinical opinion, these data reinforce the benefit seen with the addtion of cetuximab to chemotherapy compared to treatment with chemotherapy alone. With regards to data maturity, PFS and OS data from CRYSTAL and OPUS are mature and no further data is expected from these studies. In addition, as science has progressed since these studies were conducted and the benefit seen when combining cetuximab with chemotherapy in this patient population is well accepted, it is unlikely that any further large clinical trials would be undertaken comparing cetuximab/chemotherapy to chemotherapy alone in patients fit for triplet therapy. As noted earlier, it would be unethical to conduct such a clinical trial denying patients cetuximab/chemo and the associated clinical benefits. Therefore, funding decisions must be made on the data that is currently available.	
Merck Serono	<u>Cetuximab in combination with FOLFOX</u> Cetuximab in combination with FOLFOX has demonstrated clinical benefit compared to FOLFOX alone. In addition to the OPUS study, the use of cetuximab with FOLFOX is supported by clinical trial data including the FOLFOX arm from the CALGB-80405 study15, the FOLFOX arm from the APEC study10 and the CORE2 study which show strong efficacy data of 28-32 months median OS for cetuximab in combination with FOLFOX.	Comment noted. The committee's conclusions about the clinical effectiveness of cetuximab in combination with FOLFOX are specified in section 4.8 of the FAD.

	These data are consistent with the outcomes seen for cetuximab in combination with FOLFIRI reflecting similar outcomes for cetuximab/FOLFOX as cetuximab/FOLFIRI. In the CALGB-80405 study, patients were treated with cetuximab/chemotherapy vs bevacizumab/chemotherapy15. The choice of chemotherapy backbone was left up to the investigators discretion. In the RAS wild-type analysis, PFS for patients for cetuximab/FOLFOX was 11.3 months and 12.7 months for cetuximab/FOLFIRI and OS was 32.5 months and 32 months respectively for cetuximab/FOLFOX vs cetuximab/FOLFIRI. In the APEC study in RAS wild-type patients, outcomes for cetuximab/FOLFOX vs cetuximab/FOLFIRI on a 2-weekly schedule were comparable; PFS 13.3 vs 12.8 months and OS 27.8 vs 28.7 months respectively10. These studies reinforce that there are similar outcomes whether cetuximab is used in combination with either FOLFOX or FOLFIRI. The phase II OPUS study, as a relatively small data set, is most affected by sample size reductions as a result of post hoc analysis based on licence restriction. In general, when the patient population is refined from Intention-To-Treat population to the KRAS wild-type population to the RAS wild-type population, due to the exclusion of patients that do not benefit from cetuximab, there is an improvement in outcomes (Figure 1). This has been observed in multiple studies and is the rationale behind the restriction of the cetuximab indication to RAS wild-type patients. For the PFS in OPUS, this improvement in outcome was observed, with an improvement from 1.1 months to 6.2 months. Reductions in the evaluable sample size affected statistical powering. From an OS perspective, insufficient subjects could be analysed to draw a robust conclusion. Therefore, although OPUS is the study used to represent the clinical data section for cetuximab/FOLFOX in this submission due to it being the only head to head trial against FOLFOX alone, other studies support comparable outcomes are seen when cetuximab is administered with either FOLFOX or FOLFIRI. Following on from expert opinion, the committee acknowledged that FOLFOX6 is the regimen that is most commonly used in the UK, rather than. FOLFOX6 is less costly than FOLFOX4 and not the other way around, as is stated in the ACD, which we believe to be a typo. These costs are addressed elsewhere in this response.	

Merck Serono	Treatment Durations and interval In developing its model the Assessment Group utilised modelled estimates of mean treatment durations for cetuximab in combination with FOLFOX or FOLFIRI using exponential extrapolation of the median treatment durations report in the clinical trials, rather than using actual mean treatment durations from studies or real world data. Merck have supplied the actual mean treatment durations from the clinical trials which should be used in the base case model (Appendix 4). The panel noted uncertainty around length of treatment with cetuximab/chemo, and that the real world treatment duration estimated by experts was far shorter, around 6 months, than that modelled by the ERG, which was 10.7 months for cetuximab/FOLFIRI and 14.4 months for cetuximab/FOLFOX. These figures were based on a flawed and unconventional extrapolation of median treatment periods as reported in the respective clinical trials. As there is no evidence to support these overestimated treatment lengths, and in response to the Appraisal Committee's recommendation for investigating real-world treatment length in England, Merck has analysed real world data from [redacted] that have completed 1st line treatment with cetuximab plus either FOLFIRI or FOLFOX between 2012 & 2015, and the mean treatment duration in the real world was [redacted] (Appendix 5), which supports clinical expert estimate. This data is based on chart reviews conducted through market research for the period between March 2013 to October 2015 corresponds to approximately [redacted] of the CDF applications in this period and therefore can be considered to be a more accurate reflection of cetuximab treatment duration in the UK. As outlined, real world cetuximab/chemotherapy treatment durations are around [redacted], whereas treatment duration with chemotherapy alone is estimated to be approximately [redacted]) for FOLFIRI and [redacted], slightly shorter due to neuropathy) for FOLFOX based on expert clinical opinion.	Comment noted. The committee agreed following its second meeting to use treatment durations from the clinical trials
Merck Serono	End-of-Life criteria	Comment noted. The population size is no longer a consideration for end-of-life. Please see the Final CDF Technology Appraisal process and methods

	In the ACD, the NICE committee have concluded that cetuximab meets 2 of the 3 criteria for end of life for the broad metastatic population. The third criteria refers to the number of patients that are eligible for cetuximab in all indications. In relation to the size of the population for all licensed indications in England, we noted that NICE differentiated between cetuximab and panitumumab based on the indications under the license. We believe that to achieve a fair comparison between the two medicines, both should be treated on equal grounds and assessed in accordance with the size of the colorectal cancer population for balanced evaluation. Therefore Merck contends that head and neck cancer patients should not be included in this evaluation, for the reason outlined above. This is an unusual situation as the products in question do not share same licensed indications and therefore we ask the committee to take this into account when considering this criteria, particularly given that both agents have been studied in the H&N setting with cetuximab showing benefit in this setting and panitumumab failing to show benefit. Merck's understanding of the EOL criteria is that they were instated to determine the maximum number of patients that could possibly be treated with a new medicine. Cetuximab received marketing authorisation in 2004 and therefore its estimated usage can be determined with some certainty. • In mCRC cetuximab has been subject to 4302 CDF applications for mCRC in **all lines** (1st, 2nd and subsequent lines) of therapy, in the 30 month period between March 2013 and Sept 2015. • Numbers for the last year for first line cetuximab use in the mCRC population in combination with either FOLFOX or FOLFIRI, were approximately 600 for the period of Sept 2014 to Sept 2015 on the CDF (Table 1). *Cetuximab in locally advanced (LA) or recurrent metastatic (RM) squamous cell carcinoma of the head and neck (SCCHN)* In SCCHN, NICE TA145 NICE restricted the funded population to only those locally advanced SCCHN patients with a Karnofsky score of above 90 in whom all forms of	(addendum to the Guide to the Processes of Technology Appraisal and addendum to the Guide to the Methods of Technology Appraisal for further information. The committee's end-of-life considerations are outlined in section 4.20 of the FAD.

	platinum based chemotherapy were contraindicated or not tolerated. The number of patients with locally advanced (LA) SCCHN eligible for cetuximab treatment was estimated in TA145 to be 8% of the total SCCHN population. The committee were of the opinion that there are 3,000 SCCHN patients in England, therefore this equates to 240 patients (3,000 x 8%). NICE TA 172 did not recommend the use of cetuximab for SCCHN patients with recurrent or metastatic disease (RM). Cetuximab is currently available for RM SCCHN patients via the CDF and for the period of Sept 2014 to Sept 2015, there were around 150 applications in this setting. Therefore, in total it is estimated that approximately 400 patients get treated with cetuximab in England for SCCHN in both the LA and RM settings annually. *Total numbers* If this number is added to the 5,968 RAS wild type mCRC patients in England (data in TA176, updated to reflect RAS wild type subgroup), the total remains below the 7,000 limit stipulated by the end-of-life criteria. And as outlined above, only around 4,300 patients were treated with cetuximab over the period of 2.5 years (2013-2015) when cetuximab was available on the CDF in ALL lines, with approximately 600 patients treated in the first line over the course of one year, therefore it can be stated with certainty that the number of patients that would be treated with cetuximab for 1st line mCRC even combined with those treated under NICE for SCCHN would never reach 7,000. Based on real world usage, for both mCRC and SCCHN, approximately 1,000 patients would be treated annually. Cetuximab is well established in the UK, it has been available since 2011 and so has been used in clinical practice for a long period of time, and it is unlikely that treatment patterns would now change. Merck would also urge the commitee to consider the recent publication of the newly launched NICE/NHSE CDF consultation that proposes a change to the EOL criteria in the Guide to the Methods of Technology Appraisal 2013 that removes the requirement for the size of the eligible population to be less than 7,000 in England[16]. If this proposal is accepted through the consultation, this change is planned to be effective from 1st	

	April 2016. Therefore, this would then mean that when the Final Guidance for this MTA is published, cetuximab will meet the EOL criteria and qualify for the higher threshold. ***Table 1 removed, please see Merck Serono's complete ACD response in the committee papers.***	
Merck Serono	<u>Liver Resection Rates</u> *Resection rates In the LLD Population* The LLD population is a preselected subset of patients with metastatic disease confined only to the liver. Data for this preselected population supports a resection rate of between 9% (Ye et al[17]) and 12.5% (Adam) for chemotherapy alone, compared to a resection rate of between 28% and 31% for cetuximab plus chemotherapy (Folprecht et al[13], Ye et al.[17] RESECT[18]). These data likely underestimate cetuximab effect in this setting as analysis was conducted on the KRAS patient subset and not the more refined RAS wild-type population, where outcomes would be expected to be improved. We do not have RAS wild-type data from these studies. The resection rates for the broad first line mCRC population are inappropriate to consider in the context of the LLD subset of patients. The advancement of treatments and the specialisation of management of patient care through multi-disciplinary teams (MDTs) will likely also mean that these rates in reality would be higher in current practice. In support of this information Merck would like to draw the panel's attention to the following paragraph from TA176: NICE TA176 (2008) Section 4.5 states: *"It [the Appraisal Committee] heard from the clinical specialists that the number of patients receiving potentially curative liver resection in the CRYSTAL and OPUS trials was lower than that seen in UK clinical practice, which is based on management by multidisciplinary teams involving highly specialised liver surgical services. The clinical specialists stated that a more realistic rate for potentially curative resection with chemotherapy in general was approximately*	Thank you for your comment. The committee's considerations about resection rates are specified in section 4.15 of the FAD.

	12–15%, which could rise to approximately 30–35% with the addition of cetuximab." *Resection rates in the broad mCRC population* As outlined above the LLD patient population is a different group of patients to the broad first line mCRC population and there are different clinical trials and clinical data which reflect this. In this submission, the studies that support the clinical evidence are CRYSTAL and OPUS. These are studies that included patient with broad metastatic disease and not the LLD population. Therefore, resection rates reported in these studies are lower than they would be if these studies had focussed on LLD patients: CRYSTAL RAS wt resection rates - cetuximab/FOLFIRI 7.3% vs FOLFIRI alone 2.1%; OPUS KRAS wt - cetuximab/FOLFOX 9.8% vs 4.1% with FOLFOX alone. As mentioned earlier, it is also worth noting that resection rates are continuously improving over time with advancing clinical practice, patient care and surgical techniques and therefore these rates may be higher in current practice.	
Merck Serono	<u>Liver limited disease mCRC population</u> Patients with metastatic disease confined to the liver (liver-limited disease, LLD), require different clinical considerations to patients with widespread metastatic disease, as the goal of treatment in the LLD setting is to shrink tumours to the point at which a patient is able to undergo surgical liver resection, rather than treatment until progression of disease. As the committee heard from the clinical experts at the first appraisal committee meeting, the duration of cetuximab/chemotherapy treatment in LLD patients is approximately 8-12 weeks, and no more than the 16 weeks currently recommended in TA176. The clinical rationale for limiting treatment duration for LLD patients is to maximise the potential for patients receiving cetuximab with chemotherapy to get an effective response to treatment, with sufficient shrinkage to allow liver resection to proceed, while minimising the duration of treatment with irinotecan or oxaliplatin containing	Comment noted. The committee considered the 16 week stopping rule in section 4.3 of the FAD. After considering the comments received in response to the ACD in conjunction with the new evidence submitted by the companies and the assessment group, the committee recommended cetuximab and panitumumab as specified in section 1 of the FAD.

	regimens, which can both make surgical liver resection more complicated potentially compromising the effectiveness of the procedure. The numbers quoted by the Assessment group in the ACD are incongruous with both current NICE guidance in TA176, or with the evidence provided by the experts at the ACD meeting. This can be attributed to flawed modelling assumptions made by the Assessment Group in relation to the subgroup of patients with metastases confined to the liver. These assumptions are: 1. Patients remain on treatment following surgical resection of the liver, which is not the case 2. Patients continue treatment for more than 16 weeks. This is contrary to the view of the clinical experts who advised NICE during the Initial Appraisal Meeting that the duration of treatment when using cetuximab in LLD patients should be 8-12 weeks, and no more than the 16 weeks currently recommended in TA176. Applying a 16 week stopping rule in the Assessment Group's model for the liver-resection patient subgroup with the corrected administration costs and under the conditions of TA176 Patient Access Scheme (16% rebate off cetuximab NHS price when combined with FOLFOX), appropriate resection rates of 12.5% for chemotherapy and 28% for cetuximab/chemo, reduces the ICERs from £130,000/QALY to £27,581/QALY for cetuximab/FOLFIRI and from £186,000/QALY to £30,268/QALY for cetuximab/FOLFOX. This demonstrates the importance of applying this stopping rule in the model in order to appropriately reflect UK clinical practice and corresponding costs. Under current NICE guidance issued in TA176, cetuximab in combination with FOLFOX or FOLFIRI, within its licensed indication, has demonstrated cost-effectiveness and is recommended by NICE for use in patients with unresectable metastases confined to the liver. These key factors should be taken into consideration when comparing TA176 recommendations to the ongoing assessment of cetuximab in RAS wild type mCRC patient with metastasis confined to the liver:	

	i. The current assessment is based on a better defined patient population who are more likely to benefit from cetuximab, due to improved molecular targeting (all RAS wild-type patients instead of KRAS exon 2 wild-type patients) ii. A patient access scheme that is significantly increased in patient coverage in comparison to the original offering (all first line RAS wild type mCRC patients compared to mCRC patients with liver only metastasis as in TA176) iii. The proposed PAS for the total mCRC population applies to patients treated with either FOLFOX or FOLFIRI, rather than just those treated with FOLFOX in TA176 iv. In the current ERG model there is no stopping rule, Merck assumes that similarly to NICE guidance in TA176 for patients with LLD, maximum cetuximab treatment would be limited to 16 weeks. A pragmatic stance taking these factors alone into consideration, vastly improves the value of cetuximab to patients meeting these criteria, compared to the previous assessment and represent increased value to the NHS.	
Merck Serono	ACD Comment 1: *The 1-year survival rate in England and Wales is about 75%, and the 5-year survival rate is under 60%.* This comment relates to survival rates for bowel cancer, all stages, after mentioning specific incidence of metastatic bowel cancer (Stage IV), and as a result the survival rates appear to refer to metastatic disease which is inaccurate. 5 year survival for metastatic bowel cancer are much lower at 6.6%3, and this should be amended to reflect this. Bowel cancer is the UK's 2nd biggest cancer killer.	Comment noted. This text has been removed in the FAD.
Merck Serono	ACD Comment 2: *The Committee concluded that the Assessment Group had included the appropriate comparators in its base case, and noted that a scenario analysis provided results for FOLFOX6.* Merck disputes this comment. The Assessment Group acknowledged that their assessment costed FOLFOX-4, not FOLFOX-6. As previously discussed, Merck put the case that FOLFOX-6 should be costed and the clinical experts agreed that	Comment noted. The committee's considerations about FOLFOX4 and FOLFOX6 are specified in section 4.4 of the FAD.

	FOLFOX-6 was the preferred regimen in England. The Assessment Group should present a revised model that includes the cost for FOLFOX-6, not FOLFOX-4.	
Merck Serono	ACD Comment 3: *The Committee discussed the place of cetuximab and panitumumab in the treatment pathway. It understood that these drugs are combined with chemotherapy with the aim of making initially unresectable tumours resectable.* The goals of two distinct patient groups are not adequately captured or represented here. For patients with unresectable liver only metastases, patients receive neo-adjuvant therapy with cetuximab/chemotherapy, where high response rates and tumour shrinkage are the short term goals of treatment, to convert unresectable liver metastases to resectable. If this goal is achieved, the patient may undergo potentially curative liver resection. For patients who have metastases not confined to the liver, or who have been treated as above and who remain unresectable, the treatment goal is palliation and to maximise their overall survival, balanced with an acceptable quality of life for the patient. In either setting, cetuximab can be combined with either FOLFIRI or FOLFOX.	Comment noted. The committee's considerations about the treatment pathway and role of the technologies are outlined in sections 4.2, 4.3 and 4.4of the FAD.
Merck Serono	ACD Comment 4: *The Committee concluded that cetuximab and panitumumab would be offered as first-line treatments with chemotherapy to a subgroup of people with metastatic colorectal cancer: people who have symptomatic disease and high volume metastases, either inside or outside the liver, which are not initially resectable.* The comment from the clinical experts that cetuximab and panitumumab would be reserved for people with high volume symptomatic disease where the treatment is to slow disease progression as quickly as possible reflects that in real clinical practice the total patient population that oncologists choose to treat with these agents is not as wide as the total eligible patient population. The committee appear to accept this. However, this is not reflected in the assessments regarding calculations for End of Life criteria.	Comment noted. The committee's considerations about the treatment pathway and role of the technologies are outlined in sections 4.2, 4.3 and 4.4of the FAD.
Merck Serono	ACD Comment 5: i.)*The Committee heard from clinical experts that the trial populations were younger than patients seen in clinical practice. ii.) The Committee acknowledged that the clinical experts had advised that cetuximab and panitumumab would be used*	Thank you for comment. The committee's considerations about that the populations in the clinical trials of cetuximab and panitumumab are outlined in section 4.6 of the FAD.

	only in a small subgroup of people with metastatic colorectal cancer (even smaller than the population in the marketing authorisation), but noted that it had not seen evidence in this group. Merck would like to note that the clinical experts expressed that the trial populations were younger than patients regularly seen and treated in clinical practice. Clinical experts discussed that in practice cetuximab is reserved for a subgroup of mCRC patients who are fit enough to tolerate triple therapy (cetuximab/chemo) treatment and that the patients in the supportive studies were younger, had better performance status and fewer co-morbidities than the broad metastatic CRC population. Merck agrees that the patient population represented in clinical studies indeed represents a subset of the entire mCRC patient population, and that subset corresponds with those selected for anti-EGFR treatment in clinical practice, namely those of better performance status, who can tolerate and benefit from triple therapy.	
Merck Serono	ACD Comment 6: *It heard that there was no evidence that cetuximab plus FOLFOX was more effective than FOLFOX alone, but understood from the clinical experts that cetuximab would be given with FOLFIRI, not FOLFOX, in clinical practice (see section 4.27).* There are a number of clinical trials in addition to OPUS as well as clinical usage that supports the efficacy of cetuximab in combination with chemotherapy, both FOLFOX and FOLFIRI; this should be taken into account and the equivalence of benefit seen with cetuximab/FOLFIRI with cetuximab/FOLFOX be acknowledged. The OPUS RAS wild-type analysis is affected by the limited number of samples available in the post-hoc analysis but it does not represent the overall clinical efficacy dataset supporting cetuximab/FOLFOX. The use of cetuximab with FOLFOX is supported by additional clinical trial data including the FOLFOX arm from the CALGB-80405 study15, the FOLFOX arm from the APEC study10 and the CORE2 study12 which show strong efficacy data of 28-32 months median OS for cetuximab in combination with FOLFOX. These data are consistent with the outcomes seen for cetuximab in combination with FOLFIRI.	Thank you for your comment. The committee's considerations about the clinical evidence are specified in sections 4.6 to 4.12 of the FAD.

Merck Serono	ACD Comment 7: *In Merck Serono's base case, it compared:* • *cetuximab plus FOLFOX4 with FOLFOX4* • *cetuximab plus FOLFIRI with FOLFIRI* • *cetuximab plus FOLFIRI with bevacizumab plus FOLFIRI. Merck Serono provided results based on weekly dosing of cetuximab, the dosage recommended in the marketing authorisation, and also for fortnightly dosing of cetuximab, which is not specified in the marketing authorisation. NICE can issue guidance only within the marketing authorisation, so only results based on weekly dosing of cetuximab are relevant. The results in this document are based on weekly dosing of cetuximab unless otherwise stated. Merck Serono compared cetuximab plus FOLFOX with XELOX in a scenario analysis.* Cetuximab is typically administered intravenously every two weeks in combination with chemotherapy in first line mCRC in England. This dosing schedule is a doubling of the weekly cetuximab dose administered fortnightly. This treatment schedule, whilst differing from that in the Summary of Product Characteristics (SmPC), has become treatment practice. As the committee heard from one of the clinical experts from The Christie Hospital, they have not administered cetuximab on a weekly schedule for the last 8 years. Subsequently, the National Cancer Drugs Fund in England recommended this dosing regimen (NHS England website9) in February 2014. Fortnightly administration is the standard of care in many territories, including in the UK via the CDF and this dosing regimen is also supported by the NCCN, which have been deemed to be the most influential guidelines10 and the British Columbia guidelines19. There are a number of studies where cetuximab has been used on a fortnightly basis. The randomised CECOG-CORE II phase II study evaluated cetuximab/FOLFOX administered weekly or every two weeks in 152 patients (Brodowicz et al., 2013). The authors concluded that cetuximab administered every two weeks has comparable activity and a comparable safety profile as weekly dosing in combination with FOLFOX. In the APEC study in RAS wild-type patients, outcomes for cetuximab/FOLFOX vs cetuximab/FOLFIRI on a 2-weekly schedule were comparable; PFS 13.3 vs 12.8	Comment noted. The committee considered the ICERs including fortnightly dosing. Please see section 4.5 of the FAD.

	months and OS 27.8 vs 28.7 months respectively10. These clinical results are similar to those from studies carried out with weekly dosing regimens such as CRYSTAL and OPUS, which underpin the NICE assessment. In addition, Hubbard and colleagues carried out a review of several studies assessing weekly vs. every two weeks cetuximab dosing and found that the results of dosing cetuximab fortnightly were comparable to those obtained from weekly dosing. Fortnightly administration also means that cetuximab can be given on the same day as chemotherapy once fortnightly reducing clinic visits by half, which results in more convenience and better quality of life for the patient11,12 and is also therefore more economical to the NHS. The following statement is taken from the PenTAG report: "In the CRYSTAL and OPUS RCTs, cetuximab was given weekly. However, in our economic analysis, in common with Merck Serono, we assumed that cetuximab is administered fortnightly, to coincide with FOLFOX/FOLFIRI administration. Fortnightly administration is common clinical practice in the NHS. Further, Merck Serono argue on the basis of an open-label RCT and a literature review that 500mg/m² fortnightly administration is as effective as induction 400 mg/m² followed by weekly 250 mg/m² administration. We consider that this is justified by the clinical evidence." Merck contends that although the dosing schedule as outlined in the cetuximab SPC is weekly, common clinical practice is fortnightly administration. Therefore to model actual costs, fortnightly administration is a more accurate reflection of the cost burden to the NHS, whereas weekly administration would artificially inflate these figures. Merck is not suggesting NICE make a recommendation for cetuximab which is outside of its license, but rather that NICE models its calculations based on the most accurate reflection of the costs in order to determine the true QALY.	
Merck Serono	ACD Comment 8: i.)*Drug administration unit costs. Merck Serono assumed lower costs, which reduced the ICERs, compared with the Assessment Group. During consultation of the assessment report, Merck Serono suggested that the Assessment Group's estimates included double-counting. ii.) The Assessment Group estimated*	Comment noted. The unit costs of drug administration were updated in the assessment group's addendum of 4 January 2016.

	drug administration costs appropriately; double-counting of costs was unlikely and would not substantially affect the ICERs. The drug administration costs used by the Assessment Group remain unfeasibly high. Alongside the length of treatment, the cost of administration has the largest impact on model results and therefore it is important to highlight the errors made by the Assessment Group in estimating these costs. Merck continues to disagree with the costs used due to the following reasons: 1. The Assessment Group have overestimated the cost of administration (£4,714 for Cetuximab+FOLFOX-4 and £4,000 for cetuximab+FOLFIRI) because they have unnecessarily duplicated HRG costs and added extra costs that should be fully absorbed by the HRG. The Assessment Group estimation contradicts with the 2014-2015 NHS reference costs guide which states the following: "Unbundled HRGs for a number of services: These costs are generally high and only relate to a limited number of patients. Including them as an overhead on treatments and procedures would significantly distort costs and lead to wide variations. Trusts therefore report them separately as: • Chemotherapy – drug costs for cancer patients, split between procurement of regimens and delivery, with other costs included in the relevant admitted patient or outpatient setting" Furthermore, it contradicts with the costs used in estimating the cost effectiveness of cetuximab in combination with chemotherapy for mCRC in NICE TA176, in which the ERG accepted that the cost of administration used absorbed pharmacy, infusion pump and line maintenance costs. To ensure accurate estimation of administration costs, Merck have sought the advice of NHS Reference Costs directly since they are the source of the HRGs used in both the Assessment Group and Merck economic models (see accompanied letter from	

	NHS Reference Costs Team for further confirmation). The following table illustrates the difference between the Assessment Group and Merck calculations according to NHS Reference Cost advice: ***Table removed, please see Merck Serono's complete ACD response in the committee papers.*** It is clear from this table that the Assessment Group added the administration cost of cetuximab on day 8 (£302.58) in error to the administration cost of day 1 of each cycle; there were two day 8 administration costs present in both day 1 and day 8 when it should only apply to day 8. In addition, the Assessment group applied the additional costs of pharmacy, line maintenance and infusion pump equally between day 1 (cetuximab + FOLFOX) and day 8 (single cetuximab infusion) when these costs should be fully absorbed by the HRG, as NHS Reference Costs have confirmed in the accompanied letter. 2. The Assessment Group have identified several administration costs used in previous NICE publications, including previous NICE assessment of cetuximab, and chose to use the highest costs published because the cost of administering monoclonal antibodies is generally higher than chemotherapy. We find this assumption to be unfounded given the cost of administration outlined above as advised by NHS Reference Costs. By way of comparison, the same assessment group (PENTAG) have estimated an average monthly administration cost per person of £1,480 in NICE TA242 which assessed cetuximab + chemotherapy for the treatment of metastatic colorectal cancer after first-line chemotherapy [2011]. This cost is more consistent with the cost of administration calculated using NHS Reference Cost advice (£1,505) and therefore proves that the Assessment Group have overestimated the administration costs. As advised by NHS reference costs, the HRGs used in the model fully absorb the additional costs added by the Assessment Group to these HRGs (Pharmacy costs, infusion pump and line maintenance cost). If these costs are added to the HRGs, the administration costs will be more expensive than the acquisition cost of cetuximab + chemotherapy per month. In which case the acquisition cost is secondary to the	

	administration cost in terms of impact on cost effectiveness. The statement that these costs do not substantially affect the ICERs is not correct. The Assessment Group and Merck have stated that the duration of treatment, with all the costs associated with it, are the most crucial and impactful factor in the estimation of the ICER. Since cetuximab + chemotherapy mean treatment duration is longer than that with chemotherapy only, the additional PFS in the chemotherapy arm accrues more treatment costs than chemotherapy only. Therefore, any change in the administration cost should have a great impact on the model. By using £1,505 per month for cetuximab + FOLFIRI/FOLFOX-6 instead of £4,000 per month as calculated by the Assessment Group, the ICER for this combination is reduced from £227k/QALY to £141k/QALY. This is without changing any of the Assessment Group assumptions and using the model they developed for this assessment. This demonstrates that administration costs have a large impact on ICERs, if not the largest out of all model parameters.	
Merck Serono	ACD Comment 9: *The Committee heard that FOLFOX4 and FOLFOX6 are equally effective, but that FOLFOX6 costs more than FOLFOX4..* This statement is incorrect. We suspect this may be a typing error as the experts clearly stated during the appraisal meeting that FOLFOX-4 administration costs are higher than FOLFOX-6. FOLFOX-4 requires the patient to visit the clinic on 2 consecutive days, and therefore requires double the administration costs FOLFOX-6. FOLFOX-6 requires just one clinic visit for each patient, requires one cost for pharmacy time to make up the infusion, and is therefore less costly than FOLFOX-4. The clinical experts stated that the preferred regimen administered in the UK is FOLFOX-6.	Comment noted. The committee's considerations about FOLFOX4 and FOLFOX6 are specified in section 4.4 of the FAD.
Merck Serono	ACD Comment 10: *Drug acquisition costs per month. Merck Serono assumed lower costs for cetuximab, and therefore lower ICERs, than the Assessment Group. Merck Serono used higher costs for FOLFOX and FOLFIRI than the Assessment Group, which does not impact cost effectiveness because both treatment arms are affected similarly.* Merck comment:	Comment noted. All analyses used for decision-making used drug acquisition costs including the proposed discounts outlined in patient access schemes for both technologies.

	Drug acquisition costs. Merck used the NHS price for cetuximab, rather than the list price, which was used by the Assessment Group. Merck used the BNF prices for both irinotecan & oxaliplatin, not the NHS acquisition prices. Consistent process should reflect the real cost to the NHS for all drugs. We noted the use of significantly lower chemotherapy acquisition costs using the CMU eMit tool to reflect true cost to the NHS. We believe that following this approach should allow for the use of actual cost of cetuximab to the NHS for fair comparison. We have indicated in our evidence submission that "Cetuximab has been offered at a guaranteed discounted price to the NHS in agreement with the Department of Health since 2008. This agreement is not limited to a time period. The NHS acquisition prices are £136.50 (100mg/20ml vial); £682.50 (500mg/100ml vial)." However, we followed the NICE methodology in using List prices for all comparators, including cetuximab to allow for a like-to-like comparison. Therefore, the use of CMU eMit cost for chemotherapy without the use of true NHS cost of cetuximab overestimates the cost difference between cetuximab in combination with chemotherapy and chemotherapy alone. Using the model developed by the Assessment Group, the cost of cetuximab acquisition is reduced to £2,665.85 per month using the actual NHS price. Therefore, outside the consideration of cetuximab's patient access scheme price, the cost effectiveness of cetuximab should be based on the actual price to the NHS; i.e. £136.50 per 100mg vial. Table 1: List price and eMit/NHS prices for cetuximab and chemotherapy Price used in calculating cost Cetuximab acquisition cost FOLFIRI acquisition cost FOLFOX-6 acquisition cost List price £3,859 £1,797 £2,120 eMit/NHS price £2,666 £128 £91	
Merck Serono	ACD Comment 11: *The Assessment Group's estimate for average body surface area (1.85m2) was plausible.*	Comment noted. All final analyses included the distribution of BSA values. Please see section 4.16 of the FAD.

	Merck have commented on the use of 1.85 m2 in our response to the Assessment Groups report. The use of such body surface area implicitly assumes that all patients treated would be in the highest dose banding which does not take into account patients with a lower body surface area and does not reflect the actual distribution of body surface area amongst patients. In practice, there is special consideration for this variation though dose banding where the link between body surface area and costs of the drug is a step function with steps at 1.60, 1.70 and 1.80 m2 and so a weighted average should be applied.	
Merck Serono	ACD Comment 12: i.)*The Assessment Group's estimate for the cost of resection surgery (£10,440) was more plausible than Merck Serono's estimates of £2707 in its original submission. ii.) Cost of a resection operation. Merck Serono assumed a lower cost, which resulted in lower ICERs, compared with the Assessment Group.* Cost of a resection. Merck accepts that the original company submission incorrectly costed the cost of resection. It should be noted that although using a lower cost of surgical resection lowered the ICERs, it did not lower them significantly.	Comment noted
Merck Serono	ACD Comment 13: *When possible, surgically removing (resecting) the primary tumour and metastases is considered, but usually only when there are no metastases outside of the liver.* In patients with metastatic disease, surgical resection of the primary tumour is common even when metastases are not confined to the liver and are more widespread. For patients with metastatic disease confined to the liver, the best chance of long-term survival is through resection of both the primary bowel tumour and the liver metastases.	Comment noted
Merck Serono	ACD Comment 14: *The Committee heard that patients with small numbers of resectable metastases confined to the liver (about 1–3 metastases) may proceed to surgery without any chemotherapy.* This is the case if the liver metastases are "upfront resectable" and can be surgically removed without the need for any down-sizing therapy. These patients wouldn't be	Comment noted

	treated with cetuximab as they are already resectable and therefore don't require tumour shrinkage.	
Merck Serono	ACD Comment 15: i.)*Clinical experts explained that they use first-line chemotherapy for 8–12 weeks, at which point they assess whether the patient is eligible for resection.ii.) The clinical experts stated that people who have resection generally have treatment for between 8 and 12 weeks. iii.) Duration of treatment with cetuximab was shorter in the original appraisal when the company applied a 16-week stopping rule. In the current appraisal, treatment duration ranged from 38–46 weeks in the Assessment Group's model and 25 weeks in the Merck Serono model, which the Committee had concluded were overestimates (see section 4.35). The Committee noted that a stopping rule had not been explored as part of the current modelling.* Merck agrees that patients with LLD get treated for 8-12 weeks (up to 16 weeks as in NICE TA176 guidance) to provide tumour shrinkage to allow successful resection of liver metastases.	Comment noted
Merck Serono	ACD Comment 16: *The Committee heard that the Assessment Group had modelled an average of 1.6 resection operations per patients, which the clinical experts noted reflected clinical practice. The Committee concluded that the model included uncertainties, but was an adequate basis for its decision-making.* The statement that clinical experts agreed with the Assessment Group that 1.6 resection operations per patient reflects clinical practice is not correct. Clinical experts stated that the risk of operation failure is likely to be lower than 60% in practice and hence the cost of surgery calculated by the Assessment Group is overestimated.	Comment noted. Please note that this text has been removed in the FAD.
Merck Serono	ACD Comment 17: *The Committee discussed the Assessment Group's estimates of the proportion of people who have resection of liver metastases after first-line treatment. It heard from clinical experts that, for patients whose tumours are initially unresectable, chemotherapy with or without cetuximab or panitumumab could shrink the metastases enough to be resected in about 15% of people.*	Comment noted. The committee's considerations about the resection rates are outlined in section 4.15 of the FAD.

	Merck comment: The LLD population is a preselected subset of patients with metastatic disease confined only to the liver. Data for this preselected population supports a resection rate of between 9% (Ye et al) and 12.5% (Adam) for chemotherapy alone, compared to a resection rate of between 28% and 31% for cetuximab plus chemotherapy (Folprecht et al13, Ye et al.17, RESECT18). Merck would like to draw the panel's attention to the following paragraph from TA176 TA176 in 2008. Section 4.5 in NICE TA176 states: "It [the Appraisal Committee] heard from the clinical specialists that the number of patients receiving potentially curative liver resection in the CRYSTAL and OPUS trials was lower than that seen in UK clinical practice, which is based on management by multidisciplinary teams involving highly specialised liver surgical services. The clinical specialists stated that a more realistic rate for potentially curative resection with chemotherapy in general was approximately 12–15%, which could rise to approximately 30–35% with the addition of cetuximab."	
Merck Serono	ACD Comment 18: *Resection rates were higher in the original appraisal, ranging from 30–43% compared with about 7–31% in the current appraisal. These were based on clinical expert opinion and the results of an open-label phase II trial comparing cetuximab plus FOLFOX with cetuximab plus FOLFIRI (the CELIM trial). The Committee heard that the CELIM trial studied a specific subgroup of people with KRAS wild-type metastatic colorectal cancer who had metastases confined to the liver, good performance status and who were fit for surgery. It considered that the population in the CELIM trial was narrower than the population relevant to the current appraisal.* In this submission, the studies that support the clinical evidence are CRYSTAL and OPUS. These are studies that included patient with broad metastatic disease. As the patient population in these trials wasn't selected for those with LLD, resection rates are lower than they would be if they were LLD studies: CRYSTAL RAS wt resection rates	Comment noted. The committee's considerations about the resection rates are outlined in section 4.15 of the FAD.

	- cetuximab/FOLFIRI 7.3% vs FOLFIRI alone 2.1%; OPUS KRAS wt - cetuximab/FOLFOX 9.8% vs FOLFOX alone.	
Merck Serono	ACD Comment 19: *In Merck Serono's deterministic base case of all patients, using the list price for cetuximab, the incremental cost-effectiveness ratios (ICERs) were £61,894 per quality-adjusted life year (QALY) gained for cetuximab plus FOLFOX and £74,212 per QALY gained for cetuximab plus FOLFIRI, compared with chemotherapy alone. Cetuximab plus chemotherapy produced approximately 0.3 extra QALYs compared with chemotherapy alone. Merck Serono did not provide estimates of cost effectiveness for the subgroup of people with metastases confined to the liver who have cetuximab weekly.* Under the current NICE guidance issued in TA176, cetuximab in combination with FOLFOX or FOLFIRI, within its licensed indication, has demonstrated cost-effectiveness and is recommended by NICE for use in patients with unresectable metastases confined to the liver. As a result Merck did not provide an initial cost-effectiveness assessment in this appraisal, as the understanding was that the cost-effectiveness had already been established and would be improved beyond the current guidance in TA176 based on 2 key facts: a) This assessment is based on a better defined patient population who are more likely to benefit from cetuximab, due to improved molecular targeting (all RAS wild-type patients instead of KRAS exon 2 wild-type patients); b) A patient access scheme that is significantly increased in patient coverage in comparison to the original offering (all first line RAS wild type mCRC patients compared to mCRC patients with liver only metastasis as in TA176). A pragmatic stance taking these factors alone into consideration, and applying the same disease management assumptions in TA176, should vastly improve the value of cetuximab to patients meeting these criteria, compared to the previous assessment and represent increased value to the NHS.	Comment noted. The committee considered the recommendations from TA176 into account during the decision-making process. Please see section 4.1 of the FAD.

Merck Serono	ACD Comment 20: i.) *In the Assessment Group's base-case analysis of the subgroup of people with metastases confined to the liver, cetuximab and panitumumab produced more incremental QALYs than chemotherapy alone (0.40–0.57) and the ICERs were lower than for the full population. The ICERs for cetuximab (using the discounted price) plus chemotherapy were about £130,000 per QALY gained compared with chemotherapy alone. The ICER for panitumumab (using the confidential discounted price) plus chemotherapy was substantially above £30,000 per QALY gained compared with chemotherapy alone. NICE cannot report the exact ICERs for panitumumab because the patient access scheme is confidential. Ii.) The ICERs for cetuximab and panitumumab were lower in the subgroup of people with metastases confined to the liver. The ICER for cetuximab was about £127,000 per QALY gained when it was combined with FOLFOX and £129,000 per QALY gained when combined with FOLFIRI, both compared with chemotherapy alone. The ICER for panitumumab plus FOLFOX remained substantially above £30,000 per QALY gained compared with FOLFOX. NICE cannot report the exact ICERs for panitumumab because the patient access scheme is confidential.* The numbers quoted here are an inaccurate reflection of the true ICERs for the LLD patient population. This can primarily be explained by the fact that in the ERG model patients continue to get treated beyond 16 weeks, whereas in actuality patients in this group get treatment for 8-12 weeks, and up to 16 weeks, as was noted by the clinical experts. In addition, in the Assessment Groups model patients remain on treatment following surgical resection of the liver. Applying a 16 week stopping rule in the Assessment Group's model for the liver-resection patient subgroup with the corrected administration costs and the TA176 assumptions, and resection rates of 12.5% for chemotherapy and 28% for cetuximab/chemo, reduces the ICERs from £130,000/QALY to £27,581/QALY for cetuximab/FOLFIRI and from £186,000/QALY to £30,268/QALY for cetuximab/FOLFOX. This demonstrates the importance of applying this stopping rule in the model.	After considering the comments received in response to the ACD and withdrawn FAD in conjunction with the new evidence submitted by the companies and the assessment group, the committee recommended cetuximab and panitumumab as specified in section 1 of the FAD.

Merck Serono	ACD Comment 21: *The Assessment Group stated that the clinical evidence was limited because it reflected subgroup analyses. The trials were analysed post-hoc after re-evaluating tumour samples from people with KRAS wild-type exon 2 tumours, and reclassifying them by RAS wild-type status as currently defined. The Assessment Group noted that there were few samples available for re-analysis and missing data further reduced the power of some studies. The Assessment Group stated that the trial populations were generally balanced with respect to baseline characteristics, which lessened confounding bias.* The paragraph makes reference to the fact that the RAS wild-type data under consideration to represent the clinical evidence for both cetuximab and panitumumab are post-hoc sub-group analyses. While Merck do not contest this, it should be noted that modern science moves faster than clinical trials. Much research has been undertaken to understanding the molecular and genetic pathways that play a role in identifying those patients that are likely to benefit from anti-EGFR therapies such as cetuximab and panitumumab and to exclude those patients that do not benefit. These data were considered robust enough to have warranted amends to the marketing authorisations of both drugs in 2013 and increasing the personalisation of medicines such as cetuximab means that patients who gain no clinical benefit are not exposed to unnecessary side-effects for no treatment gain.	Thank you for your comment. After considering the comments received in response to the ACD and withdrawn FAD, the committee considered the uncertainties in the clinical evidence as specified in section 4.6 of the FAD.
Merck Serono	ACD Comment 22: i.) *The Committee discussed the clinical trial evidence for cetuximab and panitumumab in people with RAS wild-type metastatic colorectal cancer. It heard that the Assessment Group considered that survival data were not sufficiently mature, and that the size of the effect was confounded by the use of different second and subsequent lines of treatment across the trial arms.ii.) The Committee would have preferred to see a model based on survival data from trials, but understood that the trial data for cetuximab and panitumumab may have been confounded by second-line drugs that are not commonly used in the NHS.* With regards to data maturity, PFS and OS data from CRYSTAL and OPUS are mature and no further data is expected from these studies. In addition, as science has progressed since these studies were conducted and the benefit seen when combining	Thank you for your comment. After considering the comments received in response to the ACD and withdrawn FAD, the committee considered the uncertainties in the clinical evidence as specified in section 4.6 of the FAD.

	cetuximab with chemotherapy in this patient population is well accepted, it is unlikely that any further clinical trials would be undertaken comparing cetuximab/chemotherapy to chemotherapy alone in patients fit for triplet therapy. Therefore, funding decisions should be made on the available data. In the CRYSTAL trial [redacted] of patients in the cetuximab/FOLFIRI group and [redacted] of patients in the FOLFIRI alone group received subsequent chemotherapy treatment in the ITT population. Of this only [redacted] in the cetuximab/FOLFIRI group and [redacted] in the FOLFIRI alone group received a subsequent anti-EGFR therapy. As can be seen there was a low level of personalised medicine use in later lines of treatment. In the case of bevacizumab use, it is balanced between the two arms and so wouldn't be expected to cause an imbalance in the outcomes. Regarding subsequent anti-EGFR use, there was approximately three times the use in the FOLFIRI alone arm compared to the cetuximab/FOLFIRI arm which may have improved outcomes for those patients in the FOLFIRI alone group. Even with this, the benefits seen when adding cetuximab to FOLFIRI were still significantly better than the FOLFIRI alone group. There were similar findings in the OPUS trial with [redacted] of patients receiving a subsequent anti-cancer therapy in either arm. EGFR-targeted subsequent therapies were received by [redacted] of patients in the cetuximab/FOLFOX arm and [redacted] in the FOLFOX alone arm.	
Merck Serono	ACD Comment 23: *The Committee concluded that the clinical evidence surrounding the degree to which cetuximab and panitumumab are effective in RAS wild-type metastatic colorectal cancer was subject to considerable uncertainty.* In the context of the head to head clinical trial data under consideration here (CRYSTAL, OPUS), There is an evidence base beyond that under consideration in this appraisal that suggests that cetuximab can extend median overall survival to in excess of 30 months, which is a step change to that observed across many studies that have investigated the efficacy of multiple lines of chemotherapy, where median survival durations are in the region of 20 months.	Thank you for your comment. After considering the comments received in response to the ACD and withdrawn FAD, the committee considered the uncertainties in the clinical evidence as specified in section 4.6 of the FAD.

Merck Serono	ACD Comment 24: *The Committee recalled hearing from the clinical experts that patients in the clinical trials of cetuximab and panitumumab were younger and fitter than patients in clinical practice in England, so patients in clinical practice may not achieve the level of survival benefit estimated. The Committee considered that these estimates were not sufficiently robust.* The committee expressed reservations regarding the applicability to the UK population of the clinical trial data used to support these submissions. Clinical experts discussed that in practice cetuximab is reserved for a subgroup of mCRC patients who are fit enough to tolerate triple therapy treatment and that the patients in the supportive studies were younger, had better performance status and fewer co-morbidities than the broad metastatic CRC population. Merck agrees that the patient population represented in clinical studies indeed represents a subset of the entire mCRC patient population, and that subset corresponds with those selected for cetuximab treatment in clinical practice, namely those of better performance status, who can tolerate and benefit from triple therapy. Therefore the clinical data findings should be considered relevant to UK practice.	Thank you for your comment. After considering the comments received in response to the ACD and withdrawn FAD, the committee considered the uncertainties in the clinical evidence as specified in section 4.6 of the FAD.
Merck Serono	ACD Comment 25: *Duration of first-line treatment. The Assessment Group considered that Merck Serono underestimated the mean duration of treatments. This resulted in lower drug acquisition costs and lower ICERs than the Assessment Group's estimates. The Assessment Group noted that treatment duration was the most important issue explaining the difference between the results of the Merck Serono model and the Assessment Group's model..* Duration of first line treatment. Merck provided the mean values for treatment duration from the OPUS & CRYSTAL trials, in the response to the Assessment Group report, sent to NICE on 21st September 2015, having initially used median values, which were inconsistent with a mean calculated value from the Assessment Group. Merck notes that the Assessment Group model used a mean value extrapolated from the median using an unconventional method as opposed to using the actual uncensored mean values of treatment duration reported in the clinical trial reports provided by Merck.	Thank you for comment. The committee agreed following its second meeting to use treatment durations from the clinical trials. After considering the comments received following the withdrawn FAD, the committee concluded that a stopping rule was inappropriate and that it would only consider the all patient group. Please see section 4.3 of the FAD

	The panel noted uncertainty around length of treatment with cetuximab/chemo, and that the real world treatment duration estimated by experts was far shorter, around 6 months, than that modelled by the ERG, which was 10.7 months for cetuximab/FOLFIRI and 14.4 months for cetuximab/FOLFOX. Merck has analysed real world data from [redacted] that have completed 1st line treatment with cetuximab plus either FOLFIRI or FOLFOX between 2012 & 2015, and the mean treatment duration in the real world was [redacted] (Appendix 5), which supports clinical expert estimate. This data is based on chart reviews conducted through market research for the period between March 2013 to October 2015 corresponds to approximately [redacted] of the CDF applications in this period and therefore can be considered to be a more accurate reflection of cetuximab treatment duration in the UK. As outlined, real world cetuximab/chemotherapy treatment durations are around [redacted], whereas treatment duration with chemotherapy alone is estimated to be approximately [redacted] for FOLFIRI and slightly shorter for FOLFOX due to neuropathy at [redacted] based on expert clinical opinion.	
Merck Serono	ACD Comment 26: *The Committee understood that, in clinical trials, first-line cetuximab or panitumumab is given until disease progression. But, it heard from clinical experts that clinical practice in the UK includes treatment holidays and so patients are not treated continuously until disease progression. The Committee concluded that treatment duration with cetuximab or panitumumab in clinical trials may not reflect clinical practice in England.* Merck would like to reinforce the comments made by the clinical experts. The understanding should be that the intention in clinical trials is that treatment with either cetuximab in combination with chemotherapy would be continued until disease progression. In reality, the CRYSTAL, OPUS & FIRE-3 trials that used cetuximab in combination with either FOLFIRI or FOLFOX, the mean treatment duration was significantly shorter than the progression free survival that was observed. This is can occur due to many reasons, including of the side of effects of combination treatment and the desire of patients to have breaks from treatment. Patients in clinical trials are	Comment noted. The committee agreed following its second meeting to use treatment durations from the clinical trials

	also more likely to have longer treatment due to wider support available while in the study.	
Merck Serono	ACD Comment 27: i.)*The Committee understood that, in clinical trials, first-line cetuximab or panitumumab is given until disease progression. But, it heard from clinical experts that clinical practice in the UK includes treatment holidays and so patients are not treated continuously until disease progression. The Committee concluded that treatment duration with cetuximab or panitumumab in clinical trials may not reflect clinical practice in England. Ii.) The Committee noted that the estimates of the duration of first-line treatment differed in the models from Merck Serono and the Assessment Group. It understood from clinical experts that, in England, first-line treatment does not continue uninterrupted until disease progression.iii.) The Committee concluded that the Assessment Group's estimates of treatment duration may not reflect clinical practice, and would have preferred to see the model validated with observational data.* In developing its model the Assessment Group utilised modelled estimates of mean treatment durations for cetuximab in combination with FOLFOX or FOLFIRI using exponential extrapolation of the median treatment durations report in the clinical trials rather than using actual mean treatment durations from studies or real world data. The panel noted uncertainty around length of treatment with cetuximab/chemo, and that the real world treatment duration estimated by experts was far shorter, around 6 months, than that modelled by the ERG, which was 10.7 months for cetuximab/FOLFIRI and 14.4 months for cetuximab/FOLFOX. These figures were based on a flawed and unconventional extrapolation of median treatment periods as reported in the respective clinical trials. As there is no evidence to support these overestimated treatment lengths, and in response to the Appraisal Committee's recommendation for investigating real-world treatment length in England, Merck has analysed real world data from [redacted] that have completed 1st line treatment with cetuximab plus either FOLFIRI or FOLFOX between 2012 & 2015, and the mean treatment duration in the real world was [redacted] (Appendix 5), which supports clinical expert estimate. This data is based on chart reviews conducted through market research for the period between March 2013 to October 2015 corresponds to	Comment noted. The committee agreed following its second meeting to use treatment durations from the clinical trials

	approximately [redacted] of the CDF applications in this period and therefore can be considered to be a more accurate reflection of cetuximab treatment duration in the UK. As outlined, real world cetuximab/chemotherapy treatment durations are around [redacted], whereas treatment duration with chemotherapy alone is estimated to be approximately [redacted] for FOLFIRI and [redacted] for FOLFOX based on expert clinical opinion. Merck has supplied both the real world data and the actual mean clinical trial treatment durations.	
Merck Serono	ACD Comment 28: i.) *In the Assessment Group's base-case analysis of all patients, both cetuximab plus chemotherapy and panitumumab plus chemotherapy generated more QALYs than for chemotherapy alone: 0.15–0.35 more QALYs compared with FOLFOX and 0.30 QALYs compared with FOLFIRI. However, the additional costs using list prices were substantial: up to about £69,000 for cetuximab or panitumumab compared with FOLFOX or FOLFIRI. When the Assessment Group used the list prices for panitumumab and cetuximab, the ICERs compared with chemotherapy alone were £239,007 per QALY gained for panitumumab plus FOLFOX, £165,491 per QALY gained for cetuximab plus FOLFOX, and £227,381 per QALY gained for cetuximab plus FOLFIRI. When the Assessment Group used the discounted price for panitumumab (discount commercial in confidence), the ICER was substantially above £30,000 per QALY gained compared with FOLFOX. When the Assessment Group used the discounted price for cetuximab, the ICERs were about £135,000 per QALY gained for cetuximab plus FOLFOX and £183,000 per QALY gained for cetuximab plus FOLFIRI, both compared with chemotherapy alone. Ii.) In the overall population, the ICER for cetuximab was about £135,000 per QALY gained when it was combined with FOLFOX and £183,000 per QALY gained when combined with FOLFIRI, both compared with chemotherapy alone. The Committee noted that the ICER for panitumumab plus FOLFOX was also substantially above £30,000 per QALY gained compared with FOLFOX.* The statements above show the impact of price discounts on ICERs as estimated by the Assessment Group. Given that Merck offered a substantial PAS to the value of 35.6% off cetuximab list price, the ICERs based on the PAS discount highlight the fact	After considering the comments received in response to the ACD and withdrawn FAD in conjunction with the new evidence submitted by the companies and the assessment group, the committee recommended cetuximab and panitumumab as specified in section 1 of the FAD.

<table>
<tr><td></td><td>that cetuximab would not be cost-effective even at zero price, which shows the flaws in the methodology applied in this assessment, and that the price is not the main driver for cost effectiveness in this case. The main driver, as identified by both Merck and the Assessment group, is the length of treatment in the first line setting and the associated cost of NHS provision of healthcare. Therefore, the current methodology penalises cetuximab-chemotherapy for extending patients' survival compared to chemotherapy alone.</td><td></td></tr>
<tr><td>Merck Serono</td><td>ACD Comment 29: Table 3, page 20

<table>
<tr><th></th><th>CET+FOLFOX compared with FOLFOX</th><th>CET+FOLFIRI compared with FOLFIRI</th><th>PAN+FOLFOX compared with FOLFOX</th></tr>
<tr><td>Short life expectancy, normally <24 months</td><td>Months, mean:
22.3 (AG model)
26.7 (PRIME)</td><td>Months, mean:
21.0 (AG model)
24.9 (CRYSTAL)</td><td>Months, mean:
22.3 (AG model)
26.7 (PRIME)</td></tr>
<tr><td>Extension to life, normally ≥3 months</td><td>Months, mean:
6.6 (AG model)
0.5 (OPUS)</td><td>Months, mean:
5.5 (AG model)
8.8 (CRYSTAL)</td><td>Months, mean:
2.6 (AG model)
5.7 (PRIME)</td></tr>
<tr><td>Licensed for <7000 people in England (all indications)</td><td>• 8,807 (data in TA176, incl other indications and updated to reflect RAS wt subgroup)
• 7,567 (Merck Serono data, updated to reflect England only and incl all indications)
• 11,349 (data cited in assessment report)</td><td></td><td>• 5,968 (data in TA176, updated to reflect RAS wt subgroup)
• 4,728 (Merck Serono data, updated to England only)
• 8,511 (data cited in assessment report)</td></tr>
<tr><td colspan="4">Note that the indications for cetuximab and panitumumab differ; cetuximab is also approved for treating squamous cell cancer of the head and neck.
Abbreviations: AG, Assessment Group; CET, cetuximab; FOLFIRI, folinic acid+fluorouracil+irinotecan; FOLFOX, folinic acid+fluorouracil+oxaliplatin; incl, including; PAN, panitumumab; TA, NICE technology appraisal guidance; wt, wild-type.</td></tr>
</table>
.</td><td>Comment noted. The population size is no longer a consideration for end-of-life. Please see the Final CDF Technology Appraisal process and methods (addendum to the Guide to the Processes of Technology Appraisal and addendum to the Guide to the Methods of Technology Appraisal for further information.

The committee's end-of-life considerations are outlined in section 4.20 of the FAD.</td></tr>
</table>

	The table above shows that cetuximab has met 2 of the 3 criteria of end of life conditions for the broad mCRC population. The third criteria refers to the number of patients that are eligible for cetuximab in all indications. In relation to the size of the population for all licensed indications in England, we noted that NICE differentiated between cetuximab and panitumumab based on the indications under the license. We believe that to achieve a fair comparison between the two medicines, both should be treated on equal grounds and assessed in accordance with the size of the colorectal cancer population for balanced evaluation. Therefore Merck contends that head and neck cancer patients should not be included in this evaluation, for the reason outlined above. This is an unusual situation as the products in question do not share same licensed indications and therefore we ask the committee to take this into account when considering this criteria, particularly given that both agents have been studied in the H&N setting with cetuximab showing benefit in this setting and panitumumab failing to show benefit. Merck's understanding of the EOL criteria is that they were instated to determine the maximum number of patients that could possibly be treated with a new medicine. Cetuximab received marketing authorisation in 2004 and therefore its estimated usage can be determined with some certainty. • In mCRC cetuximab has been subject to 4302 CDF applications for mCRC in all lines (1st, 2nd and subsequent lines) of therapy, in the 30 month period between March 2013 and Sept 2015. • For first line mCRC in combination with either FOLFOX or FOLFIRI, there were approximately 600 patients treated with cetuximab for the period of Sept 2014 to Sept 2015 on the CDF. In SCCHN, NICE TA145 NICE restricted the funded population to only those locally advanced SCCHN patients with a Karnofsky score of above 90 in whom all forms of platinum based chemotherapy were contraindicated or not tolerated. The number of patients with locally advanced (LA) SCCHN eligible for cetuximab treatment was estimated in TA145 to be 8% of the total SCCHN population. The committee were of the opinion that there are 3,000 SCCHN patients in England, therefore this equates to	

	240 patients (3,000 x 8%). NICE TA 172 did not recommend the use of cetuximab for SCCHN patients with recurrent or metastatic disease (RM). Cetuximab is currently available for RM SCCHN patients via the CDF and for the period of Sept 2014 to Sept 2015, there were around 150 applications in this setting. Therefore, in total it is estimated that approximately 400 patients get treated with cetuximab in England for SCCHN in both the LA and RM settings annually. If this number is added to the 5,968 RAS wild type mCRC patients in England (data in TA176, updated to reflect RAS wild type subgroup), the total remains below the 7,000 limit stipulated by the end-of-life criteria. And as outlined above, only around 4,300 patients were treated with cetuximab over the period of 2.5 years (2013-2015) when cetuximab was available on the CDF in ALL lines, with approximately 600 patients treated in the first line annually, therefore it can be stated with certainty that the number of patients that would be treated with cetuximab for 1st line mCRC even combined with those treated under NICE for SCCHN would never reach 7,000. Based on real world usage, for both mCRC and SCCHN, approximately 1,000 patients would be treated annually. Cetuximab is well established in the UK, it has been available since 2011 and so has been used in clinical practice for a long period of time, and it is unlikely that treatment patterns would now change. Merck would also urge the commitee to consider the recent publication of the newly launched NICE/NHSE CDF consultation that proposes a change to the EOL criteria in the Guide to the Methods of Technology Appraisal 2013 that removes the requirement for the size of the eligible population to be less than 7,000 in England. If this proposal is accepted through the consultation, this change is planned to be effective from 1st April 2016. Therefore, this would then mean that when the Final Guidance for this MTA is published, cetuximab will meet the EOL criteria and qualify for the higher threshold.	
Beating Bowel Cancer	We would firstly like to thank NICE for giving us the opportunity to respond to its Appraisal Consultation Document (ACD) on cetuximab and panitumumab for the first line treatment of colorectal cancer. In particular we thank the Committee for its recognition that cetuximab and panitumumab “appear be more effective for treating tumours without mutations (known as ‘wild-type’)”	Thank you for your comment. After considering the comments received in response to the ACD and withdrawn FAD in conjunction with the new evidence submitted by the companies and the assessment group, the committee recommended

	However, we are disappointed by the Appraisal Committee's decision not recommend the use of cetuximab and panitumumab on the NHS; a decision we feel will compromise doctors' ability to provide the best international standards of care for advanced bowel cancer patients in England and will cruelly deny hundreds of eligible people with advanced bowel cancer the chance of spending valuable extra time with the loved ones We believe it to be misguided and in our opinion brings into question the methodology used to assess targeted, end of life treatment in patients with advanced cancer. As a charity supporting patients we are acutely aware of the impact that this negative decision will have on the lives of the patients and families we support. A final negative NICE appraisal will have an impact on the psychological state of patients and their families; as there will be no options available to them at a very advanced stage. We are gravely concerned for the future of patients with advanced bowel cancer and also for the doctors that treat them. The interaction between doctor and patient will be compromised by being unable to offer all the drugs which are standard elsewhere in the Europe, and enabling patients to participate in international trials which mandate the use of these agents. The ability of NICE to give a positive assessment would have been seen as a test case for how a new, more flexible NICE methodology could work for cancer drugs, in particular flexibility around the assessment of End of Life drugs and their affordability to the NHS. While recognising their clinical effectiveness, the Committee concluded that even if they were provided for free they would still not be cost-effective, as the methodology used takes into account all the associated treatment costs, including the partner chemo regimens and hospital expenses. We run the risk of treatment for advanced bowel cancer in this country going backwards with patients diagnosed in 2016 facing worse care than patient diagnosed in 2015 The decision means that both drugs will now only be available to NHS patients in England via the Cancer Drugs Fund, but this comes to an end in March next year, after which patients with metastatic bowel cancer will no longer be able to access a personalised therapy in the country. With the uncertainty around the Cancer Drugs Fund, we need NICE to reconsider its decision not to approve these drugs before the UK slips behind the rest of Europe and the world. Otherwise, we will be back to square one, with thousands of patients not getting the drugs they need and deserve—drugs which over the past four years have	cetuximab and panitumumab as specified in section 1 of the FAD.

	been proved to make an immense difference to patients' and their families' and friends' lives. In closing, as a patient-focused charities we are committed to doing all we can to make the drug available to people on the NHS in England. NICE must also continue to talk with the manufacturers Merck and Amgen work towards finding a solution urgently to ensure the future of advanced bowel treatments does not grind to a halt. We need to find a solution now before bowel cancer patients start having their lives cut short. **Has all of the relevant evidence been taken into account?** No. We are concerned that appraisal committee has adopted an overcautious attitude towards uncertainty. The treatments have contributed significantly to improving outcomes and increasing Quality of Life for patients with advanced bowel cancer. There is clear evidence, through the Cancer Drugs Fund / SACT data that survival depends on receiving as many drugs as possible during the patient 'journey', with each new treatment adding incremental gains. Survival rates for advanced bowel cancer were a median of only 8 months 20 years ago. The most recent trials reveal median survival for patients with RAS wild type tumours to be in excess of 30 months– a striking improvement in a relatively short period of time. Adding almost 2 years to median survival (with 50% of patients living longer than 30 months) is of enormous clinical impact and of great benefit to patients and their family. We would urge the Committee to reconsider the full patient expert testimony it heard directly from Ben Ashworth, 36, a terminally-ill father of three from Preston. In its consideration of the evidence we feel the committee has not taken fully into account the full extent of the benefits for patients and their families in terms of extension of life. In the document it states that "the key benefit of cetuximab treatment was that the adverse reactions (such as skin reactions) were much more manageable than the adverse reactions they had previously experienced with chemotherapy alone (including debilitating fatigue and neuropathy." The adverse effects of the treatment were the least relevant. We believe that this vastly understates the real value of this treatment delivered to Ben and his family. In 2013 Ben who was given a terminal prognosis and life expectancy of just 6-12 months. The most important outcome of his treatment has been the precious extra time that he has been able to have with his family, watching his young daughters grow up. Also, Ben explained the vast improvement in his quality of life, which has seen him leading a very active. To help cope with his chemotherapy Ben embarked on a mission to run a marathon a month. To date he has participated in over 16 marathons despite the fact that he is currently in active treatment.	

	I would also bring the Committee's attention to a second patient who also submitted written evidence of his experience of receiving cetuximab as a first line treatment for bowel cancer. Barry Murphy, aged 70 was diagnosed in 2012 when his bowel cancer had spread to his liver. Barry was put on a FOLFOX in combination with cetuximab. Surgery and folfox/cetuximab delivered the best results giving him a complete year without symptoms or further treatment. Barry said: "I am very grateful that my first line treatment included Cetuximab. Because of that I believe my prospects for beating the disease were greatly improved and my confidence in the team treating me and the NHS in general was firmly strengthened." **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The Assessment Group noted that treatment duration was the most important issue explaining the difference between the results of the Merck model and the Assessment Groups model. The mean time on 1st-line drug treatment is extremely important because it affects the total mean cost of drug acquisition and administration per person. Differences in assumptions for duration of treatment will add knock on costs, which in turn will push up the cost per QALY (ICER) further beyond the NICE threshold. In the current appraisal, treatment duration ranged from 38– 46 weeks in the Assessment Group's model and 25 weeks in the Merck model, which the Committee had concluded were overestimates. Clinical experts who gave evidence to the Committee advised that Merck's estimates of treatment duration better reflected clinical practice in England than the Assessment Group's. Our Medical Advisory Board has advised us that clinical practice is 24-30 weeks at most. This shorter duration will impact greatly on the cost of ongoing treatment. **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** No We feel this decision is particularly short-sighted given the fact that bowel cancer is the UK's second biggest cancer killer and the fourth most common cancer. Almost 16,000[i] people die each year in the UK – a life every 32 minutes. A higher number of bowel cancers are diagnosed at a more advanced stage in England, compared to other	

	countries. Patients with advanced bowel cancer have among the worst survival rates, with only 7% surviving more than 5 years. These represent two of the few treatments options left for advanced bowel cancer, which have been the standard of care for ten years or more. This decision will mean that patients with advanced bowel cancer will be offered nothing other than standard treatments. Recently bowel cancer doctors came together to warn of a return the "dark ages" cancer treatment. We cannot go back to a time of the original postcode lottery when patients in England were denied medicines that are routinely available in other parts of the UK and Europe and where patients diagnosed with advanced bowel cancer in 2016 will receive a worse standard of care than those diagnosed in 2014. We feel that this would be unfair. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?** No **Are there any equality -related issues that need special consideration and are not covered in the appraisal consultation document?** The NHS Constitution makes it clear that a core duty of the NHS is to promote equality. As leading bowel cancer charities supporting patients we have long campaigned to allow greater access to drugs where there is clear, clinical evidence that a patient would benefit. Although the clinical evidence for the use of these treatments is clear, not all patients will be able to access the treatments that their clinicians wish to prescribe if this appraisal received a final negative recommendation, resulting in a widening disparity in accessing cancer drugs for patients across the UK. We are concerned that the UK, including Scotland, still lags behind Europe in terms of survival and access to medicines. The resulting final guidance from this ongoing appraisal will supersede any previous positive NICE guidance in first-line which means that there will be no targeted treatment options available in England and Wales. Also, importantly, given that this is a MTA it is highly likely that it will apply in Scotland and supersede the current (restricted) positive guidance for cetuximab for first-line in Scotland. There is a real risk that there will be no targeted treatments available in England, Wales and Scotland.	

	Most of these drugs are already licensed for use in the UK and we run the risk that future access will mean they will only be obtained only through private health care. This will result in patients facing a two-tier health system. While some cancer patients may be able to afford these drugs, others will not. This raises the prospect of inequality in health care which many people will see as cruel and would damage the long-term confidence in the NHS. In terms of achieving age equality we would question how NICE deals with age when making decisions about which treatments to fund at the end of life. NICE use of the QALY in assessing overall relative cost effectiveness of treatments that are mainly for older people means that there is an inequality in treatment of individuals with cancer which is predominantly a disease of older age Bowel cancer mortality is strongly related to age, with the highest mortality rates being in older men and women. In the UK between 2010 and 2012, an average of 57% of bowel cancer deaths were in men and women, aged 75 years and over. England and Wales have the worst five-year survival rates for cancer in Europe among the over 75s[ii]. We want to make sure older people are offered cancer treatment based on their needs, not on their age. Regardless of age, everyone should get the treatment that's right for them.	
Royal College of Physicians	write on behalf of the NCRI/RCP/RCR/ACP who wish to jointly respond to the above consultation. We are grateful for the opportunity to submit the following comments: **1. Factual corrections** We believe that both clinical experts stated that FOLFOX 4 is a more expensive regimen than FOLFOX6, due to the need for attendance for a bolus dose of 5FU on day 2 in FOLFOX4, but this appears to have been transcribed incorrectly in the ACD. Secondly, on page 23, the report states that patients who develop disease progression following liver resection may be offered further surgery followed by chemotherapy. The majority of patients in this situation are likely to progress with inoperable and incurable disease and so proceed straight to palliative chemotherapy. **2. Concern over the generalisability of the trial data to the English metastatic colorectal cancer population.** In the CRYSTAL and PRIME trials the median age of patients was 60 and 62 and over 90% were of performance status 0-1. In routine clinical practice within the NHS our patients with metastatic colorectal cancer are older and often of poorer performance status. However, due to the potential toxicity of the combination of a biological agent	Thank you for your comment. After considering the comments received in response to the ACD and withdrawn FAD in conjunction with the new evidence submitted by the companies and the assessment group, the committee recommended cetuximab and panitumumab as specified in section 1 of the FAD. The committee's considerations about: • FOLFOX4 and FOLFOX6 are specified in section 4.4 of the FAD, • The generalisability of the trials in section 4.6 of the FAD, • End-of-life in section 4.0 of the FAD.

	In addition to chemotherapy the vast majority of patients offered this treatment option will be of a performance status of 0-1, so will more closely reflect the population recruited within the clinical trials. These decisions are based on the patient's performance status and symptoms, the extent of disease and the patient's wishes including their potential tolerance of specific toxicities and the importance to them of prolonged progression-free and overall survival. Published SACT data from January 2014 to December 2014 show that only 278 first cycles of FOLFIRI plus cetuximab were given, with a total number of 2224 cycles given. Although the data is not complete, the majority of NHS Trusts were submitting data at this point. **3. Robustness of trial data** The management of colorectal cancer has remained the same for many years, with little improvement in outcomes for patients with widespread metastatic disease. The introduction of the biological agents, in particular the anti-EGFR antibodies, has transformed the management of some of these patients with rapid improvement of symptoms and both statistically and clinically significant improvements in survival. The colorectal oncology community believe the robustness of the trial data and in particular the overall survival data from CRYSTAL and PRIME in the relevant biomarker-selected subgroups. In 2004 Tournigand et al published a trial in which patients were randomised to receive FOLFIRI followed by FOLFOX on disease progression, or FOLFOX followed by FOLFIRI. The overall survival in this study was 21.5 months compared to 20.6 months. These survival figures are almost identical (in the RAS wild type population) to the chemotherapy only arm in the CRYSTAL study (20.2 months) and the PRIME trial (19.7 months). We feel that the concerns raised over the effect of subsequent treatments (that are not funded by the NHS after NICE approval or through the Cancer Drugs Fund) on overall survival should be considered as minimal. Over a 10 year period the addition of cetuximab and panitumumab has been the only major advance in the first line treatment of colorectal cancer. **4. End of life criteria** We believe that panitumumab and cetuximab should fall within the end of life criteria. The committee agreed that for both drugs the only field that fell outside the set criteria was the number of patients who would be eligible for treatment. The PenTag model suggest that 95% of the population of England, Wales and Scotland live within England, Merck suggests this figure is 84% and our calculations	

	based on mid 2014 population data suggests this is 87%, so altering the calculations on the model. The end of life criteria states the treatment is licensed or otherwise indicated for small patient populations and will take into account the cumulative population for each licensed indication. It seems extraordinary that the patient population with head and neck cancers are included within this current calculation, as the indication for the use of cetuximab in this population is either with radiotherapy in locally advanced disease or in combination with platinum based chemotherapy in metastatic disease and therefore should be considered distinct from the indication in the metastatic colorectal cancer population. **5. Methodological issues** The conflation (described in the section above) of the use of the targeted agents under review in entirely separate cancers, in this case in a much more co-morbid population, and with different combination of systemic therapies and/or radiotherapy is incomprehensible to our patients and to the clinical community. The use of survival statistics (eg mean overall survival) which are never used by clinicians and the use of modelled data (eg mean overall survival modelled from mean progression-free survival abstracted from trial data) rather than actual data is also inappropriate in our view. We believe that these methodological flaws significantly undermine the validity of the NICE process as regards the use of these drugs in the view of both patients and clinicians. Our experts believe that the addition of the anti-EGFR antibodies to chemotherapy has made a significant advance in the treatment of metastatic colorectal cancer, for a relatively small group of patients selected based on their performance status and extent of disease. The SACT data demonstrates that use of cetuximab with FOLFIRI has been modest. Our experts have concerns over many of the assumptions made by PenTAG in their modelling and feel that both cetuximab and panitumumab should meet end of life criteria if the head and neck indication is excluded and the correct population of England used. Overall, our experts believe that if the ACD is upheld, patients with metastatic colorectal cancer will return to limited options of treatment. This will not only have an impact on outcomes but will also severely affect the ability of patients in England to	

	have access to international studies of new treatments; which will expect the use of anti-EGFR antibodies in previous lines of treatment. This would clearly have a detrimental effect on patients, clinicians and the national targets set for trial recruitment. Our experts note that these agents are deeply embedded into the guidelines for the management of metastatic colorectal cancer written by the American Society of Clinical Oncology and the European Society of Medical Oncology, after due consideration of the published data. The UK will therefore be alone amongst the developed world, if this ACD is upheld.	

Comments received from clinical specialists and patient experts

Nominating organisation	Comment [sic]	Response
Consultant in Medical Oncology, nominated by Roche – clinical expert	Firstly, I would again like to thank you for inviting me as one of the clinical experts during the NICE appraisal for use of anti-EGFR agents in colorectal cancer on the 15th October 2015. I note with huge regret that NICE is minded to decline the funding for cetuximab & panitumumab for stage IV colorectal cancer. I think this is a hugely retrograde step that the NHS will take in the management of one of the most common cancers in the country. The omission of these targeted drugs will take back management of this condition by more than a decade. This decision appears to have been taken despite the consistent overall survival that has been demonstrated in multiple clinical trials. There are other trials such as FIRE3 which understandably could not be considered as they did not contain a non-antibody arm in the trial design; nevertheless have shown significant clinically and statistically relevant improvement in overall survival. These are ubiquitously considered as standard drugs in management of this cancer in the Ras wild type population. Clinical trial participation in experimental trials is likely to be jeopardised if our patients have not received all standard therapies possible and anti-EGFR is certainly recognised worldwide as being an essential class of drugs in Ras wild type CRC patients. There are certain comments/reservations I would like to point out in the document and which you may wish to consider. I appreciate they may well not make a huge difference in the economic models but nevertheless feel strongly enough to highlight them below. 2.1 5 year survival is under 60%. Should read under 5-10% 4.14 Assessment Group are reluctant to use overall survival endpoints from clinical trials ostensibly in light of perceived use of second line dugs not	Thank you for your comment. After considering the comments received in response to the ACD and withdrawn FAD in conjunction with the new evidence submitted by the companies and the assessment group, the committee recommended cetuximab and panitumumab as specified in section 1 of the FAD.

Nominating organisation	Comment [sic]	Response
	commonly used in the NHS. This has been mentioned a few times in the document. I am not entirely sure or clear of the robustness of this assumption. Overall survival has to be considered the gold standard in clinical trials and has to be rated above other end points. The arms actually were quite balanced in my opinion in the well conducted trials that were discussed. 4.17 I am unclear as to how the mean duration of treatment estimation has affected the economic modelling but suggest the one obtained from clinical trials would be more reliable and be the one that is used. 4.18 Note comment above. Again would suggest using OS directly from randomised controlled trials 4.25 ''Resection is successful in about 90% patients.'' Just to clarify by this we did not mean 90% of patients receiving these drugs went for resection. In various databases about 13-15% of patients with previously unresectable liver disease became resectable courtesy systemic treatments. **Resection rates** are proportional to **response rates** from treatment regimens which in turn are increased by use of **anti-EGFR agents**. In good MDTs vast majority of patients deemed resectable on basis of post treatment scans are indeed successfully able to have a liver resection (in personal practice 80-90%). Our sentiments above are more clearly & accurately summarised in section 4.36 4.28 Treatment holidays with cetuximab. In England we have been using the cetuximab within CDF guidelines which do not allow treatment breaks (in excess of 4 weeks) unless there are exceptional circumstances. This clinical practice is therefore in line with what transpires in clinical trials. 4.29 Note 4.14 above. Also in clinical trials the population was relatively younger; this is not unique solely in the trials in question. This is universally true for almost all colorectal trials and infact non CRC oncological trials and should have no bearing on real life practice. We would take biological age into consideration when using drugs rather than the chronological age; in practice therefore the age factor is not relevant and should not be cited as a source of uncertainty. 4.41 'from clinical experts that life expectancy is longer when mets confined to the liver.' I don't think this is true at all. We must have been misconstrued here; patients with disease confined to the liver do not necessarily fare better (unless they have been able to have resectional surgery). Infact in absence of liver surgery (prospects of which are enhanced by anti-EGFR use) they do much worse compared to patients with little or no liver affliction from disease.	

Comments received from commentators

Commentator	Comment [sic]	Response
Roche	No comment	Noted.
Department of Health	No comment.	Noted.

Comments received from members of the public

Role*	Section	Comment [sic]	Response
Healthcare Other	1	We have recently reviewed the National Institute for Health and Care Excellenceâ€™s (NICE) appraisal consultation document for the use of cetuximab and panitumumab in patient with previously untreated metastatic colorectal cancer (mCRC) and are interested in receiving your guidance prior to submitting comments by the December 8, 2015 deadline based on newer information we have available. Our understanding after reviewing the above mentioned document is that NICE has determined that the use of both cetuximab and panitumumab in the patient population described above is not recommended and that this decision is primarily due to the lack of demonstrated cost-effectiveness of EGFR inhibitors in KRAS/RAS wild-type mCRC patients. IntegraGen has recently discovered and validated a biomarker, miR-31-3p, which identifies a specific subpopulation of KRAS wild-type mCRC patients who are more likely to benefit from cetuximab and panitumumab therapy (approximately 70% of the total patient population). We believe the use of this biomarker would enable a more targeted utilization of anti-EGFR inhibitors in this patient population improving the cost utility of these agents.	Thank you for your comment. After considering the comments received in response to the ACD and withdrawn FAD in conjunction with the new evidence submitted by the companies and the assessment group, the committee recommended cetuximab and panitumumab as specified in section 1 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 [sic]	Response
		In conjunction with the principal investigators of several large randomized studies, we have recently validated the ability of miR-31-3p to identify a population of patients who gain more benefit from cetuximab and panitumumab with regard to both survival and response. This conclusion is based on separate analyses of miR-31-3p expression in tumor samples obtained from patients enrolled in the New EPOC, PICCOLO, and FIRE-3 studies. While the initial discovery and validation studies with miR-31-3p in KRAS wild-type mCRC patients have been published (http://goo.gl/kB4Tlv), the results from the New EPOC and PICCOLO studies have only recently been presented at ASCO and ESMO with a manuscript submission for the former planned for the near future. Our initial analysis of the miR-31-3p expression in tumor samples from the FIRE-3 study has only recently been completed and we plan to complete the full statistical analysis in the very near future and then submit the results to ASCO 2016. Since results from our studies to date from 8 separate patient cohorts have been consistent in regards to the ability of miR-31-3p to identify a specific subpopulation of KRAS wild-type mCRC patients who are more likely to benefit from cetuximab and panitumumab, we believe these results would be of value to NICE since this biomarker could be utilized to better target the use of cetuximab and panitumumab for patients more likely to respond to therapy, improving the cost-effectiveness of these drugs. Prior to submitting a response to the preliminary guidance document, we were interested in feedback from NICE relative to the Appraisal Committeeâ€™s willingness to review late-breaking data which is relevant to the focus on their review. If there is indeed willingness to review such data, we would plan to compile a detailed response which thoroughly reviews the clinical data obtained to date from studies and analyses of miR-31-3p in KRAS/RAS WT mCRC patients.	

Role*	Section	Comment [sic]	Response
		Thank you for your efforts and we appreciate your willingness to provide us with guidance.	
NHS Professional	1	The ACD is extremely worrying for any patient with bowel cancer in the UK and any oncologist involved in the treatment of metastatic colorectal cancer (mCRC). This proposed guideline will remove the availability of a targeted biological therapy from patients with RAS wild type mCRC. This is a proven, licensed and accepted strategy for treating this disease internationally. This guideline will therefore result in the earlier death of thousands of patients with mCRC in the UK annually. The whole way the assessment group has made assumptions and calculations appears fundamentally flawed. The use of PFS over OS seems bizarre given that final OS data have been presented and over 80% of survival events had occured in PRIME. The importance of a 5.6 month increase in OS seems to have been lost on the assessment group. Moreover, removal of EGFR targeted therapy in the neoadjuvant setting for operable liver mets is a disaster. The incremental extra patients that would have been cured by such a response are now going to die of mCRC and suffer the indignity and cost of multiple lines of chemotherapy for advanced disease. Everyone in the oncological community is looking to see how NICE rises to the challenge of taking over from the CDF. This is a very, very bad sign and raises serious questions over NICE's ability to be involved in the commissioning of cancer drugs in the future.	Thank you for your comment. The committee agreed following its second meeting to use OS from the clinical trials. After considering the comments received in response to the ACD and withdrawn FAD in conjunction with the new evidence submitted by the companies and the assessment group, the committee recommended cetuximab and panitumumab as specified in section 1 of the FAD.
NHS Professional	1	We would like the committee to consider the following points before reaching a final decision: 1) With colorectal cancer being the third most common cancer in England and with poor overall 5-year survival. Removing these two drugs will have a significant impact on all Pan RAS WT patients which represents half the colorectal cancer patient population.	Thank you for your comment. The committee agreed following its second meeting to use OS from the clinical trials. After considering the comments received in response to the ACD and withdrawn FAD in conjunction with the new evidence submitted by the companies and the

Role*	Section	Comment [sic]	Response
		2) We feel data is mature enough to allow usage of median OS rather than PFS to calculate QUALYs. We feel this will have potentially a significant impact on the calculations 3) We feel that the accepted mature data has shown the following: a. Kohne et al Presented a pooled analysis (ASCO GI 2010) of the OPUS and CRYSTAL data showing a significant improvement in median OS for K-RAS WT patients receiving Cetuximab and Folfiri vs Folfiri alone (23.5 vs 19.5 months) HR 0.82 p-value 0.0062 as well a significant improvement in PFS (9.6 vs 7.6 months) HR 0.66 and p-value of < 0.0001 and an improvement in over al l response rate (57.3% vs 38.5%) Odds ratio 2.16 p-value <0.0001 b. CRYSTAL showed an improvement in median OS in K-RAS WT patients receiving Cetuximab plus Folfiri vs folfiri (23.5 vs 20 months) HR = 0.796 snd a p-value of 0.0093 c. PRIME updated data demonstrated a 5 months improvement in OS for the Pantimumab + Folfox compared to folfox alone with a HR of 0.83 and a p-Value of 0.03 in WT KRAS patients d. Almost all of the studies looking at anti-EGFR plus chemotherapy vs chemotherapy alone have reported significant improvement in overall response rates. 4) We feel with more up to date and comprehensive RAS testing will allow better patient selection and usage of personalised medicine which can only improve outcomes. 5) We also feel that end of life criteria should be applied to this group of patients, given their severely limited life expectancy and the relative significant improvement in median overall survival seen with the use of anti-EGFR therapy and whilst colorectal cancer is a common cancer, we feel selecting patients using robust RAS testing would enforce end of life criteria application to this group of patients 6) The UK in general and England in particular has been the seat for excellent world class clinical research and innovation.	assessment group, the committee recommended cetuximab and panitumumab as specified in section 1 of the FAD.

Role*	Section	Comment [sic]	Response
		Taking this stance on innovative and effective treatment options will not only lead to a decline in our research ability 7) As a group we have an extensive experience in treating metastatic bowel cancer and feel that losing the use of anti-EGFR drugs will negatively impact on our patientâ€™s wellbeing, quality of life, and overall survival and this is something we find unacceptable.	
NHS Professional	1	On behalf of my clinical Colleagues at the [redacted] Oncology Centre, one of the busiest in the country, I have been asked to share our view that the removal of either of the EGFR inhibitors from the list of options for advanced colorectal cancer patients would be a mistake.	Thank you for your comment. After considering the comments received in response to the ACD and withdrawn FAD in conjunction with the new evidence submitted by the companies and the assessment group, the committee recommended cetuximab and panitumumab as specified in section 1 of the FAD
NHS Professional	1	Firstly my thanks to the Cancer Drug Fund to allow clinicians to use Panitumumab and Cetuximab in the first line management of RAS wild metastatic colorectal cancers. Also the flexibility to use them either with Folfox or Folfiri is welcome. As targetted biological agents these are the only drugs that are currently available for use. They remain truly targetted drugs as they are selected only for RAS wild population. Hence they offer these patients a great advantage in disease control both in terms of OS and PFS. With regards to Panitumumab, it is widely used in the Continent. As a humanised mono clonal antibody it is easier to use with lesser allergic reactions. PRIME Trial reinforces the 5.6 months gained in OS and PFS when Panitumumab is added to the chemotherapy back bone. As a practising clinician I would request for these agents to be continued to be available for use and request NICE to support. As RAS testing has become more robust and accurate, there is , in my opinion, a strong case for antibodies to benefit this small group of patients.	Thank you for your comment. After considering the comments received in response to the ACD and withdrawn FAD in conjunction with the new evidence submitted by the companies and the assessment group, the committee recommended cetuximab and panitumumab as specified in section 1 of the FAD

Role*	Section	Comment [sic]	Response
NHS Professional	1	i agree anti-egfr treatments should be standard of care on Nice not on cdf since it is biomarker driven and has good evidence base.	Thank you for your comment. After considering the comments received in response to the ACD and withdrawn FAD in conjunction with the new evidence submitted by the companies and the assessment group, the committee recommended cetuximab and panitumumab as specified in section 1 of the FAD
NHS Professional	1	As a medical oncologist with sub-speciality practise in colorectal cancer, it is a huge concern that this class of drugs which have a proven track record of disease reduction and survival advantage would be denied to appropriate molecularly defined patient population	Thank you for your comment. After considering the comments received in response to the ACD and withdrawn FAD in conjunction with the new evidence submitted by the companies and the assessment group, the committee recommended cetuximab and panitumumab as specified in section 1 of the FAD
NHS Professional	1	The role of EGFR inhibitors (cetuximab, panitumumab) has been studied in multiple studies. There is a robust data for OS in both 1st and 3rd line both with chemoterapy and versus best supportive care. The most recent studies PRIME and FIRE3 has defined the patient selection further and this has improved the OS further. Adopting PFS as the end point for the appraiasl is ignoring the results that has changed practice for this group of patients. The OS has imporved by 7 months in the FIRE3 study and by 5.6 months in the PRIME study. This is the largest improvement in OS in mCRC and th edata appears mature as more than 80% of events had taken place. This should be taken in consderation. The ACD states that these drugs do not the end of life criteria in 3rd line. This group of patients are highly selected by the RAS status and have progressed on previous therapy. There life expectancey is usually less then 6 months at best and therefore the statment ought to be reconsidered.	Thank you for your comment. The committee's end-of-life considerations are outlined in section 4.20 of the FAD. After considering the comments received in response to the ACD and withdrawn FAD in conjunction with the new evidence submitted by the companies and the assessment group, the committee recommended cetuximab and panitumumab as specified in section 1 of the FAD
NHS Professional	1	The treatments being assessed are valuable and clinically effective toold for the management of patients with incurable colorectal cancer. The trials included in the analysis of which the largest and most informative are the CRYSTAL and PRIME studies are Phase	Thank you for your comment. After considering the comments received in response to the ACD in conjunction with the new evidence submitted by the companies and the assessment group, the

Role*	Section	Comment [sic]	Response
		3 trials with mature follow-up. Patients with resectable liver only or predominant metastatic disease were not eligible for these studies. Patients in this sub-group have already been assessed in previous NICE guidance and the value of reviewing this group again within the context of this analysis is uncertain. As is described in the analysis only ~10% of patients will have a "successful" liver resection and then atleast half of these patients will relapse with disease which is not amenable to further surgery. The value of EGFR mAb treatment is the extension to progression free but more importantly overall survival which they provide. Not considering these agents as end of life treatments is a perverse decision given the context of treatment even if you feel the analysis in that context would not change the final cost-effectiveness decision. The panel should consider re-assessing the data based on Overll Survival being the main endpoint. Concerns regarding the quality of the trial data and the generalisability to the overall population of cancer patients are noted. Patients in these studies were younger than the overall population with advanced colorectal cancer but this has also been the case for every significant colorectal cancer trial evaluated previously including those supporting the use of standard chemotherapeutic agents such as oxaliplatin, irinotecan and capecitabine. This is not a unique factor associated with research into these agents but is a general problem with the assessment of systemic treatments in patients with a range of malignancies. The survival of patients with colorectal cancer is 20-30 months. The follow-up for all the trials considered is sufficient to demonstrate a difference is overall survival with confidence. The statement that the survival data is insufficiently true is incorrect.	committee recommended cetuximab and panitumumab as specified in section 1 of the FAD: • The committee's end-of-life considerations are outlined in section 4.20 of the FAD. • The committee agreed following its second meeting to use OS from the clinical trials. • The committee considered the uncertainties in the clinical evidence as specified in section 4.6 of the FAD and concluded that, for the purpose of this appraisal, the populations in the clinical trials of cetuximab and panitumumab were broadly generalisable to clinical practice in the NHS. .

Role*	Section	Comment [sic]	Response
		The reviewers correctly point to the fact that these trials have been subjected to post-hoc analyses which raise concerns regarding their statistical power and the risk of confounding factors. However, the post-hoc analyses reflect the rapid changes that have occured in our knowledge of the biology of colorectal cancer. All of the clinical trials recruited over the last decade have needed to undego analyses based on RAS and BRAF mutation status. Whilst some of these analyses from recent trials have been planned prospectively many have been performed retrospectively. Although the critique is in-part valid the evidence base will not be significantly enhanced through further follow-up. . Additional trials such as FIRE3 and the CALGB study include additional agents in their randomisation which would not be available through the NHS so I assume these studies have not been chosen for analysis based on these factors. Nevertheless these studies provide an insight into the prolongation of overall survival with the incorporation of these drugs (and other) into standard practice. From a broader context the debate about the clinical effectiveness rather than cost-effectiveness of these agents has been settled and internationally both of these agents are considered to be standard drugs which are available for patients with advanced colorectal cancer to receive. A decision not to fund these drugs sets the UK health system apart from those in other developed countries. Additionally it will significantly affect the ability of the UK to participate in international trials investigating systemic treatment for colorectal cancer. This has already been affected by the lack of availability of VEGF targeting mAbs and will be further undermined by the inability of UK clinicians to administer EGFR mAb therapy. Finally there is also an issue about whether the processes used to evaluate drugs in TA are fit for purpose as the UK system and the international standard practice has diverged. Inevitably some of the overall survival advantages seen with the use of the EGFR mAb agents is due to the subsequent use of additional agents each having an incremental effect. Internationally cetuximab,	

Role*	Section	Comment [sic]	Response
		panitumumab, bevacizumab, aflibercept and regorafenib are all considered standard agents. In all on-going and future international studies there will be widespread use of these agents. In this context the assessment of new drugs for colorectal cancer appears to be futile in the current TA system as no evidence will be admissable given the difference between the studies and "real world" UK practice. I appreciate the difficult decisions regarding cost effectiveness which need to be made but the current system does not appear to be working for colorectal cancer patients and based on the rationale provided for the decisions its difficult to have any confidence that I will be able to offer patients under my care any of the treatments which are in development currently or have demonstrated improvements in PFS or OS over the last few years.	
NHS Professional	1	Colorectal cancer is the 3rd most common cancer in England. Despite advances in the treatment of advanced disease the prognosis remains poor with a 5 year overall survival rate of only 5-10%. The development of the anti-EGFR antibodies cetuximab and panitumumab represents a significant advance in the management of metastatic colorectal cancer, which has led to a clinically meaningful improvement in overall survival (OS). Tumour analysis for RAS and BRAF mutations represents a clear move towards personalized treatment of colorectal cancer that enables the rational selection of patients most likely to respond to therapy, and prevents unnecessary treatment of those patients unlikely to respond. The use of anti-EGFR antibodies in RAS wild-type patients is standard of care in other European countries, and is recommend by clinical guidelines of the European Society of Medical Oncology and the National Cancer Institute. Without access to these drugs, there is a clear unmet need for patients with advanced colorectal RAS wild-type tumours. These patients will have no access to these drugs despite robust evidence of clinically meaningful improvements in OS with the addition of anti-EGFR antibodies to first line chemotherapy. Furthermore, the recent removal of cetuximab and panitumumab as 3rd line therapy	Thank you for your comment. After considering the comments received in response to the ACD and withdrawn FAD in conjunction with the new evidence submitted by the companies and the assessment group, the committee recommended cetuximab and panitumumab as specified in section 1 of the FAD

Role*	Section	Comment [sic]	Response
		from the Cancer Drug Fund (CDF) means these patients now have limited lines of active treatment. The recent changes to the CDF have resulted in inferior outcomes for a number of our patients, and have complicated clinical decision making. Overall this has had a negative impact on the treatment options available for patients. Having read the consultation documents it is apparent that not all of the available evidence has been taken into account. We note that the CALGB-80405 trial, which compared cetuximab plus FOLFOX or FOLFIRI with bevacizumab plus FOLFOX or FOLFIRI, was excluded from the analysis as it did not randomly allocate patients to FOLFOX or FOLFIRI and the trial results were available only in abstract form. The Fire-3 phase III trial (AIO KRK-0306) published in the Lancet Oncology1 in 2014 was also not included. This was a head to head comparison of FOLFIRI plus either cetuximab or bevacizumab as first-line treatment in patients with metastatic colorectal cancer (who had KRAS wild-type disease). Whilst patients were not allocated to a chemotherapy alone arm, the median OS in the FOLFIRI and cetuximab arm of 33 months represents a significant advance on historical controls. In this large study of 752 enrolled patients, KRAS wild-type tumours were confirmed in 592 patients, who were then randomised 1:1 to receive first-line FOLFIRI every two weeks plus either cetuximab at 400 mg/m2 on day 1 followed by 250 mg/m2 weekly (arm A) or bevacizumab at 5 mg/kg every 2 weeks (arm B). The results from the overall study population favoured arm A, with median OS in cetuximab treated patients nearly four months longer than in the bevacizumab arm. The results presented were from a preplanned analysis that evaluated the effect of KRAS mutations in exons 2, 3 & 4 exon 4 and NRAS exon 2,3, & 4 and BRAF (V600E) on the overall response rate (ORR), progression-free survival (PFS) and OS on treatment arms A and B of the FIRE-3 trial. A total of 444 (75%) patients had available tumour tissue; of these, sequencing of all known RAS mutations was possible in 396 patients. Greater benefit was demonstrated with FOLFIRI plus	

Role*	Section	Comment [sic]	Response
		cetuximab in the overall intention to treat population of 592 patients with KRAS wild type disease; ORR was 62.0% and 58.0% in arm A and B, respectively (p = 0.183 [FisherÂ´s one-sided test]). "	
NHS Professional	1	whilst I appreciate both drugs are expensive (and we can debate cost effectiveness) there is no doubt regarding the efficacy of both cetuximab and panitumumab on the basis of CRYSTAL/PRIME trials and the subsequent data from FIRE3/CALGB where OS was over 30 months in both studies with chemo + cetuximab.	Thank you for your comment. After considering the comments received in response to the ACD and withdrawn FAD in conjunction with the new evidence submitted by the companies and the assessment group, the committee recommended cetuximab and panitumumab as specified in section 1 of the FAD
NHS Professional	1	The results of the PRIME trial analysis (following an updated analysis of RAS status) clearly demonstrate the superiority of combination treatment with FOLFOX and Panitumumab versus FOLFOX alone. Patients receiving FOLFOX-Panitumumab have a median overall survival that is over 5 months greater (26.0 vs. 20.2) than the FOLFOX alone arm. To deny such an effective treatment to patients with a significantly limited life-expectancy will only cause the gap in cancer survival rates between the UK and our comparable European neighbours to widen.	Thank you for your comment. After considering the comments received in response to the ACD and withdrawn FAD in conjunction with the new evidence submitted by the companies and the assessment group, the committee recommended cetuximab and panitumumab as specified in section 1 of the FAD
NHS Professional	1	"The use of anti-EGFR therapy is well defined in multiple setting in mCRC, and following withdrawal of funding for anti-angiogenic therapy (bevacizumab and aflibercept) these remain the sole biological agents used for patients with this disease. Notably, in contrast to anti-angiogenic therapy, for anti-EGFR therapy there is a biomarker selected patient population for whom treatment with anti-EGFR therapy is more likely to yield benefits in survival thus limiting the financial impact of the use of these drugs. I would like to make the following comments with respect to the ACD which has been published. Concerns were raised regarding the lack of robustness of the overall survival (OS) data for anti-EGFR therapies as: Subsequent treatments used post-progression may have prolonged the overall survival gain for anti-EGR therapy In PRIME study 18% of patients who were treated with FOLFOX alone received anti-EGFR therapy second line as did 8% who had	Thank you for your comment. After considering the comments received in response to the ACD and withdrawn FAD in conjunction with the new evidence submitted by the companies and the assessment group, the committee recommended cetuximab and panitumumab as specified in section 1 of the FAD: • The committee considered the uncertainties in the clinical evidence as specified in section 4.6 of the FAD and concluded that, for the purpose of this appraisal, the populations in the clinical trials of cetuximab and panitumumab were broadly generalisable to clinical practice in

Role*	Section	Comment [sic]	Response
		been treated with FOLFOX-panitumumab. Twelve and 15% of patients treated with FOLFOX and FOLFOX-P received bevacizumab respectively. Firstly, as treatment was continued until progression in PRIME, rechallenge with an anti-EGFR therapy for patients previously treated with panitumumab (and therefore resistant to EGFR inhibition) is unlikely to have significantly affected survival outcomes. Secondly, if patients who had not previously received an EGFR inhibitor(FOLFOX treated patients) were treated subsequently with panitumumab then this would reduce the survival benefit demonstrated in the trial to panitumumab. Thirdly, the proportion of patients who received second line chemotherapy was higher (62% vs 53%) in patients treated with FOLFOX alone first line which would also negatively influence survival outcomes for panitumumab treated patients (and not extend the survival benefit). Finally, as anti-angiogenic therapy was used in approximately equivalent proportions of patients in each arm this can be assumed to have a negligible differential effect. In the CRYSTAL study post progression anti-EGFR therapy was used in 6.2% of patients in the cetuximab-FOLFIRI group and 25.4% of patients in the FOLFIRI alone group. Therefore the same argument applies â€“ this could only potentially attenuate the survival benefit of cetuximab. Similarly, in line with PRIME, the proportion of patients who were treated with chemotherapy second line was higher in patients who did not receive cetuximab first line (63.9% vs 68.8% respectively). Therefore it is not clear to us how the effects of post progression therapy can be used as a rationale for rejecting the use of the robust overall survival data for either cetuximab or panitumumab in these first line studies. . Treatments used post progression in the CRYSTAL and PRIME studies are no longer used in the NHS Regarding the comment that treatments used post progression in CRYSTAL and PRIME are no longer used in the NHS and that the overall survival data for this study should not be used for this reason, this may also be solidly refuted. Firstly, anti-angiogenic	the NHS. Please see section 4.6 of the FAD. • The population size is no longer a consideration for end-of-life. Please see the Final CDF Technology Appraisal process and methods (addendum to the Guide to the Processes of Technology Appraisal and addendum to the Guide to the Methods of Technology Appraisal for further information. The committee's end-of-life considerations are outlined in section 4.20 of the FAD.

Role*	Section	Comment [sic]	Response
		therapies are no longer funded foir NHS patients (although continue to be used worldwide) , but were used in equivalent numbers of patients in each arm in PRIME. Secondly, anti EGFR therapy may not be used beyond first line, but in each trial this was used in more patients in the control arm (and would have been ineffective in the smaller number of patients in the experimental arms). Controlling for this would only extend the survival benefit due to first line use of anti-EGFR therapy. Immature survival data The survival data are commented to be immature. In the original CRYSTAL publication almost 70% of patients had died, whereas in the updated analysis of PRIME 82% of patients had died which we believe is sufficient to make a robust assessment of the efficacy of the experimental arm in either study. " "Further concerns were raised regarding: Uncertainties in the clinical evidence base for anti-EGFR therapies given subgroup analysis and small sample size The committee considered that the clinical evidence was limited as it represented subgroup analysis, and that there were â€œfew samples available for re-analysisâ€• . While it is certainly true that this does represent a post-hoc subgroup analysis we do not believe that this in itself is a reason to reject this evidence. Evidence from subgroup analysis of phase III randomised trials is accepted as sufficiently robust to determine licensing indications as extended RAS testing is now mandatory before administration of anti-EGFR therapy for patients with mCRC (FDA and EMA regulations). It is difficult to understand how the requirement evidence of subgroup activity for funding could be so much more stringent that which guides assessment of patient safety and benefit from a regulatory perspective. The comment stating that â€œfew samples were available for analysisâ€• is simply untrue; in PRIME the rate of ascertainment of RAS and BRAF status was 89%, and was assessed in 1047 of 1183 patients. This is a very high proportion of patients in any trial to have available for biomarker	

Role*	Section	Comment [sic]	Response
		assessment. To draw an important parallel, NICE approval was granted for the BRAF inhibitor dabrafenib based on the results of the BREAK 3 trial, which randomised 250 patients with BRAF mutant melanoma to dabrafenib or chemotherapy. In PRIME, 512 RAS wild type patients were randomised to FOLFOX vs FOLFOX panitumumab. Similarly in the CRYSTAL trial 367 RAS wild type patients are evaluable for survival assessment. Together these numbers equate to almost nine hundred patients. Although this hypothesis was not pre-specified for either study, these numbers mean that these are practice changing analyses as evidenced by the subsequent licensing changes and therefore survival data should not be ignored an untrue claim of â€œsmall sample sizeâ€• . Lack of generalisibility of the clinical trial population in the relevant clinical trials While concerns regarding the external validity of clinical trials are common, this is not a valid reason to withhold anti-EGFR therapy for NHS patients. To further this argument one could argue that no treatment based on a clinical trial should be extended to NHS patients, which is clearly not credible. Eligibility criteria are necessary for clinical trials to protect the patient and the scientific value of the trial. However, when extending treatments to a broader patient population oncologists (who are both responsible and liable) will consider what the eligibility criteria were for a trial, and are unlikely to extend treatment to patients who do not meet those criteria. In this setting, the key question is whether patients will tolerate doublet chemotherapy and not the addition of anti-EGFR antibody treatment which is associated with limited additional toxicity compared to chemotherapy alone. If a fit patient is appropriate for doublet chemotherapy, then they are very likely to tolerate combination chemotherapy plus anti-EGFR treatment and the results of the study are generalisable to those patients. It is relevant to state at this point that of course many NHS patients (including my own) participated in these studies and that clearly this population exists in the UK.	

Role*	Section	Comment [sic]	Response
		" "Anti-EGFR therapies do not meet the End of Life (EoL) criteria overall as it does not meet the criterion of small patient population Firstly, if end of life criteria entail that less than 7000 patients per year in England may be treated with a drug, it is likely that either cetuximab or panitumumab will meet this goal. Approximately 15000 patients per year in the UK will die from advanced colorectal cancer. Of these approximately half will have a RAS mutation which will render them unsuitable for anti-EGFR therapy. However there will be another proportion (relating the previous point above) who have co-morbidities or a performance status which renders them unsuitable for doublet chemotherapy (and therefore an anti-EGFR inhibitor). If we conservatively estimate this to be 10-15% (and it is likely to be higher), then the absolute number of patients treated with anti-EGFR therapy is likely to be less than 7000. This is notwithstanding the fact that recently the â€œsmall populationâ€• criterion for EoL criteria has been challenged as valid reason not to extend the possibility of treatment to patients with cancer. Why should patients with a more common cancer be disadvantaged by this fact? This is underlined by the revision of the CDF application of NICE EoL criteria as proposed in the document â€œConsultation on proposals for a new cancer drugs fund (CDF) operating model from 1st April 2016â€• (https://www.nice.org.uk/Media/Default/About/what-we-do/our-programmes/technology-appraisals/cdf-consultation-document.pdf) which proposes to exclude this as a relevant criterion from future assessments. " "A final and pertinent point which is not addressed in the NICE appraisal is that withdrawal of anti-EGFR therapy for patients with advanced colorectal cancer will significantly impact on the capacity of the UK oncologists and their patients to participate in clinical trials. The UK has a research infrastructure which is world renowned, and in which academic research is part supported by a symbiotic relationship with the pharmaceutical industry through	

Role*	Section	Comment [sic]	Response
		participation in commercial clinical trials. As many clinical trials recruit patients to â€œProduct Xâ€• plus the standard of care which in this case worldwide is chemotherapy plus an anti-EGFR inhibitor, the UK will no longer be an attractive destination for pharmaceutical companies wishing to perform such research. This has knock-on effects for patients in the later stages of treatment too because if they have not received a full complement of available treatments in the first line setting then they are ineligible for studies in second and third line. The implications of this for patients are devastating in terms of access to promising new drugs. However the implications for UK research may be equally profound, lack of funding investment may lead to decreased academic activity, loss of research jobs and a decline in the UKâ€™s standing as an academic powerhouse for gastrointestinal oncology trials. Whilst we acknowledge that this does not directly impact on the economic cost-benefit analysis for individual patients it may have economic effects on society as whole. In conclusion, survival for patients with advanced colorectal cancer in the UK was previously significantly inferior to other comparable countries however in recent years the UK has narrowed the gap in this regard (Walters et al, Br J Cancer. 2015 Sep 1; 113(5): 848â€“860). As median overall survival for patients with advanced colorectal has is improved significantly with the use of anti-EGFR therapy it would very regretful to limit access to these life extending drugs and revert UK gastrointestinal oncology to an era more than a decade ago. We therefore urge the committee to reconsider this evaluation. "	

Comments received following 3rd appraisal committee meeting

Commentator	Comment [sic]	Response
Amgen	We welcome the opportunity for further consideration of this appraisal, following withdrawal of the FAD and the issue of the subsequent AG Addendum Report. We are confident that our response will now allow NICE to make a positive recommendation for panitumumab in the overall population.	Thank you for your comment. After considering the comments received in response to the withdrawn FAD, the committee recommended cetuximab and panitumumab as specified in section 1 of the FAD.
Amgen	In the withdrawn FAD, the ICER for panitumumab in the overall population (using the appraisal committee's preferred assumptions) was [redacted] including a [redacted] PAS. The committee concluded that panitumumab plus chemotherapy fulfilled the criteria to be considered a life-extending, end of life treatment in the overall population; however given that the ICER exceeded the EoL threshold of £50,000, it did not consider panitumumab to be a cost-effective use of NHS resources.	Comment noted.
Amgen	We consider it important to create a simple route forward for recommendation and avoid revisiting the considerations which underpin the overall population ICER; the result of an appraisal process lasting over 18 months. We have therefore taken the important step to further increase the PAS discount, to [redacted], which ensures that the overall population ICER remains below £50,000; even in the worst-case scenario when exploring uncertainty by varying resection rates. Table 1 presents ICERs for the overall population based on the committee's preferred assumptions with the [redacted]% PAS and with the revised PAS of [redacted]% for panitumumab, exploring upper and lower bound ICERs by varying resection rates from 0% to 20%. ***Table 1 removed, please see Amgen's complete response to the withdrawn FAD in the committee papers.***	Comment noted. The final analysis took into account the revised patient access scheme.
Amgen	With the increased PAS discount, panitumumab is safely cost-effective below the EoL threshold, producing a final decision-making ICER of [redacted], notably lower than previously ([redacted]). The lower bound ICER (with a 20% resection rate for panitumumab) is highly cost-effective at [redacted], and the upper bound ICER (with resection rates set to 0%) still remains below the EoL threshold at [redacted].	Comment noted. The committee concluded that it was appropriate to use resection rates from the clinical trials (see section 4.12 of the FAD).

Commentator	Comment [sic]	Response
Amgen	We believe that the clinical and cost effectiveness case for panitumumab in the overall population is robust. The further increased PAS we have offered mitigates the risk to the NHS regarding any residual uncertainty. Access to panitumumab and cetuximab through the Cancer Drugs Fund (CDF) has delivered critical improvements in outcomes for previously untreated mCRC patients. This appraisal presents an opportunity to move panitumumab into baseline commissioning and provide patients with the first ever NICE approved targeted treatment in this life limiting condition. We therefore propose that NICE recommends panitumumab in combination with FOLFOX or FOLFIRI for use in the overall population.	Comment noted. After considering the comments received in response to the withdrawn FAD, the committee recommended cetuximab and panitumumab as specified in section 1 of the FAD.

Commentator	Comment [sic]	Response
Amgen	2. Detailed response to key issues The overall population should be used for decision-making and it is neither clinically appropriate nor robust to separate out subgroups: • It is common in randomised controlled trials (RCTs), including PRIME, for there to be patient sub-populations that potentially confer improved prognosis (e.g. age, gender, ECOG status, primary tumour and site of metastases - LLD or elsewhere). Panitumumab has clearly demonstrated a robust OS gain in the overall population (hazard ratio [HR] 0.77, 95% confidence interval [CI] 0.64, 0.94) regardless of patient sub-populations. In addition, panitumumab remains clinically effective in the non LLD sub-population, with a similar HR to the overall population that is nominally significant (HR 0.79, 95% CI 0.64, 0.98). The interaction between treatment and site of metastases (LLD or elsewhere) was not statistically significant with a p-value of 0.71. Therefore there is no strong clinical rationale to separate out subgroups (such as LLD and non-LLD subgroups). • In the LLD subgroup, improved prognosis is driven largely by those patients who have resection, whilst all other LLD patients will be treated palliatively to progression. Separating the whole LLD subgroup is therefore not a robust way of addressing the committee's concerns regarding the improved prognosis conferred by resection. We believe it is better to address this issue using the overall population for panitumumab and to conduct scenario analyses varying resection rates, rather than separating out clinically implausible subgroups. • Importantly, the proportion of LLD patients is only 17.6% of the overall population in the PRIME RCT and any impact on the ICER due to improved survival is small. Indeed, the significantly lower ICER for the LLD subgroup presented in the AG assessment report (around £30,000) is driven by the 16 week treatment stopping rule for panitumumab. Without the stopping rule, the ICER for the LLD subgroup is not markedly lower than the overall population ICER, further supporting the case that the overall population ICER is robust and should be used for decision-making.	Comment noted. After considering the comments received following the withdrawn FAD, the committee concluded that it would only consider the total population. Please see section 4.3 of the FAD

Commentator	Comment [sic]	Response
Amgen	The impact of resection on the overall population ICER (based on committee's preferred assumption for resection) is likely to be small and any uncertainty limited: • The committee noted that patients in the LLD subgroup were more likely to have resection, leading to improved prognosis. • However, the resection rates (taken from the PRIME RCT) and used in the NICE cost-effectiveness analysis to generate the ICER in the overall population, based on the committee's preferred assumptions , were low (12.6% for panitumumab+FOLFOX and 10.7% for FOLFOX), with negligible differences between treatment arms. Consequently, the impact of resection rates on the overall population ICER for panitumumab is likely to be small.	Comment noted. The committee concluded that it was appropriate to use resection rates from the clinical trials (see section 4.12 of the FAD).

Commentator	Comment [sic]	Response
Amgen	We propose to create a simple route forward for recommendation using the committee's preferred assumptions for panitumumab in the overall population and mitigate any additional uncertainty through a further increased PAS discount: • The committee acknowledged that the overall population ICERs, based on the committee's preferred assumptions, are likely to be lower in practice. However to create a simple route forward, we continue to use, conservatively, the committee's preferred assumptions in the overall population, to generate revised ICERs. • To address concerns regarding the uncertainty in the overall population, we have explored scenarios around the ICER generated using the committee's preferred assumptions [redacted]), based on different resection rates for panitumumab in place of the committee's preferred assumption of 12.6% (PRIME resection rate) o Increase in the resection rate to 20% for panitumumab+FOLFOX: This reflects clinical expert opinion that the estimates of resection for panitumumab (and cetuximab) could be higher in practice (around 15% to 20%), and results in a potential lower bound ICER of £[redacted]; providing reassurance that the ICER generated using the committee's preferred assumptions in the overall population (£[redacted]) is conservative. o Reduction in the resection rate to 0% for both the panitumumab+FOLFOX and FOLFOX arms: This resection rate, although clinically implausible, results in a potential upper bound ICER of £[redacted] and serves to explore concerns regarding uncertainty. • Although the upper bound scenario is clinically implausible, we have further increased the PAS discount ([redacted]) to mitigate any additional uncertainty and ensure that the overall population ICER remains below £50,000, even in this worst-case scenario. Results based on the [redacted]% PAS and the revised [redacted]% PAS are presented in Table 2. • With the increased PAS discount, panitumumab is safely cost-effective below the EoL threshold producing a final decision-making ICER of £[redacted], notably lower than previously (£[redacted]) using the committee's preferred assumptions. The lower bound ICER (with 20% resection rate for panitumumab) is highly cost-effective at £[redacted], and the upper bound ICER (with resection rates set to 0%) still remains below the EoL threshold at £[redacted]. ***Table 2 removed, please see Amgen's complete response to the withdrawn FAD in the committee papers.***	Comment noted. The committee concluded that it was appropriate to use resection rates from the clinical trials (see section 4.12 of the FAD) and recommended cetuximab and panitumumab as specified in section 1 of the FAD.

Commentator	Comment [sic]	Response
Amgen	We believe that the clinical and cost effectiveness case for panitumumab in the overall population is sufficiently robust. The further increased PAS we have offered mitigates the risk to the NHS regarding any residual uncertainty. We therefore propose that NICE recommends panitumumab in combination with FOLFOX or FOLFIRI for use in the overall population.	Comment noted. The committee recommended cetuximab and panitumumab as specified in section 1 of the FAD.
Merck Serono	1.1. The current all patient model reflects the UK treatment paradigm in colorectal cancer The decision problem in this MTA, as set out in its original scope, reflects the drugs' licences, namely the use of cetuximab and panitumumab in RAS wt metastatic colorectal cancer. Figure 1 below illustrates this treatment paradigm, reflecting the way in which the EGFR inhibitors are used in the UK, as life-extending medicines for all metastatic colorectal cancer patients. As a total population, these patients have high unmet need and, as confirmed by the Committee, meet end of life criteria. ***Figure 1 removed, please see Merck Serono's complete response to the withdrawn FAD in the committee papers.***	Thank you for your comment
Merck Serono	The decision problem in this MTA, as set out in its original scope, reflects the drugs' licences, namely the use of cetuximab and panitumumab in RAS wt metastatic colorectal cancer. Figure 1 below illustrates this treatment paradigm, reflecting the way in which the EGFR inhibitors are used in the UK, as life-extending medicines for all metastatic colorectal cancer patients. As a total population, these patients have high unmet need and, as confirmed by the Committee, meet end of life criteria. ***Figure 1 removed, please see Merck Serono's complete response to the withdrawn FAD in the committee papers.***	Comment noted. After considering the comments received following the withdrawn FAD, the committee concluded that it would only consider the total population. Please see section 4.3 of the FAD.
Merck Serono	Further, a stopping rule is artificial. The majority of patients who are not eligible for liver resection continue to receive life-extending treatment if they are deriving benefit from the medicine. That is to say, for patients who are not resected (the vast majority, e.g. 93% in the CRYSTAL trial) no 'stopping rule' is applied in real life. Patient prognosis in this unresected population is comparable irrespective of location of the metastases.	Comment noted. After considering the comments received following the withdrawn FAD, the committee concluded that a stopping rule was inappropriate. Please see section 4.3 of the FAD.
Merck Serono	The all-patient model represents this clinical paradigm exactly and is therefore the relevant model for the decision problem set out by NICE in the scope of this appraisal.	Comment noted. After considering the comments received following the withdrawn FAD, the committee concluded that it would only consider the total population. Please see section 4.3 of the FAD.

Commentator	Comment [sic]	Response
Merck Serono	1.2. LLD patients do not drive cost effectiveness in the all patient model The cost-effectiveness of LLD patients in the LLD model is driven by the stopping rule. Without a stopping rule, LLD patients are no more or less cost-effective than the all patient group. This is evidenced by PenTAG's own analyses where in the addendum between the 2nd and 3rd meetings, the ICER for the overall population (assuming weekly dosing and OS correction) is the same as seen in the LLD model without a stopping rule [redacted]) .	Comment noted. After considering the comments received following the withdrawn FAD, the committee concluded that a stopping rule was inappropriate and that it would only consider the all patient group. Please see section 4.3 of the FAD.
Merck Serono	1.3. Revised confidential patient access scheme Merck have revised the level of the discount to cetuximab's list price that we previously agreed with the Department of Health. The level of the discount remains commercial in confidence. We have received confirmation from the Department that they are content with the revision and that this can be considered as part of this ongoing appraisal. There is little doubt that cetuximab is a clinically effective medicine and all parties in this appraisal have acknowledged the need for EGFRi treatments for all patients with metastatic colorectal cancer; there are no alternative treatment options. Merck is extremely committed to maintaining access for these patients. The revised cetuximab price, from [redacted] discount to [redacted] further underwrites the uncertainties that remain in the economic case.	Comment noted. The final analysis took into account the revised patient access scheme.
Merck Serono	1.4. Cost-effectiveness of cetuximab (PenTAG's model incorporating cetuximab's revised discount) We acknowledge PenTAG's recent additional analyses as laid out in their most recent addendum . The results presented therein are little different to their previous analyses, and they reflect the base case ICERs, at cetuximab's previous price, now including results when 100% fortnightly dosing is assumed.	Comment noted. The committee considered the ICERs including fortnightly dosing. Please see section 4.5 of the FAD.
Merck Serono	The incorporation of a distribution of BSA values reduces the ICERs by approximately £1k. We thank PenTAG for including this element and demonstrating this. Although PenTAG describe its impact as marginal it is nevertheless more accurate.	Comment noted. All final analyses included the distribution of BSA values. Please see section 4.16 of the FAD.

Commentator	Comment [sic]	Response
Merck Serono	PenTAG's addendum, however, is overcomplicated by the inclusion of numerous LLD analyses and a series of analyses which do not reflect the Committee's preferred assumptions outlined in the withdrawn FAD. These add an unnecessary level of complexity to the addendum and risk distracting the Committee from the key remaining subject of discussion, namely cost effectiveness in the all-patient population, applying the Committee's preferred assumptions (i.e. trial resection rates, OS values adjusted for post-study treatments, PenTAG's distribution of BSA values (rather than means) and a consideration of fortnightly dosing).	Comment noted. The committee only considered analyses including its preferred assumptions. Other analyses were included in the addendum for completeness.
Merck Serono	The Committee have indicated a willingness to take into account the cost of fortnightly dosing, which is routine clinical practice in the UK. In Table 1, results of the economic model are presented alongside the full range of assumptions about the proportion of patients receiving cetuximab fortnightly. In Appendices 1 and 2 we have provided supportive data to reassure the Committee regarding the extent of fortnightly dosing in England and Wales. This appears to be ~80% compared to ~20% weekly dosing. It is Merck's understanding that this can be ratified by analysis of SACT data. When these real world dosing patterns are factored into the economic model using a weighted average of fortnightly and weekly results, the ICER for cetuximab plus FOLFIRI vs FOLFIRI alone is [redacted]QALY. ***Table 1 removed, please see Merck Serono's complete response to the withdrawn FAD in the committee papers.***	Comment noted. The committee considered the ICERs including fortnightly dosing. Please see section 4.5 of the FAD.
Merck Serono	Targeted therapies have been available in the UK to mCRC patients since 2011, and without access to them, the chemotherapies in use a decade ago would be the only alternatives. The clinical evidence for cetuximab as a treatment for RAS-wt mCRC is strong. The CRYSTAL study shows a significant overall survival gain versus chemotherapy alone; 8 month median survival gain. Throughout the course of this MTA, Merck have remained fully committed to working with NICE to appropriately represent the economic value of the treatment to the NHS, and to ensuring that patients in England and Wales continue to benefit from access to this life-extending medicine. We have summarised the Committee's deliberations in this document and additionally we hope that by revisiting the clinical paradigm, the model structure and by revising the cetuximab discount, we have addressed any remaining areas of uncertainty in the Committee's mind. Under the preferred assumptions that the Committee previously agreed, cetuximab is a cost-effective use of NHS resources for all patients in this indication.	Comment noted. After considering the comments received in response to the withdrawn FAD, the committee recommended cetuximab and panitumumab as specified in section 1 of the FAD.

Commentator	Comment [sic]	Response
Beating Bowel Cancer and Bowel Cancer UK	As the two leading bowel cancer charities we welcome the decision to withdraw the final appraisal determination document (FAD) for the appraisal of cetuximab and panitumumab for previously untreated metastatic colorectal cancer. We are pleased that the Committee is re-evaluating this appraisal and has provided us with the opportunity to present our view on the FAD and further evidence. In this brief submission we outline our reasons for disagreeing with the previous FAD and provide further evidence that demonstrate cetuximab is administered 2-weekly in the UK.	Thank you for your comment. After considering the comments received in response to the withdrawn FAD, the committee recommended cetuximab and panitumumab as specified in section 1 of the FAD.
Beating Bowel Cancer and Bowel Cancer UK	While we were pleased that the end of life criteria had been met and would be applied to this appraisal, we disagreed with the FAD for the following reasons: 1. The criteria are too restrictive. The proposed recommendation for the use of cetuximab and panitumumab severely restricts the population who can benefit from these targeted therapies. Overall approximately 50% of people with bowel cancer will either be diagnosed with metastatic disease or go on to develop it and half of these will be RAS wild type. Of these patients, those with liver-limited disease make up a small proportion of this population. NICE's own costing template estimates that this figure is 10%. This means the vast majority, 90%, will be denied the potential benefit of this targeted therapy.	Comment noted. After considering the comments received following the withdrawn FAD, the committee concluded that it would only consider the total population. Please see section 4.3 of the FAD.
Beating Bowel Cancer and Bowel Cancer UK	The guidance is a significant departure from clinical practice and opinion. A recommendation for all RAS wild type patients has wide clinical support. Furthermore both treatments were recommended under the Cancer Drugs Fund for a wider indication. The NICE final guidance decreases the choice that both patients and clinicians have when deciding what course of treatment to opt for. It would mean that there would be no first line precision therapy for RAS wild type patients who have widespread metastases. We know that chemotherapy given with an EGFR antibody, such as cetuximab or panitumumab, can lead to a median survival rate in excess of 30 months. A letter to Sir Andrew Dillon signed by the Chairs of the Medical Advisory Boards of Bowel Cancer UK and Beating Bowel Cancer, along with the signatories of over 40 oncologists supporting the continued use of both cetuximab and panitumumab is attached in Appendix 1. ***Appendix 1 removed, please see* Beating Bowel Cancer and Bowel Cancer UK*'s complete response to the withdrawn FAD in the committee papers.***	Comment noted. After considering the clinical evidence for each treatment (see section 4 of the FAD), the committee recommended cetuximab and panitumumab as specified in section 1 of the FAD.

Commentator	Comment [sic]	Response
Beating Bowel Cancer and Bowel Cancer UK	3. The guidance will have a detrimental impact on the whole of the UK. Both Scotland and Wales have recommended cetuximab as a first line treatment for all RAS wild type patients for some time now – in Scotland this guidance has been in place since January 2015 and in Wales since December 2015. However as NICE TA guidance supersedes AWMSG guidance and NICE MTAs also usually supersede SMC advice consequently the FAD risks putting the whole of the UK back in terms of access to medicines for people with widespread metastases.	Comment noted.

Beating Bowel Cancer and Bowel Cancer UK	4. Cetuximab is administered fortnightly in the UK. In the FAD the Committee set out a willingness to take into consideration that in clinical practice cetuximab is administered fortnightly rather than weekly. Appendices 2 and 3 set out supporting evidence on the extent of this practice in the UK. The raw data has been from two sources: first, the SACT database and second, from a survey of prescribing practices carried out by Beating Bowel Cancer. a. SACT Dataset1 (Appendix 2) A request was made to SACT for the number of doses of cetuximab administered at different dose-levels. The weekly dose is 250mg/m2 and the 2-weekly dose is 500mg/m2. SACT also provided the median surface area for male (1.98m2) and female (1.76m2) patients (enclosed – appendix 2), Therefore the weekly dose would be around 400-500mg and the 2-weekly dose will be double this (800-1000mg). The SACT data attached shows that in England only 25% of patients received the lower dose via the weekly schedule whereas, 75% received the higher dose via the 2-weekly schedule (slide 2). The data has not been filtered by line of treatment. This means that some of the cetuximab may have been given 3rd or 4th line setting, as continuation of treatment that was commenced when this was available via the Cancer Drugs Fund (CDF). However, as cetuximab was only approved for use on the CDF as a first line treatment during 2016, we believe that this is a good representation of the first line prescribing practices of oncologists in England. This information has been generated from nearly 34,000 administrations of cetuximab (slide 3) and therefore we would say is robust evidence for the use of 2-weekly cetuximab in England. b. A survey of oncologists, carried out by Beating Bowel Cancer2 (Appendix 3) During a 2-week period between the 21st December 2016 and the 4th January 2017 a number of oncologists in the UK were sent a short survey via email on whether they prescribe cetuximab on a weekly or 2-weekly basis. A total of 64 replies were received. The results show that an overwhelmingly 98% of clinicians prescribe it in the 2-weekly schedule and only one Oncologist prescribes weekly cetuximab. The CDF only allowed a 2-weekly schedule. However, even though this was the case, there were no statements regretting that clinicians were not able to administer cetuximab weekly. Some of the other comments were recorded in the raw data that is enclosed with this submission. These include references for evidence and statements that the 2-weekly schedule is preferable for busy chemotherapy units and halves the number of visits that patients would have to make to hospitals. It is therefore efficacious and saves hospital and patient time and is therefore cheaper because of this. ***Appendices 2 and 3 removed, please see* Beating Bowel Cancer and Bowel Cancer UK*'s complete response to the withdrawn FAD in the committee papers.***	Comment noted. The committee considered the ICERs including fortnightly dosing. Please see section 4.5 of the FAD.

Commentator	Comment [sic]	Response
Beating Bowel Cancer and Bowel Cancer UK	It is for these reasons that we believe that cetuximab and panitumumab should be recommended as a first line treatment option for all RAS wild type patients. It would be a tragedy if the Committee did not recommend these two treatments and would be in contrast not only to other parts of the UK but the rest of Europe and North America. This will lead to a real crisis for bowel cancer patients and the treatment of metastatic disease across the UK. This would be a disastrous step, which will take us backwards and bring to a halt the progress in patient care that was achieved by the Cancer Drugs Fund, as well as significantly shorten survival rates of people with metastatic colorectal cancer in England. The Medical Advisory Board members of both charities also fully support this position.	Comment noted. After considering the comments received in response to the withdrawn FAD, the committee recommended cetuximab and panitumumab as specified in section 1 of the FAD.
NCRI-ACP-RCP-RCR	As stakeholders, we were very surprised and very saddened when we read through the NICE FAD whose recommendation in October 2016 was to allow Cetuximab or Panitumumab in combination with either 5-fluorouracil, folinic acid and oxaliplatin (FOLFOX) or with 5-fluorouracil, folinic acid and irinotecan (FOLFIRI) are recommended as options for previously untreated epidermal growth factor receptor (EGFR)-expressing, RAS wild type metastatic colorectal cancer in adults, only if: - the metastases are confined to the liver and are unresectable without treatment - the person is fit enough to have surgery after treatment with cetuximab or panitumumab - treatment lasts no longer than 16 weeks, at which point the liver is assessed for resection, and - the companies provide cetuximab and panitumumab with the discounts agreed in the patient access scheme.	Comment noted. After considering the comments received in response to the withdrawn FAD, the committee recommended cetuximab and panitumumab as specified in section 1 of the FAD.

Commentator	Comment [sic]	Response
NCRI-ACP-RCP-RCR	As colorectal clinicians, we strongly believe that the anti-EGFR antibodies Cetuximab and Panitumumab have made an enormous and beneficial impact in the management of patients with widespread metastatic colorectal cancer in the first-line setting, particularly those who are symptomatic with a high volume disease burden. The FIRE-3 and CALGB 80405 trials (which were not analysed in this assessment) have clearly shown significant benefits in terms of depth and duration of response and improved overall survival for the biomarker-selected group of patients with KRAS/NRAS wild-type disease who received anti-EGFR antibodies along with FOLFIRI or FOLFOX chemotherapy. These trials were started many years ago, involve several thousands of patients, and subsequent analyses of treatment post-progression in second and third-line and beyond have included patients who only received an anti-EGFR antibody in first-line, and neither anti-VEGF treatments nor repeat exposure to anti-EGFR treatments subsequently. These trial populations fit with current use of Cetuximab and Panitumumab as has been permitted in the CDF in the UK. The data from these subsequent analyses of these trials fits very well with our experience as UK colorectal oncologists. There is clear benefit to our patients who receive these drugs in first-line therapy. Optimal treatment in the first line setting is absolutely essential as only 45-60% of patients commence second line treatment, even in the most specialist centres in the UK, and only 20-35% commence third-line treatment.	Comment noted. After considering the clinical evidence for each treatment (see section 4 of the FAD), the committee recommended cetuximab and panitumumab as specified in section 1 of the FAD.

Commentator	Comment [sic]	Response
NCRI-ACP-RCP-RCR	We are concerned that there may have been some confusion in the committee between the benefits of first-line palliative use of EGFR inhibitors in RAS wild type metastatic colorectal cancer with chemotherapy (which represents approximately 90% of their use) and the liver only setting where we are allowed up to 16 weeks of Cetuximab with combination chemotherapy in TA176 to try to downstage to allow potentially curative surgery (which represents approximately 10% of use). In the draft FAD, a broadened liver-only metastatic colorectal cancer indication is permitted by the addition of Panitumumab to Cetuximab for use with either FOLFIRI or FOLFOX. We welcome the potential to best match the specific EGFR inhibitor to the chemotherapy backbone with which it will be given. However, and much more importantly, this recommendation ignores the clear benefit seen in first-line palliative use of these EGFR antibodies with chemotherapy in the vast majority of our RAS wild type metastatic colorectal cancer patients. The life extension (as seen in both published and presented data from clinical trials and from 'real world' audits and data collections) is very significant, as is the improved symptom control and quality of life overall. We believe that the key indication in first-line use of these drugs for our patients must be to improve the quantity and quality of life of those whose metastatic tumours will never become curable via surgery. In all respects other than that of cost, these patients meet end of life criteria. We hope that a new level of discount will be made available by the companies involved through the NICE confidential patient access scheme that will deal with this one unmet criterion.	Comment noted. After considering the comments received following the withdrawn FAD, the committee concluded that it would only consider the total population and that a stopping rule was inappropriate. Please see section 4.3 of the FAD.

Commentator	Comment [sic]	Response
NCRI-ACP-RCP-RCR	The CELIM trial demonstrated a favourable long-term survival for patients with initially sub-optimal or unresectable RAS wild type colorectal liver-only metastases who respond to conversion therapy with Cetuximab and either FOLFIRI or FOLFOX chemotherapy and undergo secondary resection. Patients who underwent R0 resection achieved a better median overall survival of 53.9 months than the 21.9 months seen those who did not. The median disease-free survival for R0 resected patients was 9.9 months, and the 5 year overall survival rate was 46.2%. The maximum permitted usage of 16 weeks of EGFR inhibitors when attempting to downstage to resection ignores this CELIM trial data (on which TA176 was based) where complete R0 resections were done in 35 of 105 patients (33%) with the median number of treatment cycles before surgery being 8 (range 4–27). This excludes ongoing use to allow surgery in about half of patients who may ultimately become resectable. We suggest that NICE should allow ongoing use of these drugs with chemotherapy, and do not limit this, with resection attempted when this has become technically possible on repeat imaging, whether that be after 8, 12, 16, 24 or more weeks of combination treatment. Our practice as colorectal oncologists working in a multi-disciplinary fashion with our liver surgeons is not to try to maximally downstage, but to downstage to a point where surgery becomes possible while trying to minimise the degree of liver toxicity from these drugs, and so we limit our duration of use to the least doses of EGFR inhibitors and chemotherapy needed. This stopping rule in TA176 use of 16 weeks affects the outcomes of the whole population with metastatic colorectal cancer treated - we know that the overall survival of patients with liver only metastatic colorectal cancer receiving EGFR inhibitors with chemo who are unable to be resected is the same as those who are receiving palliative intent treatment for more widespread metastatic colorectal cancer from the outset, and hence the cost-effectiveness of their treatment will also be the same.	Comment noted. After considering the clinical evidence for each treatment (see section 4 of the FAD), the committee recommended cetuximab and panitumumab as specified in section 1 of the FAD.
NCRI-ACP-RCP-RCR	This FAD will also impact very negatively on the ability of the UK to participate in global clinical trials (where use of anti-EGFR treatments in RAS wildtype metastatic colorectal cancer is assumed to be standard care) in all of first, second and third line settings and beyond and so further deny UK patients the opportunity to receive novel agents, and minimise innovation across the NHS.	Comment noted.

Commentator	Comment [sic]	Response
NCRI-ACP-RCP-RCR	We realise that the NICE assessment of these drugs is based on their current licensed indication, but note that there are other practical issues relevant to their use which impact on this guidance that we feel should be further considered: (i) In this era of precision medicine, we have sufficiently robust data that the presence of activating mutations in BRAF impact on effectiveness of anti-EGFR antibodies. There is no evidence of that survival outcomes are worse from the use of EGFR inhibitors in patients with BRAF mutant metastatic colorectal cancer (unlike their use in patients with RAS mutant metastatic colorectal cancer), but there is evidence of dysbenefit through exposure to EGFR inhibitor toxicities, inconvenience for patients, additional use of staffing resource and additional drug costs. Hence, as clinicians we advise use in patients with BRAF mutant metastatic colorectal cancer only in the context of clinical trials. This group represents 8-10% of metastatic colorectal cancer patients overall, but are enriched to the higher proportion of 15-20% in the RAS wild type population that this guidance applies to. A recommendation from NICE about use in the BRAF mutant group being restricted to clinical trials would further reduce the population of patients with RAS wild type tumours receiving these drugs, hence further improving cost effectiveness and avoiding unnecessary toxicities.	Comment noted he committee considered the uncertainties in the clinical evidence as specified in section 4.6 of the FAD.
NCRI-ACP-RCP-RCR	(ii) Patients whose tumours do not express EGFR on immunohistochemistry (~10% overall) are excluded from use of EGFR inhibitors in this recommendation although we have known from multiple clinical, translational and basic science reports that EGFR expression has no bearing on the probability of response or any other outcome from use of these drugs. This is an old and outdated piece of data in the drug licence, but would exclude metastatic colorectal cancer patients who could potentially benefit if this was applied.	Comment noted. EGFR expression has only been mentioned in the FAD when referring to the marketing authorisation for cetuximab.
NCRI-ACP-RCP-RCR	(iii) Our clinical standard of 2 weekly use of Cetuximab (not weekly) reduces costs, chair time and other resource utilisation and positively impacts again on cost effectiveness. In this FAD, NICE modelled cost effectiveness using weekly dosing and not 2 weekly dosing. This reflects the licensed schedule but not our real world practice, including use with combination chemotherapy via the CDF. Historically over the period 2014 – 2016, SACT data shows that three quarters of patients in England and Wales received 2 weekly Cetuximab in first, second and third line. We also know from a poll in December 2016 with responses from 64 consultant colorectal oncologists (including representation from England, Wales, Scotland and N. Ireland) that nowadays over 95% of specialists prescribe Cetuximab in the 2 weekly schedule in the first-line setting for metastatic colorectal cancer.	Comment noted. The committee considered the ICERs including fortnightly dosing. Please see section 4.5 of the FAD.

Commentator	Comment [sic]	Response
NCRI-ACP-RCP-RCR	We strongly and respectfully urge NICE to consider the points we raise in this letter at the forthcoming committee meeting. We passionately wish to optimise the outcomes for our current and future patients with metastatic colorectal cancer in both the palliative and potentially curative settings. We also want to ensure that NICE continues to command the full confidence of the colorectal cancer community in the UK of patients and their families, clinicians and cancer charities. This would be achieved through a recommendation to allow use of both EGFR antibodies with chemotherapy in the whole population of patients with RAS wild type metastatic colorectal, irrespective of potentially curative or definitely palliative intent of treatment. We feel that such a recommendation is critically important given the impact that NICE guidance has not only on our four UK devolved nations, but also widely outside these islands.	Comment noted. After considering the clinical evidence for each treatment (see section 4 of the FAD), the committee recommended cetuximab and panitumumab as specified in section 1 of the FAD.
NHS England	1. The evidence base has shifted very significantly over the past 10 years for better identifying advanced colorectal cancer patients who are most likely to benefit from cetuximab/panitumuab and this has resulted in narrowing the use of these two drugs in patients according to their tumour RAS status. In the same time frame however, the numbers of patients selected for liver surgery and other types of surgery (eg resection of lung metastases) have increased substantially as imaging and surgical techniques improve, new types of dealing with liver metastases evolve and the morbidity of surgery lessens. Many more patients with metastatic colorectal cancer are thus having radical approaches to their metastatic disease than was evident when the cetuximab/panitumumab trials were performed.	Thank you for your comment.
NHS England	2. The current selection of patients for liver surgery is now much more performed once the maximal response to chemotherapy has been achieved. Thus a definition of operable or inoperable liver metastases prior to the start of chemotherapy is no longer as clinically relevant as it was. As a consequence, NHS England regards this upfront separation of 'inoperable but may become operable' as not being helpful in the current management of patients, especially if there is a cap on treatment duration with cetuximab and panitumumab when the degree of response at that time may not be maximal.	Comment noted. Comment noted. After considering the comments received following the withdrawn FAD, the committee concluded that it would only consider the total population and that a stopping rule was inappropriate. Please see section 4.3 of the FAD.
NHS England	3. A further issue is that chemotherapy in patients even with operable colorectal cancer liver metastases is being used as primary treatment before surgery as surgeons recognise that the ease of surgery and local control of liver disease are augmented by the response to treatment, let alone the benefits of chemotherapy in terms of potentially impacting on any microscopic disease elsewhere.	Comment noted. This is now reflected in the FAD. Please see section 4.3.

Commentator	Comment [sic]	Response
NHS England	4. As has been alluded to in paragraph 2 above, a stopping rule is difficult to implement for a treatment that has definitely worked and shrunk liver metastases but has not delivered the opportunity for surgery. Such patients ask the obvious question as to why treatment is being stopped when it is working and a maximal response (and thus the assessment as to radical intervention) has not yet definitely occurred.	Comment noted. After considering the comments received following the withdrawn FAD, the committee concluded that a stopping rule was inappropriate. Please see section 4.3 of the FAD.
NHS England	5. NHS England thus regards the upfront separation of patients into having disease that is operable/inoperable/inoperable but may become operable as currently artificial and of much less use and relevance than it may have been when TA 176 was produced. It thus urges the NICE Technology Appraisal Committee to consider the patients with metastatic colorectal cancer as a whole rather than splitting the patients up into categories which have changed and are likely to further change as imaging and surgery evolve.	Comment noted. After considering the comments received following the withdrawn FAD, the committee concluded that it would only consider the total population. Please see section 4.3 of the FAD.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cetuximab and panitumumab for previously untreated metastatic colorectal cancer

Response to appraisal consultation document

Prepared by:

8th December 2015

File name	Version	Contains confidential information	Date
		Yes AIC: Highlighted in yellow and underlined CIC: Highlighted in blue and underlined	December 2015

Contents

1 Executive Summary

We have carefully reviewed the Appraisal Committee's consideration of the evidence on panitumumab for previously untreated metastatic colorectal cancer (mCRC). We are disappointed by the conclusions reached and the resulting preliminary guidance not to recommend panitumumab. We welcome the opportunity to respond to the Appraisal Consultation Document (ACD). In our response, we address the key issues highlighted in the ACD, specifically regarding robustness of the evidence base and overall survival (OS) data for panitumumab and qualification of panitumumab for End of Life (EoL) criteria.

We believe that the evaluation of panitumumab as an EoL therapy, modelled using robust OS data, together with the [redacted] increased patient access scheme (PAS) ([redacted]), would demonstrate panitumumab to be a cost effective treatment; achieving an ICER [redacted] accepted for EoL treatments.

Access to panitumumab and cetuximab through the Cancer Drugs Fund (CDF) has delivered critical improvements in outcomes for previously untreated mCRC patients. This appraisal presents an opportunity to move panitumumab into baseline commissioning and provide patients with a vital therapeutic alternative in this life limiting condition.

Strength of the clinical evidence base for panitumumab

The ACD makes unsubstantiated statements that the clinical benefit for panitumumab is subject to uncertainty given that it is *"based on post-hoc subgroup analyses of clinical trial data"* and is *"based on small data sets with missing data, which reduced the chance that these analyses would uncover true differences between treatments".*

The uncertainties raised in the ACD regarding the clinical evidence base for anti-EGFR therapies in patients with wild-type (WT) RAS tumours, do not apply to panitumumab. The key clinical evidence for panitumumab comes from a pre-specified subgroup analysis of 512 WT RAS mCRC patients from the pivotal head-to-head randomised controlled trial (RCT) (PRIME) which compared panitumumab plus FOLFOX with FOLFOX. The RAS ascertainment rate was high (90% of all randomised patients) and clinically meaningful and statistically significant benefits in progression-free survival (PFS) and OS in favour of panitumumab were demonstrated. This analysis demonstrated that the benefit–risk profile of panitumumab was improved by excluding patients with mutated RAS status and formed the basis for the revised indication for WT RAS mCRC patients from the European Medicines Agency (EMA).

This robust set of evidence for panitumumab plus FOLFOX in WT RAS mCRC patients contrasts with the uncertainties associated with the evidence base for cetuximab plus FOLFOX which relate to low sample size and missing data. However these should not be attributed to panitumumab.

Generalisability of the trial population in PRIME to patients treated in the NHS

The ACD concluded that the population studied in the PRIME RCT was younger and fitter than patients seen in clinical practice in England and that this was a source of uncertainty in the clinical and cost effectiveness results. It is generally expected that RCTs recruit younger and fitter patients than the broader populations treated in the NHS, and PRIME is no exception. We think it reasonable to assume that the results from PRIME can be generalised to the NHS population and note that NICE have taken a similar, pragmatic, stance on this in other appraisals.

Robustness of the OS gain for panitumumab

Although the ACD states that the NICE preferred approach would be to use OS data (4.33, pg 27), this disappointingly has not informed the base case incremental cost effectiveness ratio (ICER) for panitumumab. Instead, PFS data has been used, which in turn is a surrogate marker for OS. The Appraisal Committee deemed *"that survival data were not sufficiently mature, and that the size of the effect was confounded by the use of different second and subsequent lines of treatment across the trial arms"* and *"these treatments are associated with prolonged survival and are also not widely available in the NHS"*.

Amgen believes that the OS data for panitumumab is robust and should be used in the economic model, in preference to PFS data, to inform the base case ICER: The OS data from PRIME is sufficiently mature, since the majority of patients (82%) had died by the time of the analysis. Robust analysis of the impact of subsequent treatments on OS in WT RAS patients confirms previously presented analyses in WT KRAS patients: They consistently demonstrate that the impact of subsequent therapies would have been to attenuate the OS gain for panitumumab. They also address ACD concerns regarding second-line therapies not commonly used in the NHS, by demonstrating that they do not prolong OS gain for panitumumab. Therefore the OS gain observed in PRIME (a median 5.6 months) should be considered conservative. This was recognised by the Assessment Group who acknowledged the use of OS to be highly plausible and considered the resulting ICER for panitumumab to be an upper bound, given that survival could have been greater.

Critically, the face validity of the PFS-based model, used as the base case by the Assessment Group, is questionable, since OS results generated from the PFS model are highly inconsistent with those from the PRIME and OPUS trials.

The use of OS is the preferred approach and was indeed recognised as such in the ACD. Therefore in using PFS, instead of robust OS data from a large multicentre international RCT to inform the base case ICER, the Appraisal Committee has not taken into account all relevant evidence from clinical trials in estimating the base case ICER for panitumumab. Therefore the ensuing recommendations contained in the ACD do not form a sound and suitable basis for guidance to the NHS.

Consideration of the EoL criteria for panitumumab

We agree with the Committee's conclusion in the ACD that panitumumab meets the EoL criterion for short life expectancy and the criterion for extension to life. However, the Committee concluded that overall panitumumab does not qualify for EoL because of uncertainty regarding the criterion for small patient numbers (<7,000 threshold). It

is noteworthy that the Committee was presented with 3 estimates of population size, of which two fell well within the 7,000 threshold. Consequently, the conclusion that panitumumab does not meet this EoL criterion is not a balanced one, given that it is driven by the one estimate (of 8,511) that exceeded the threshold. Further, this higher estimate is incorrect and likely to be an overestimate, since it is based on a population broader than that licensed for panitumumab; in our response we estimate the eligible licensed population to be 5,123, which is well below the 7,000 threshold. Therefore panitumumab meets all three EoL criteria and as such should qualify as life-extending, end of life treatment.

It is also worth noting that previous EoL determinations by NICE have placed less importance on this criterion and accepted treatments whose estimates of patient numbers were less certain and exceeded the threshold. Importantly, the ongoing CDF consultation proposes the removal of the criterion around patient population from the current EoL criteria, citing that this criterion has rarely been engaged by NICE. Although the NHS England / CDF consultation is ongoing, it is expected to be published in April 2016, at the same time as final guidance for panitumumab is expected. It is important for the Committee to be aware of the impending changes to the EoL criteria, since panitumumab would certainly qualify for EoL under the new proposals. There is also the risk that if the final guidance for panitumumab is not aligned with the CDF consultation regarding EoL criteria, it may not form a sound and suitable basis for guidance to the NHS.

We urge the Appraisal Committee to recognise that panitumumab meets the current EoL criteria and will also meet the revised EoL criteria proposed under the ongoing CDF consultation.

Assessment of the ICER for panitumumab using the robust OS data and assuming EoL criteria are met

The Committee state in the ACD that *"even if the end-of-life criteria were met, an unacceptably large weighting would need to be put on the QALY to bring the ICERs for cetuximab and panitumumab into the range representing a cost-effective treatment"*. (4.41, pg 35)

This conclusion is misleading for panitumumab. Whilst this may be true for a base case using suboptimal survival data, i.e. PFS data, it is not correct when using OS data. Indeed, the Assessment Group estimated the ICER for panitumumab based on OS data (and including the previous confidential PAS) to be [redacted], which although not within the threshold considered when appraising EoL treatments (£50K), [redacted]. It is also noteworthy that this estimate is based on the lower resection rate of 12.6% for panitumumab, whilst use of the 15% resection rate advised by the clinical experts (and acknowledged in the ACD) would have improved the ICER for panitumumab to below [redacted].

Consideration of a revised base case ICER for panitumumab using the robust OS data, assuming EoL criteria are met, and applying the [redacted] increased confidential PAS for panitumumab

We believe that in our response we have addressed concerns regarding the strength of the evidence base, the robustness of the OS data and qualification for EoL criteria.

A revised base case ICER using OS and assuming EoL criteria are fulfilled, together with the offer of a [redacted] increased PAS ([redacted]) in order to mitigate the risk to the NHS resulting from any residual uncertainties in the evidence base, demonstrates that panitumumab is a cost effective EoL treatment.

We believe that the clinical and cost effectiveness case for panitumumab is sufficiently robust. Further, the increased PAS we have offered mitigates the risk to the NHS regarding any residual uncertainty. We therefore propose that NICE recommend panitumumab for use in previously untreated metastatic colorectal cancer patients.

2 Strength of the clinical evidence base for panitumumab

Uncertainties regarding the clinical evidence base

The uncertainties raised in the ACD regarding the clinical evidence base for anti-EGFR therapies in patients with WT RAS tumours do not apply to panitumumab.

The key clinical evidence for panitumumab comes from a pre-specified subgroup analysis of 512 WT RAS mCRC patients from the pivotal head-to-head RCT (PRIME). The RAS ascertainment rate was high (90% of all randomised patients) and clinically meaningful and statistically significant benefits in PFS and OS in favour of panitumumab plus FOLFOX were demonstrated. This robust analysis formed the basis for the revised indication for WT RAS mCRC patients from the EMA.

The OS data from PRIME are sufficiently mature, since the majority of patients (82%) had died by the time of the analysis.

The uncertainties associated with the evidence base for cetuximab plus FOLFOX relating to low sample size, and missing data should not be attributed to panitumumab.

Generalisability of the trial population in PRIME to NHS patients

It is expected that RCT populations (such as that for PRIME) are generally fitter and younger than the broader patient populations treated in the NHS. However it is reasonable to assume that the results from PRIME can be generalised to the wider patient population.

Uncertainties regarding the clinical evidence base

The ACD repeatedly noted concerns around the strength of the evidence base for panitumumab:

"The Assessment Group stated that the clinical evidence was limited because it reflected subgroup analyses. The trials were analysed post-hoc after re-evaluating tumour samples from people with KRAS wild-type exon 2 tumours, and reclassifying them by RAS wild-type status as currently defined. The Assessment Group noted that there were few samples available for re-analysis and missing data further reduced the power of some studies". (Page 9, 4.3)

"The Committee heard that the evidence for cetuximab and panitumumab in people with RAS wild-type colorectal cancer is based on post-hoc subgroup analyses of clinical trial data. The Committee understood that analyses were based on small data sets with missing data, which reduced the chance that these analyses would uncover true differences between treatments. The Committee concluded that, although the current data are more mature than in NICE's technology appraisal guidance on cetuximab for the first-line treatment of metastatic colorectal cancer, there is more uncertainty in the evidence base because it involved smaller populations". (Page 25, 4.30)

"The Committee concluded that the clinical evidence surrounding the degree to which cetuximab and panitumumab are effective in RAS wild-type metastatic colorectal cancer was subject to considerable uncertainty". (Page 27, 4.32)

We believe that the uncertainties that have been raised around the clinical evidence base in patients with WT RAS tumours do not apply to the comparison of panitumumab plus FOLFOX versus FOLFOX. The clinical evidence for panitumumab plus FOLFOX versus FOLFOX comes from the PRIME study which randomised more than 1000 patients. PRIME included a large number of patients with WT RAS tumours (n=512), the RAS ascertainment rate was high (90% of all randomised patients) and clinically meaningful and statistically significant benefits in PFS and OS in favour of panitumumab plus FOLFOX were demonstrated (Douillard et al, 2013). The PRIME WT RAS evidence was based on a pre-specified subgroup analysis that was accepted by the EMA, with baseline patient characteristics similar to the WT KRAS population and the intent to treat (ITT) population. The size of the WT RAS subgroup (n=512) compares favourably with that of the previously licensed WT KRAS population (n= 656 in PRIME) and the width of confidence intervals around the hazard ratios (HRs) for PFS and OS are similar in the 2 populations, suggesting that loss of precision is not an issue when moving from the WT KRAS population to the WT RAS population (Table 1). It should also be noted that a subgroup analysis was unavoidable since the ability of RAS mutation status to predict response to treatment was unknown when the PRIME trial was designed.

Table 1. Comparison of PRIME and OPUS clinical evidence

	PRIME (Panitumumab+FOLFOX vs. FOLFOX)		**OPUS (Cetuximab+FOLFOX vs. FOLFOX)**	
	WT KRAS	**WT RAS**	**WT KRAS**	**WT RAS**
N	656	512	179	87
RAS ascertainment rate, %	N/A	90	N/A	66
PFS				
HR (95% CI)	0.80 (0.66, 0.97)	0.72 (0.58, 0.90)	0.567 (0.375, 0.856)	0.53 (0.27, 1.04)
Width of 95% CI around HR	0.31	0.32	0.48	0.77
OS				
HR (95% CI)	0.83 (0.70, 0.98)	0.77 (0.64, 0.94)	0.855 (0.599, 1.219)	0.94 (0.56, 1.56)
Width of 95% CI around HR	0.28	0.30	0.62	1.00
Maturity of OS data, n (%) died	535 (82)	422 (82)	126 (70)	63 (72)

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; pmab, panitumumab; N/A, not applicable; OS, overall survival; WT, wild-type.
Source: PRIME (Douillard et al, 2013; Amgen, 2013), OPUS (Bokemeyer et al, 2015; Bokemeyer et al, 2011)

We therefore do not accept the concerns regarding low sample size and missing data, and the consequent lack of power, apply to the evidence base for panitumumab. Instead, the uncertainty in the evidence base relates primarily to the

OPUS study comparing cetuximab plus FOLFOX with FOLFOX. OPUS included only 87 patients with WT RAS tumours, had a much lower RAS ascertainment rate (66%) and confidence intervals around HRs were substantially wider than in PRIME, particularly in the WT RAS subgroup (Table 1).

It is notable that the EMA stated "*although cetuximab data by RAS status are only derived from the randomised phase II study OPUS, the biological rationale supporting the efficacy in patients with RAS wild type tumours only is strong and the conclusions are supported by data related to panitumumab*" (European Medicines Agency, 2013). This underscores the strength of panitumumab data, as it was used to augment the evidence base in patients with RAS WT tumours for cetuximab.

Regarding maturity of the OS data, 82% of patients with WT RAS tumours in PRIME had died at the time of the updated analysis of OS compared with 72% of patients in OPUS (Table 1). We would argue that the PRIME data are sufficiently mature and that NICE have been pragmatic and regularly have recommended therapies based on OS data that are not fully mature, e.g. TA319 (National Institute for Health and Care Excellence, 2014a).

In summary, we believe that there is robust clinical evidence comparing panitumumab plus FOLFOX versus FOLFOX in WT RAS patients which demonstrates a statistically significant and clinically meaningful median OS gain of 5.6 months. Therefore the uncertainties raised in the ACD, regarding low sample size and missing data relate specifically to the evidence base for cetuximab plus FOLFOX and should not be attributed to panitumumab.

Generalisability of the trial population in PRIME to patients treated in the NHS

The ACD queried the relevance of the trial population in the pivotal phase 3 clinical trial (PRIME) to patients treated in the NHS.

"The Committee heard from clinical experts that the trial populations were younger than patients seen in clinical practice. The Committee concluded that the populations in the clinical trials of cetuximab and panitumumab differed from patients in clinical practice in England, and that this difference was a source of uncertainty in the clinical- and cost-effectiveness results". (Page 25, 4.29)

RCTs are considered the gold standard for assessing new interventions due to control of bias, however it is acknowledged that entry criteria can lead to populations that differ from those seen in routine clinical practice (Ballman et al, 2014). We think it is reasonable to assume that results from PRIME can be generalised to the wider NHS patient population and are not aware of any evidence to suggest otherwise. NICE have taken a pragmatic stance on this in other appraisals, e.g. TA221 (National Institute for Health and Care Excellence, 2011).

3 Robustness of the OS gain for panitumumab

The OS data for panitumumab is robust and should be used in preference to PFS data in the economic model, to inform the base case ICER.

Robust analyses evaluating the impact of subsequent treatments on OS in the PRIME study have consistently demonstrated that their impact would have been to attenuate the OS gain for panitumumab, meaning that the OS gain observed in PRIME (median 5.6 months) should be considered conservative.

The Assessment Group acknowledged the use of OS to be highly plausible and considered the resulting ICER for panitumumab to be an upper bound, given that survival could have been greater.

The face validity of a PFS-based model, used as the base case, is questionable since the OS results generated are highly inconsistent with those from the PRIME and OPUS trials.

The ACD noted concerns regarding the robustness of the OS gain for panitumumab

"The Assessment Group assumed in its base-case analysis that the duration of survival after first-line treatment was independent of first-line treatment (that is, any treatment effect from first-line drugs stopped when disease progressed). By contrast, in the randomised controlled trials, overall survival reflected response to both first and subsequent lines of treatment. However, the Assessment Group considered it inappropriate to assume this in its model because the trials included second-line drugs that are not commonly used in the NHS (including second-line panitumumab, cetuximab and bevacizumab) and may prolong survival. It also noted that second-line treatments were imbalanced across the trial arms. In addition, it considered that the survival data from trials were not mature enough. Therefore the Assessment Group modelled only progression-free survival from the randomised controlled trials, not overall survival". (Page 14, 3.13)

We believe that the economic model should be based on OS which is widely recognised as the "gold standard" endpoint in oncology trials from a clinical and patient perspective (Driscoll et al, 2009). It is common for patients to move on to subsequent lines of treatment (which may prolong survival) post-progression in oncology trials and we note that NICE has previously accepted economic models based on OS in this situation, e.g. TA319, TA268 and TA269 (National Institute for Health and Care Excellence, 2014a; National Institute for Health and Care Excellence, 2012a; National Institute for Health and Care Excellence, 2012b). We acknowledge that subsequent treatments may prolong survival (in particular second-line anti-EGFR therapy and bevacizumab which are not commonly used in the NHS) and that these were not balanced across treatment arms in PRIME. It should be noted that the proportion of WT RAS patients receiving any subsequent anti-tumour therapy was slightly higher in the FOLFOX arm compared with the panitumumab arm (67% vs 58%): Use of traditional chemotherapy agents was slightly higher in the FOLFOX arm (64% vs 54%), whilst use of bevacizumab was broadly similar for the FOLFOX and panitumumab plus FOLFOX arms respectively (13% vs 16%). However

subsequent anti-EGFR therapy was more commonly received in the FOLFOX arm than in the panitumumab plus FOLFOX arm (19% vs 7%).

In our response to the Assessment Report, we presented analysis which used a variety of recognised statistical methods to explore the impact of subsequent anti-EGFR therapy on the OS benefit in PRIME in WT KRAS patients (Douillard et al, 2012). We now present further analysis in the WT RAS population of interest, using the inverse probability of censoring weighted (IPCW) method; the OS HR for panitumumab plus FOLFOX versus FOLFOX is 0.69 (95% CI 0.50 to 0.95) compared with the ITT analysis HR of 0.77 (95% CI 0.64 to 0.94) (Table 2).

The results from the WT RAS analysis confirms those presented for KRAS and suggest that the true OS benefit for panitumumab plus FOLFOX versus FOLFOX is larger than that observed in the PRIME trial (Table 2). The Assessment Group acknowledged this during the first Appraisal Committee meeting and stated likewise in their response to consultee comments that the ICER for panitumumab plus FOLFOX versus FOLFOX can be considered an upper bound (in OS scenario analysis).

In addition, the ACD concerns about the use of second-line drugs that are not commonly used in the NHS are only relevant if they serve to prolong the OS gain for panitumumab. The results presented in the table below show that these concerns are unfounded, as they do not inflate the OS gain for panitumumab.

Table 2. Impact of subsequent anti-EGFR therapy on OS in PRIME

	OS HR (95% CI) Panitumumab plus FOLFOX vs FOLFOX	
	WT KRAS[a]	**WT RAS[b]**
Intent to treat analysis	0.88 (0.73, 1.06)	0.77 (0.64, 0.94)
Statistical model for influence of subsequent anti-EGFR therapy		
Branson & Whitehead, 2002	0.84 (0.68, 1.05)	
Robins & Tsiatis, 1992	0.83 (0.66, 1.04)	
Allison, 1995	0.68 (0.55, 0.83)	
Inverse probability of censoring weighted (IPCW)	0.74 (0.56, 0.97)	0.69 (0.50, 0.95)

CI, confidence interval; HR, hazard ratio; OS, overall survival; WT, wild-type.
[a] Based on final analysis (data cut-off 02 August 2010).
[b] Based on OS update analysis (data cut-off 24 January 2013).
Source: WT KRAS: (Douillard et al, 2012); WT RAS: (Peeters et al, 2013).

The validity of a PFS-based model for the base case is questionable given that OS results generated from the model are not consistent with results from the PRIME and OPUS trials: In Table 3 of the ACD the base case model mean OS gain for panitumumab plus FOLFOX versus FOLFOX is 2.6 months, which is substantially lower than the mean OS gain of 5.7 months in PRIME. Similarly, the base case model mean OS gain for cetuximab plus FOLFOX versus FOLFOX is 6.6 months, which is much higher than the mean OS gain of 0.5 months in OPUS.

In summary, we do not accept that an OS model is inappropriate and indeed the Assessment Group have stated that OS is an important scenario analysis in their

response to consultee comments. Analysis of the impact of subsequent therapies on OS suggests that the OS benefit observed is an underestimate of the true benefit of panitumumab plus FOLFOX compared with FOLFOX. This also addresses ACD concerns regarding second-line therapies not commonly used in the NHS, by demonstrating that they do not prolong OS gain for panitumumab. Therefore we consider OS data in PRIME is robust and should be used in the economic model, in preference to PFS data, to inform the base case ICER.

4 Consideration of the EoL criteria for panitumumab

The ACD concluded that panitumumab meets the EoL criterion of short life expectancy and the criterion of extension to life. However, the conclusion that panitumumab does not meet the criterion for small patient population (< 7000 people) is not a balanced one, given that it is driven by the only one estimate (out of three) which gives a population size that exceeds the threshold.

The higher estimate for population size (8511 patients) is also incorrect, since it is based on a broader population than that licensed for panitumumab in England and is therefore likely to be an overestimate.

Previous EoL determinations by NICE have placed less importance on this criterion and accepted treatments whose estimates of patient numbers were less certain and potentially exceeded the threshold.

The ongoing consultation on the Cancer Drugs Fund (CDF) proposes the removal of the criterion regarding patient population from the current EoL criteria, citing that this criterion has rarely been engaged by NICE.

Panitumumab meets the current EoL criteria and will also meet the revised EoL criteria proposed under the ongoing CDF consultation.

The Appraisal Committee considered the evidence presented on the EoL criteria and concluded that the while panitumumab fulfilled the criteria of short life expectancy and extension to life, there was uncertainty around the criterion of small patient population (< 7000 people) and therefore it deemed that EoL status was “probably not met” for panitumumab.

The Assessment Report included three population estimates for the RAS WT mCRC population: 5,968, 4,728 and 8,511, the first two being Merck Serono estimates and the last the Assessment Group’s estimate of the population. The decision that panitumumab does not meet EoL criteria was based solely on the one estimate that exceeded 7,000 and consequently is unbalanced. More importantly, the Assessment Group’s estimate of 8,511 is an overestimate as it is based on a population that is broader than the population licensed for treatment with panitumumab: The license for panitumumab is limited to WT RAS patients who are eligible for certain chemotherapy regimens (FOLFOX or FOLFIRI in the first-line setting and FOLFIRI in the second-line setting for patients who have received first-line fluoropyrimidine-based chemotherapy excluding irinotecan) The estimate of 8,511 is based on the total (instead of the licensed) wild type RAS population, regardless of the type of chemotherapy regimen these patients would be eligible for.

Using the IMS Oncology Analyser (an oncology patient-record database based on clinician-reported case histories from UK patients and considered the most established and robust data source of market share data) we demonstrate that the population size falls well below the criterion of 7,000 when considering the patients eligible for panitumumab as per its license indication in different lines of therapy.

- The number of patients treated with FOLFOX or FOLFIRI in the first- line setting who would be eligible for panitumumab first-line therapy, in accordance with its license, was estimated to be 3,250 (Figure 1).
- The number of patients eligible for panitumumab second-line therapy, in accordance with its license, was estimated to be 1,693 (Figure 2).
- The number of patients eligible for panitumumab third-line monotherapy (after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens), in accordance with its license, was estimated to be 180 (Figure 3). This was based on the Tappenden algorithm (Tappenden et al, 2007), where 5% of the total second-line chemotherapy population goes on to receive third line chemotherapy.

Therefore a total of 5,123 patients are eligible for panitumumab across the first, second and third-line settings, which is well below the suggested population limit for EoL criteria.

It is highly likely that this estimate of population size is an overestimate. In the first-line setting, the market share of patients previously treated with FOLFOX/FOLFIRI regimens (45.2%, Figure 1) also included regimens in combination with a biologic. In the second-line setting, the market share of patients previously treated with fluoropyrimidine combination therapy without irinotecan (47.1%, Figure 2), included cetuximab treatment (although in practice retreatment with an anti-EGFR inhibitor would be highly unlikely). It is also noteworthy that in the previous NICE assessment of aflibercept in TA307 (National Institute for Health and Care Excellence, 2014b), the total second-line chemotherapy population in mCRC accepted by the Committee was 4,000 patients (Wade et al, 2013). This is again much smaller than the estimate of total second-line chemotherapy population of 7,190 in Figure 2.

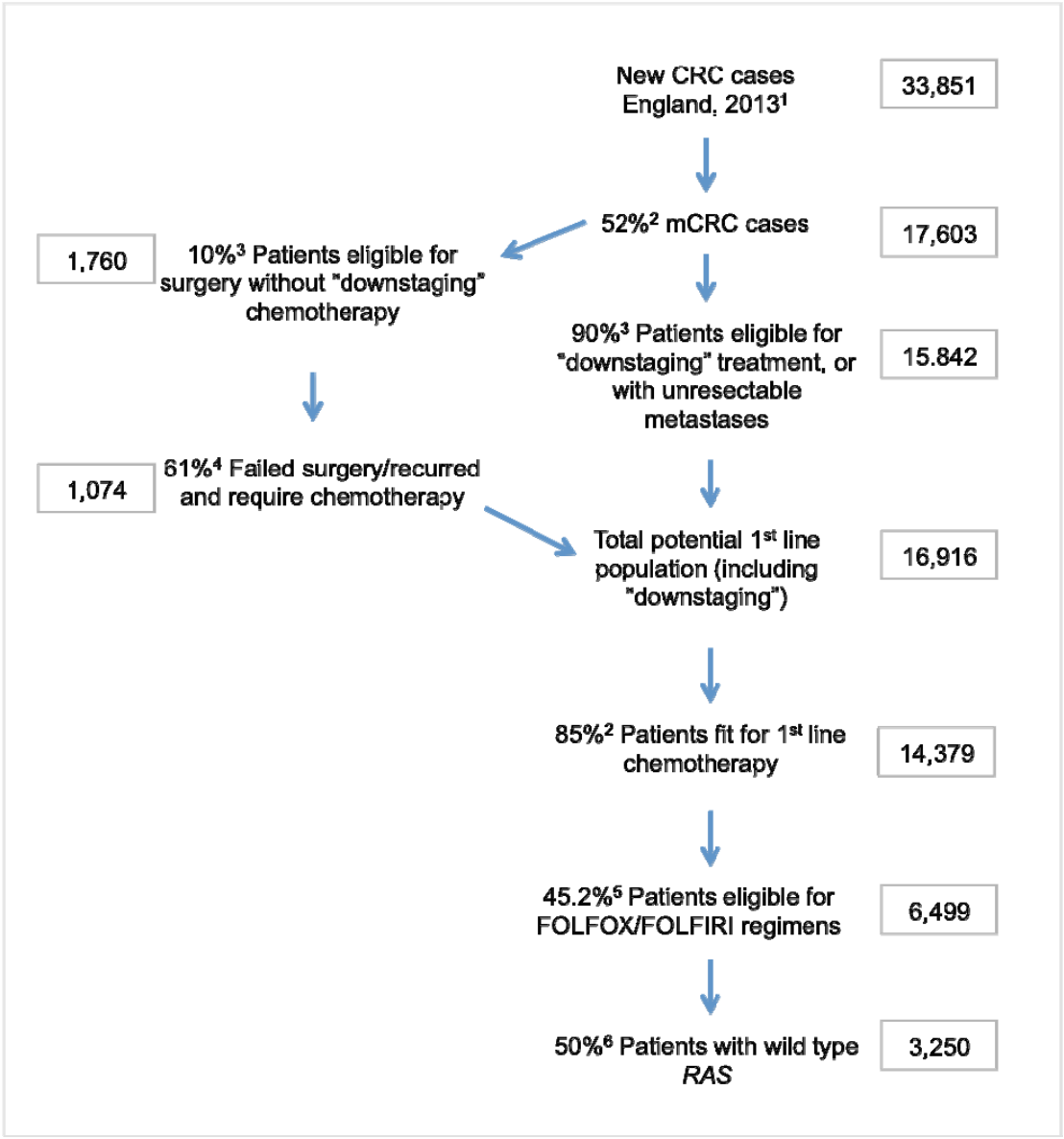
The Appraisal Committee's conclusion that panitumumab does not meet the population size EoL criterion is also inconsistent with previous EoL determinations where NICE have placed less importance on this criterion and accepted treatments whose estimates of patient numbers were less certain and exceeded the threshold (<7000). Examples include TA309 (National Institute for Health and Care Excellence, 2014c) and TA208 (National institute for Health and Care Excellence, 2010).

The ongoing consultation jointly published by NHS England and NICE for the future of the CDF proposes the removal of the restriction of cumulative patient population from the current EoL criteria, recognising that ***"this criterion has rarely been engaged"***. Although the NHS England / CDF consultation is ongoing and is expected to be published in April 2016, it is important for the Committee to be aware of the impending changes to the EoL criteria, since panitumumab would certainly qualify for EoL under the new proposals. Importantly, the current considerations of the Committee that panitumumab does not meet EoL criteria would no longer be relevant when guidance on this appraisal (ID794) comes to be published in April next year.

We have demonstrated that when using the current EoL criteria (which include the criterion on small patient population size), the panitumumab licensed population falls well within the upper bound of 7,000 patients and should therefore qualify as an EoL treatment. In addition, panitumumab will also meet the revised changes to the EoL

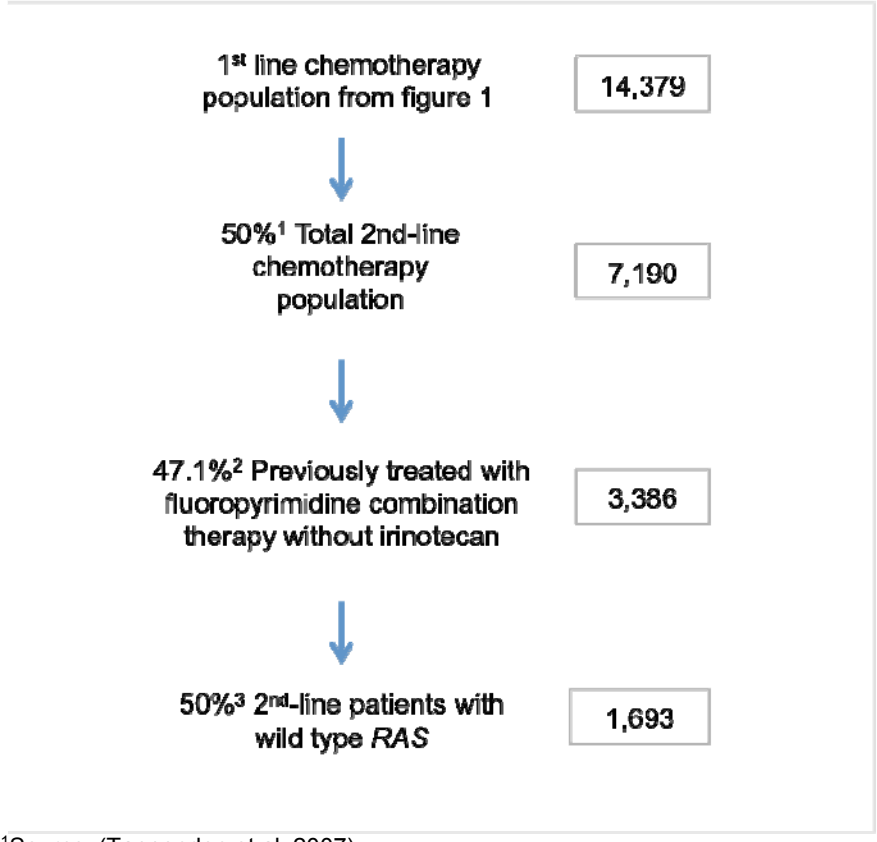
criteria proposed under the ongoing CDF consultation, with the removal of the criterion for small patient population size.

Figure 1. First-line patient algorithm



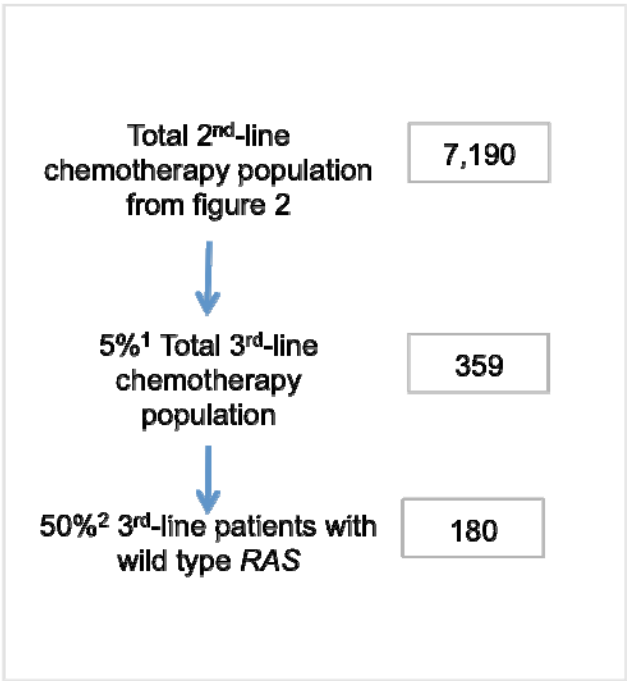
[1] Source: (National Cancer Intelligence Network, 2013)
[2] Source: (Tappenden et al, 2007)
[3] Source: (Tappenden et al, 2013)
[4] Source: (Lam et al, 2014)
[5] Source: IMS Oncology Analyser, Q3 2014 data
[6] Source: current ID794 assessment report

Figure 2. Second-line patient algorithm



[1]Source: (Tappenden et al, 2007)
[2]Source: IMS Oncology Analyser, Q3 2014 data
[3]Source: current ID794 assessment report

Figure 3. Third-line patient algorithm



[1] Source: (Tappenden et al, 2007)
[2] Source: current ID794 assessment report

5 Assessment of the ICER for panitumumab using the robust OS data and assuming the EoL life criteria are met

The Assessment Group estimated the ICER for panitumumab to be [redacted], based on OS data and including the previous confidential PAS.

This is not substantially above the threshold considered when appraising EoL treatments (£50K).

Further, the use of the higher resection rate advised by the clinical experts (and acknowledged in the ACD) would improve the ICER for panitumumab to below [redacted].

The Committee state in the ACD that *"even if the end-of-life criteria were met, an unacceptably large weighting would need to be put on the QALY to bring the ICERs for cetuximab and panitumumab into the range representing a cost-effective treatment"*. *(Page 35, 4.41)*

This conclusion is misleading for panitumumab. Whilst this may be true for a base case using suboptimal survival data, i.e. PFS data, it is incorrect when using OS data from the PRIME study to inform the base case model. Indeed, the Assessment Group estimated the ICER for panitumumab based on OS data and including the previous [redacted] confidential PAS to be [redacted], which although is not within the threshold considered when appraising EoL treatments, is close to it. It is also noteworthy that the ICER is expected to decrease further when a resection rate of 15%, as advised by experts, is applied instead of the current lower resection rate of 12.6% for panitumumab.

6 Consideration of a revised base case ICER for panitumumab using robust OS data, assuming EoL criteria are fulfilled, and applying the increased confidential PAS for panitumumab

Panitumumab represents a cost effective use of NHS resources when using OS data and when EoL criteria are fulfilled, together with the offer of [redacted] increased PAS ([redacted]).

Colorectal cancer is the third most common cancer in England and prognosis is poor in patients with metastatic disease. It is for these patients with a clear unmet need for whom there are no NICE-approved targeted therapies for the first line treatment of mCRC. Panitumumab in this setting offers a chance of providing significant patient benefit and would be a valuable option for these patients. If the Appraisal Committee's draft guidance is published as final guidance, there will no first-line targeted treatment options available to NHS patients with mCRC.

Although the panitumumab OS data were considered strong for the purpose of regulatory approval in the RAS WT patient population, the ACD raises questions around the strength of the clinical evidence base and the robustness of OS data in this setting. We have addressed these concerns in our response and are now offering what we believe to be [redacted] increased PAS ([redacted]) in order to mitigate the risk to the NHS resulting from any residual uncertainties in the evidence base and to demonstrate the cost effectiveness of panitumumab (when OS data is used and when panitumumab is deemed to meet the EoL criteria).

We would strongly recommend that the Committee consider a more plausible revised base case analysis based on the use of robust and highly plausible OS data and the fulfilment of current EoL considerations (including policy considerations around the removal of the EoL criterion on small patient population size), specifically:

- Use a model structure based on OS
- Apply EoL considerations to panitumumab
- Apply the increased confidential discount of [redacted] to the drug cost of panitumumab
- Assume a resection rate of 15% as advised by experts

We believe this more plausible revised base case, considering all the factors above, would bring the ICER for panitumumab into a range representing a cost-effective treatment.

7 Factual Inaccuracies

We wish to highlight two factual inaccuracies within the ACD and propose the recommended corrections as described in Table 3 below.

Table 3. Factual inaccuracies in the ACD

ACD Section	Factual Inaccuracy	Recommended Correction
2.1	The 5-year survival rate for mCRC is stated as 'under 60%'	The value stated in the NICE final scope document is 6.6% so this should be corrected to 'under 10%'
4.39	The ACD states 'The Committee understood from the clinical experts that the Assessment Group had overestimated resection rates. The Assessment Group had not presented ICERs using lower resection rates, but informed the Committee **that lower resection rates would increase the ICERs and worsen cost effectiveness'**	This statement is not correct for panitumumab. The resection rate used in the model for panitumumab is 12.6% which is below the 15% rate recommended by the clinical experts (section 4.36 of ACD) and therefore is not an overestimate. Using the 15% rate advised would decrease the ICER for panitumumab and improve cost effectiveness.

8 References

Amgen. Data on file. Supplemental CSR 20050203 overall survival update, 6 May 2013. 2013.

Ballman KV, Mauer M, Wedding U, et al. Reply to L.K. Mell et al. *J Clin Oncol*. 2014;32:1090-1091.

Bokemeyer C, Bondarenko I, Hartmann JT, et al. Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: the OPUS study. *Ann Oncol*. 2011;22:1535-1546.

Bokemeyer C, Kohne CH, Ciardiello F, et al. FOLFOX4 plus cetuximab treatment and RAS mutations in colorectal cancer. *Eur J Cancer*. 2015;51:1243-1252.

Douillard JY, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. *N Engl J Med*. 2013;369:1023–1034.

Douillard JY, Peeters M, Rong A, et al. Effect of post-protocol anti-epidermal growth factor receptor monoclonal antibody therapy on survival outcomes in patients with wild-type KRAS metastatic colorectal cancer treated with panitumumab plus chemotherapy. Poster presented at European Society for Medical Oncology, Vienna. 2012.

Driscoll JJ, Rixe O. Overall survival: still the gold standard: why overall survival remains the definitive end point in cancer clinical trials. *Cancer J*. 2009;15:401-405.

European Medicines Agency. Assessment Report - Erbitux. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000558/WC500160158.pdf (access date 28 September 2015). 2013.

Lam VW, Laurence JM, Pang T, et al. A systematic review of a liver-first approach in patients with colorectal cancer and synchronous colorectal liver metastases. *HPB (Oxford)*. 2014;16:101-108.

National Cancer Intelligence Network. Stage breakdown by CCG. Available at http://www.ncin.org.uk/publications/survival_by_stage (access date 20 November 2015). 2013.

National institute for Health and Care Excellence. Technology Appraisal 208. Trastuzumab for the treatment of HER2-positive metastatic gastric cancer. November 2010. Available from http://www.nice.org.uk/guidance/TA208 (access date 8 December 2015). 2010.

National Institute for Health and Care Excellence. Technology Appraisal 221. Romiplostim for the treatment of chronic immune (idiopathic) thrombocytopenic purpura. April 2011. Available from http://www.nice.org.uk/guidance/TA221 (access date 1 December 2015). 2011.

National Institute for Health and Care Excellence. Technology Appraisal 268. Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma. December 2012. Available from http://www.nice.org.uk/guidance/TA268 (access date 1 December 2015). 2012a.

National Institute for Health and Care Excellence. Technology Appraisal 269. Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation‑positive malignant melanoma. December 2012. Available from http://www.nice.org.uk/guidance/TA269 (access date 1 December 2015). 2012b.

National Institute for Health and Care Excellence. Technology Appraisal 319. Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma. July 2014. Available from

https://www.nice.org.uk/Guidance/TA319 (access date 1 December 2015). 2014a.

National Institute for Health and Care Excellence. Technology Appraisal 307. Aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy. March 2014. Available from http://www.nice.org.uk/guidance/TA307 (access date 8 December 2015). 2014b.

National Institute for Health and Care Excellence. Technology Appraisal 309. Pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer. April 2014. Available from http://www.nice.org.uk/guidance/TA309 (access date 8 December 2015). 2014c.

Peeters M, Douillard JY, Siena S ea, et al. Impact of post-protocol anti-epidermal growth factor receptor therapy on survival in wild-type KRAS/NRAS metastatic colorectal cancer: Data from the PRIME study. Poster presented at Markers in Cancer - a joint meeting by ASCO, EORTC and NCI, Brussels, 7-9 November 2013. 2013.

Tappenden P, Chilcott J, Brennan A, et al. Using whole disease modeling to inform resource allocation decisions: economic evaluation of a clinical guideline for colorectal cancer using a single model. *Value Health*. 2013;16:542-553.

Tappenden P, Jones R, Paisley S, Carroll C. Systematic review and economic evaluation of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer. *Health Technol Assess*. 2007;11:1-128, iii-iv.

Wade R, Simmonds M, Rodriguea-Lopez R, et al. TA307: Aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy - ERG report. 2013.

9 Appendix A

Summary of treatment patterns for patients with previously untreated mCRC (IMS Oncology Analyser Data Extract – 1st-line mCRC regimens Q3 2014)

Regimen (chemo only)	**%**	**FOLFIRI/FOLFOX-based**	**Fluoropyrimidine-based combo therapy without irinotecan**
CAPEC	18.6%		
5FU/OXAL	11.4%	Yes	Yes
CAPEC/OXAL	11.0%		Yes
5FU/IRIN	7.6%	Yes	
5FU/FA/OXAL	4.8%	Yes	Yes
5FU	4.3%		
5FU/AFLI/IRIN	1.0%	Yes	
CAPEC/IRIN	1.0%		
5FU/FA/IRIN	1.0%	Yes	
5FU/FA	0.5%		
IRIN	0.5%		
5FU/AFLI/FA/IRIN	0.5%	Yes	
CAPEC/IRIN/OXAL	0.5%		
IMAT	0.5%		
Regimen (with biologic)	%		
BEVA/CAPEC/OXAL	14.8%		Yes
5FU/BEVA/IRIN	5.2%	Yes	
5FU/CETUX/IRIN	5.2%	Yes	
5FU/BEVA/OXAL	3.3%	Yes	Yes
BEVA/CAPEC	2.9%		
5FU/CETUX/FA/IRIN	1.9%	Yes	
5FU/BEVA/FA/IRIN	1.9%	Yes	
BEVA/CAPEC/IRIN	0.5%		
5FU/BEVA/FA/OXAL	0.5%	Yes	Yes

5FU/CETUX/OXAL	0.5%	Yes	Yes
5FU/CETUX/FA/OXAL	0.5%	Yes	Yes
Totals		**45.2%**	**47.1%**

5-FU, 5-Fluorouracil; AFLI, aflibercept; BEVA, bevacizumab; CAPEC, capecitabine; CETUX, cetuximab; FA,folinic acid; IMAT, Imatinib; IRIN, irinotecan; OXAL, oxaliplatin

Note: This IMS data set was the same as that underpinning the treatment patterns shown in Table 5 of our submission. In Table 5 some of the biologic regimens were consolidated for simplicity. Totals are not exact sums of the % column due to rounding of decimal places.

Multiple Technology Appraisal (MTA)

Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer [ID794]

Merck Serono's comments on Appraisal Consultation Document

8th December 2015

Multiple Technology Appraisal (MTA)

Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer [ID794]

Merck Serono's comments on Appraisal Consultation Document

Merck is disappointed by the committee's preliminary decision to not recommend cetuximab for treatment of patients with mCRC and believe a number of key areas in the Appraisal Consultation Document (ACD) should be revised which are outlined here in our response. The Appraisal Committee have requested feedback on a number of questions including those noted here.

- **Has all of the relevant evidence been taken into account?**

  Merck does not agree that all the relevant evidence has been taken into account. Namely, there is a wealth of clinical evidence and clinical usage that supports the efficacy of cetuximab in combination with chemotherapy, both FOLFOX and FOLFIRI; this should be taken into account and the equivalence of benefit seen with cetuximab/FOLFIRI with cetuximab/FOLFOX be acknowledged.

- **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**
  No, the clinical and cost effectiveness analyses conducted are based upon inaccurate treatment durations, treatment schedule and administration costs and therefore do not reflect a true representation of the clinical environment nor the appropriate costs to the NHS.

- **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**
  No, these recommendations would mean that cetuximab, which has been available for treatment of patients with metastatic colorectal cancer (mCRC) since 2011 would no longer be widely available via the NHS and that the majority of mCRC patients would only have access to chemotherapy, without any personalised medicines, for treatment of their metastatic disease and therefore represents a step backwards for patient care.

General issues with the ACD findings

1) **Assessment group drug administration Costs.** There are serious and substantive errors with the administration costs ascribed in the ERG model, which render its estimation of administration cost non-credible. This has been confirmed by Department of Health, Reference Costs Team (Appendix 1 & 2) and the revised cost should be applied to future modelling. The appropriate administration costs are £830 per month for chemotherapy administration, and £849 per month for cetuximab plus chemotherapy administration, assuming the fortnightly administration routinely used in clinical practice.

2) **Weekly dosing regimen used by NICE.** The provisional recommendations in the ACD are not a suitable basis for guidance to the NHS as NICE has ignored the fact that cetuximab is predominantly administered in the NHS as a fortnightly dose and instead has applied weekly administration costs in the model. NICE should seek to model those costs which most closely reflect current UK practice, while remaining mindful of the licenced indication.
3) **Applicability of clinical data to the UK population was questioned.** Merck contests this. The clinical data underpinning this submission are relevant to the UK population; those patients treated in the clinical trials with cetuximab/chemotherapy represent the patient population that would be considered fit for treatment with cetuximab/chemotherapy in UK clinical practice.

The broad first line metastatic colorectal cancer population

1) **Limitation of post-hoc analyses.** The post hoc RAS analyses presented in this submission represent the advances in the scientific understanding of personalised medicine over the last 10 years. These RAS data were robust enough to be accepted by EMA for a license change in 2013. In addition, with the advancement seen in personalised medicine, it would be unethical to conduct a clinical trial in RAS wild-type patients fit for triplet treatment (cetuximab/chemotherapy) and offer them chemotherapy alone, denying them the additional survival benefit obtained from cetuximab combined with chemotherapy.
2) **Questions regarding cetuximab/FOLFOX efficacy.** There are a number of clinical trials in addition to OPUS as well as clinical usage that supports the efficacy of cetuximab in combination with chemotherapy, both FOLFOX and FOLFIRI; this should be taken into account and the equivalence of benefit seen with cetuximab/FOLFIRI with cetuximab/FOLFOX be acknowledged. The OPUS RAS wild-type analysis is affected by the limited number of samples available in the post-hoc analysis but it does not represent the overall clinical efficacy dataset supporting cetuximab/FOLFOX.
3) **Assessment group overestimation of treatment duration.** The modelled treatment duration from the ERG grossly overstates reality and in turn inflates the ICER. The actual mean treatment durations from the clinical trials have been supplied and it was confirmed by clinical experts at the committee meeting that these are more representative than the modelled treatment durations from the ERG. Real world data suggests a mean treatment duration for cetuximab plus chemotherapy of 23.7 weeks.
4) **End of Life criteria.** Merck disputes that the cetuximab patient population exceeds 7,000. Cetuximab is a well-established drug in the UK, not a new treatment and meets end of life criteria based on the number of patients that are actually treated , reflecting the true potential population and therefore should be granted a fully extended QALY threshold.

The liver limited disease (LLD) sub-population

1) **Confusion around patient populations in the ACD.** There seemed to be some confusion regarding differentiating between the broad mCRC population and the LLD mCRC population. The LLD population is a specific subset of patients with initially unresectable liver-only metastasis that could be downsized with cetuximab, allowing for potentially curative resection. Approximately 15-20% of the mCRC population will have metastases that are confined to the liver upon presentation with metastatic disease. Compared to the general mCRC population, the LLD population have a better prognosis and are treated with curative intent as opposed to palliative treatment. The scope of this MTA is for patients with previously untreated mCRC, therefore the total population, not just the LLD sub-population, therefore the focus of the Merck submission was the total population.
2) **Cost effective in NICE TA176 but not in current analysis.** Cetuximab in combination with chemotherapy has previously been evaluated as cost effective in this patient population. A smaller restricted patient population (all RAS wild-type instead of KRAS wild-type) which has the potential to enhance outcomes, would be expected to increase, not decrease this cost effectiveness but this is what has been seen in the ERG model. Therefore, Merck contests that with a refinement of the patient population cetuximab plus chemotherapy remains cost effective when moving from the KRAS to the RAS wild-type LLD mCRC patient population.

Therefore, Merck feel that there are a number of outstanding issues that need to be addressed in order for an accurate assessment to be completed and will continue to work constructively with the NICE committee and the clinical experts to address and understand potential areas of methodological differences, to make a fully informed and appropriate decision with regards to this appraisal.

Introduction

Merck is disappointed with the preliminary NICE conclusion not to recommend NHS funding for cetuximab in combination with chemotherapy, for RAS wild-type metastatic colorectal cancer as outlined in the ACD.

Colorectal cancer is the second biggest cancer killer in the UK[1]. The 5 year survival rate for patients diagnosed with colorectal cancer is 58%[2], whereas for those patients with metastatic colorectal cancer (mCRC) the 5 year survival rate is only 6.6%[3]. highlighting the unmet need for these patients. A number of studies have shown that colorectal cancer survival in England is still behind comparably wealthy countries[4,5]. For patients with advanced disease, appropriate drug therapy is crucial to extending the length and quality of life that colorectal cancer patients have left at the end of their lives. It is in this context that the use of 1st line cetuximab combined with chemotherapy (FOLFIRI or FOLFOX) can be part of the treatment plan for appropriate patients.

Improvements in understanding the importance of the RAS biomarker in mCRC has allowed for significant improvements in identifying appropriate patients who may be considered for treatment with cetuximab which would be expected to also show improvements in the cost-effectiveness to the NHS. Cetuximab has had an EU marketing authorisation since 2004 and is a well-established medicine that has been used worldwide in nearly 600,000 patients and recommended in both NCCN[6] and ESMO[7] guidelines for colorectal cancer. Since the inception of the Cancer Drugs Fund (CDF) in April 2011, over 5,500 patients have been treated with cetuximab and it has been maintained on the CDF list while other drugs for mCRC have been removed, highlighting both the strength of clinical data and the value clinicians place on its availability. Without access to cetuximab the lives of patients and families suffering from mCRC will be significantly impacted. There are considerable areas of confusion within the ACD document that warrant attention and these areas are addressed below.

Although in the ACD the committee's preliminary guidance is not to recommend cetuximab, the Committee concluded that adding cetuximab to chemotherapy provides benefits to patients with RAS wild-type metastatic colorectal cancer. Merck will continue to work constructively with NICE to address and understand potential areas of methodological differences that should be addressed, to make a fully informed and appropriate decision with regards to this appraisal.

Drug Administration Costs

The drug administration costs used by the Assessment Group remain unfeasibly high. Merck has uncovered that the Assessment group have indeed made errors regarding administration costs and included costs in the model that are already included in the HRG, thereby double-counting costs. This has been confirmed by Department of Health, Reference Costs Team as outlined in the attached letter (Appendix 2). Alongside the length of treatment, the cost of administration has the largest impact on model results and therefore it is important to highlight the errors made by the Assessment Group in estimating these costs. These erroneous costs are a key factor driving divergence between the ERG model and the reality of colorectal cancer treatment costs in England and Wales.

The Assessment Group have overestimated costs through both duplication of costs and the unnecessary addition of costs which are in fact fully absorbed by the HRG. Based on the actual costs confirmed by NHSE, Merck have recalculated the administration costs involved. The model should be corrected, with chemotherapy administration cost at £830 per month, and cetuximab plus chemotherapy administration cost at £849 per month when using fortnightly dosing (or £1,505 per month if administered weekly).

These costs are robust and are in line with other assessments in this therapy area, including one by the same Assessment group[8], and should be the costs utilised for modelling going forward within this assessment. A full analysis of the errors identified, corrections applied, and NHS reference costs confirmation can be found in appendices 1 & 2.

Fortnightly cetuximab administration

Cetuximab is typically administered intravenously every two weeks in combination with chemotherapy in first line mCRC in England. This dosing schedule is a doubling of the weekly cetuximab dose administered every 2 weeks. This treatment schedule, whilst differing from that in the Summary of Product Characteristics (SmPC), does not alter the total dose of cetuximab administered but rather the administration schedule and has become common treatment practice. As the committee heard from one of the clinical experts from The Christie Hospital, they have not administered cetuximab on a weekly schedule for the last 8 years at the Christie. The National Cancer Drugs Fund (CDF) in England recommended this dosing regimen (NHS England website[9]) in February 2014. Fortnightly administration is the standard of care in many territories, including in the UK via the CDF and this dosing regimen is also supported by the NCCN guidelines[6], which oncologists voted to be the most influential oncology guidelines at a guidelines update session at the most recent European Cancer Conference (ECC) meeting and the British Columbia guidelines.

There are a number of studies where cetuximab has been used on a fortnightly basis. The randomised CECOG-CORE II phase II study evaluated cetuximab/FOLFOX administered weekly or every two weeks in 152 patients[12]. The authors concluded that cetuximab administered every two weeks has comparable activity and a comparable safety profile as weekly dosing in combination with FOLFOX. In the APEC study in RAS wild-type patients, outcomes for cetuximab/FOLFOX vs cetuximab/FOLFIRI on a 2-weekly schedule were comparable; PFS 13.3 vs 12.8 months and OS 27.8 vs 28.7 months respectively[10]. These clinical results are similar to those from studies carried out with weekly dosing regimens such as CRYSTAL and OPUS, which underpin this NICE assessment. In addition, Hubbard and colleagues[11] carried out a review of several studies assessing weekly vs. every two weeks cetuximab dosing and found that the results of dosing cetuximab every 2 weeks were comparable to those obtained from weekly dosing.

Fortnightly administration also means that cetuximab can be given on the same day as chemotherapy once every 2 weeks reducing clinic visits by half, which results in more convenience and better quality of life for the patient[11,12] and is also therefore more economical to the NHS.

The following statement is taken from the PenTAG report:

> *"In the CRYSTAL and OPUS RCTs, cetuximab was given weekly. However, in our economic analysis, in common with Merck Serono, we assumed that cetuximab is administered fortnightly, to coincide with FOLFOX/FOLFIRI administration. Fortnightly administration is common clinical practice in the NHS. Further, Merck Serono argue on the basis of an open-label RCT and a literature review that 500mg/m² fortnightly administration is as effective as induction 400 mg/m² followed by weekly 250 mg/m² administration. We consider that this is justified by the clinical evidence."*

Merck contends that although the dosing schedule as outlined in the cetuximab SPC is weekly, common clinical practice in England is 2-weekly administration. There is no change in the total dose of cetuximab administered, just the schedule of administration. Therefore, to model actual costs, 2 weekly administration is a more accurate reflection of the cost burden to the NHS, whereas weekly administration would artificially inflate these figures. Merck is not suggesting NICE make a recommendation for cetuximab which is outside of its license, but rather that NICE models its calculations based on the most accurate reflection of the costs in order to determine the true QALY.

Applicability of clinical trial data to the UK population

The committee expressed reservations regarding the applicability to the UK population of the clinical trial data used to support this submission. Clinical experts discussed that in practice cetuximab is reserved for a subgroup of mCRC patients who are fit enough to tolerate triple therapy (cetuximab/chemo) treatment and that the patients in the supportive studies were younger, had better performance status and fewer co-morbidities than the broad metastatic CRC population. Merck agrees that the patient population represented in clinical studies indeed represents a subset of the entire mCRC patient population, and that subset corresponds with those selected for cetuximab treatment in clinical practice, namely those of better performance status, who can tolerate and benefit from triple therapy (cetuximab plus FOLFOX or FOLFIRI). Therefore the clinical data findings should be considered relevant to UK practice.

Broad Metastatic CRC Population - The Focus of this Assessment

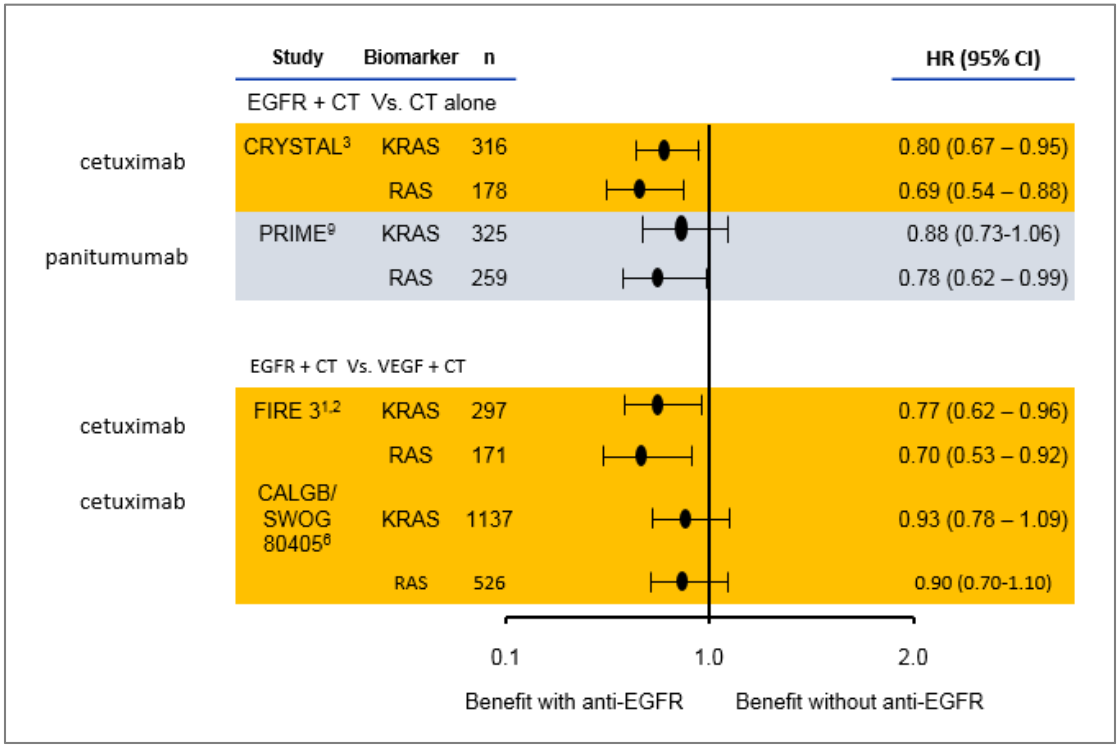
RAS wt analysis of cetuximab in combination with chemotherapy in the broad metastatic disease CRC population

Concern has been expressed by the NICE committee that the RAS wild-type data under consideration to represent the clinical evidence for both cetuximab and panitumumab have limitations due to being post-hoc sub-group analyses. Merck do not contest this, and acknowledge that it increases uncertainty around results.

However, it should be noted that modern science moves faster than clinical trials. Much research has been undertaken to understand the molecular and genetic pathways that play a role in identifying those patients that are likely to benefit from personalised medicines such as cetuximab and to exclude those patients that do not benefit. These data were considered robust enough to have warranted amendment of the marketing authorisation from the European Medicines Agency (EMA) in 2013 and have been accepted by the clinical panel of the CDF and the Scottish Medicines Consortium in their appraisal of first-line cetuximab (guidance 1012/14). In situations such as these, where biomarkers are identified subsequent to the completion of a clinical trial, conducting analysis of archived samples is the only viable option. Increased understanding of these biological pathways and improved personalisation of medicines such as cetuximab, means that patients who gain no clinical benefit are not exposed to unnecessary side-effects for no treatment gain. With the increased focus on personalised medicines in the advancement of oncology treatments, this phenomenon is likely to be more frequently observed with emerging new therapies which will continue to be a challenge for NICE in the future.

Notably the treated population has been successively restricted, first from all patients (the original intent to treat (ITT) population) to KRAS wild-type patients only, then from KRAS wild-type patients to All RAS (KRAS and NRAS wild-type patients). As the targeted population was restricted, so the hazard ratio improved (Figure 1).

Figure 1. Improved hazard ratios in studies when population refined from KRAS to RAS wild-type



Merck contends that the clinical data presented supports the efficacy of cetuximab in combination with either FOLFOX or FOLFIRI chemotherapy backbones. In the large CRYSTAL study, superiority of cetuximab plus FOLFIRI compared to FOLFIRI alone was demonstrated across endpoints. The smaller phase 2 OPUS study was affected by the limited number of RAS wild-type samples available for

analysis. Despite this, in the OPUS study the PFS improved when the population was refined from KRAS wild-type to RAS wild-type. The overall survival data demonstrated in the KRAS wild-type population became non-significant in the RAS wild-type patient population due to limited patient numbers, but as discussed earlier, the economic models developed by Merck and the Assessment Group are based on PFS. In this context, the ERG approach of modelling data seems the most appropriate way to address these uncertainties.

Moreover these studies may underestimate the magnitude of impact on survival. [redacted] The confounding effect of later line anti-EGFR therapy is likely to have led to understatement of the true survival benefit of 1st line cetuximab.

Examination of first line studies beyond that under consideration in this appraisal suggests that cetuximab in combination with FOLFOX or FOLFIRI can extend median overall survival to in excess of 30 months (FIRE3 – 33.1 months[14], CALGB-80405 - 32 months[15], CECOG/CORE2 – 28.5 months[12]). Assuming chemotherapy only provides approximately 20 months OS, which is what has been shown in numerous clinical trials and is reinforced by expert clinical opinion, these data reinforce the benefit seen with the addtion of cetuximab to chemotherapy compared to treatment with chemotherapy alone.

With regards to data maturity, PFS and OS data from CRYSTAL and OPUS are mature and no further data is expected from these studies. In addition, as science has progressed since these studies were conducted and the benefit seen when combining cetuximab with chemotherapy in this patient population is well accepted, it is unlikely that any further large clinical trials would be undertaken comparing cetuximab/chemotherapy to chemotherapy alone in patients fit for triplet therapy. As noted earlier, it would be unethical to conduct such a clinical trial denying patients cetuximab/chemo and the associated clinical benefits. Therefore, funding decisions must be made on the data that is currently available.

Cetuximab in combination with FOLFOX

Cetuximab in combination with FOLFOX has demonstrated clinical benefit compared to FOLFOX alone. In addition to the OPUS study, the use of cetuximab with FOLFOX is supported by clinical trial data including the FOLFOX arm from the CALGB-80405 study[15], the FOLFOX arm from the APEC study[10] and the CORE2 study which show strong efficacy data of 28-32 months median OS for cetuximab in combination with FOLFOX.

These data are consistent with the outcomes seen for cetuximab in combination with FOLFIRI reflecting similar outcomes for cetuximab/FOLFOX as cetuximab/FOLFIRI. In the CALGB-80405 study, patients were treated with cetuximab/chemotherapy vs bevacizumab/chemotherapy[15]. The choice of chemotherapy backbone was left up to the investigators discretion. In the RAS wild-type analysis, PFS for patients for cetuximab/FOLFOX was 11.3 months and 12.7 months for cetuximab/FOLFIRI and OS

was 32.5 months and 32 months respectively for cetuximab/FOLFOX vs cetuximab/FOLFIRI. In the APEC study in RAS wild-type patients, outcomes for cetuximab/FOLFOX vs cetuximab/FOLFIRI on a 2-weekly schedule were comparable; PFS 13.3 vs 12.8 months and OS 27.8 vs 28.7 months respectively[10]. These studies reinforce that there are similar outcomes whether cetuximab is used in combination with either FOLFOX or FOLFIRI.

The phase II OPUS study, as a relatively small data set, is most affected by sample size reductions as a result of post hoc analysis based on licence restriction. In general, when the patient population is refined from Intention-To-Treat population to the KRAS wild-type population to the RAS wild-type population, due to the exclusion of patients that do not benefit from cetuximab, there is an improvement in outcomes (Figure 1). This has been observed in multiple studies and is the rationale behind the restriction of the cetuximab indication to RAS wild-type patients. For the PFS in OPUS, this improvement in outcome was observed, with an improvement from 1.1 months to 6.2 months. Reductions in the evaluable sample size affected statistical powering. From an OS perspective, insufficient subjects could be analysed to draw a robust conclusion.

Therefore, although OPUS is the study used to represent the clinical data section for cetuximab/FOLFOX in this submission due to it being the only head to head trial against FOLFOX alone, other studies support comparable outcomes are seen when cetuximab is administered with either FOLFOX or FOLFIRI.

FOLFOX6 vs FOLFOX4

Following on from expert opinion, the committee acknowledged that FOLFOX6 is the regimen that is most commonly used in the UK, rather than. FOLFOX6 is less costly than FOLFOX4 and not the other way around, as is stated in the ACD, which we believe to be a typo. These costs are addressed elsewhere in this response.

Treatment Durations and interval

In developing its model the Assessment Group utilised modelled estimates of mean treatment durations for cetuximab in combination with FOLFOX or FOLFIRI using exponential extrapolation of the median treatment durations report in the clinical trials, rather than using actual mean treatment durations from studies or real world data. Merck have supplied the actual mean treatment durations from the clinical trials which should be used in the base case model (Appendix 4).

The panel noted uncertainty around length of treatment with cetuximab/chemo, and that the real world treatment duration estimated by experts was far shorter, around 6 months, than that modelled by the ERG, which was 10.7 months for cetuximab/FOLFIRI and 14.4 months for cetuximab/FOLFOX. These figures were based on a flawed and unconventional extrapolation of median treatment periods as reported in the respective clinical trials. As there is no evidence to support these overestimated treatment lengths, and in response to the Appraisal Committee's recommendation for investigating real-world treatment length in England, Merck has analysed real world data from [redacted] that have completed 1st line treatment with cetuximab plus either FOLFIRI or FOLFOX between 2012 &

2015, and the mean treatment duration in the real world was [redacted] (Appendix 5), which supports clinical expert estimate. This data is based on chart reviews conducted through market research for the period between March 2013 to October 2015 corresponds to approximately [redacted] of the CDF applications in this period and therefore can be considered to be a more accurate reflection of cetuximab treatment duration in the UK.

As outlined, real world cetuximab/chemotherapy treatment durations are around [redacted], whereas treatment duration with chemotherapy alone is estimated to be approximately [redacted] for FOLFIRI and [redacted], slightly shorter due to neuropathy) for FOLFOX based on expert clinical opinion.

End-of-Life criteria

In the ACD, the NICE committee have concluded that cetuximab meets 2 of the 3 criteria for end of life for the broad metastatic population. The third criteria refers to the number of patients that are eligible for cetuximab in all indications.

In relation to the size of the population for all licensed indications in England, we noted that NICE differentiated between cetuximab and panitumumab based on the indications under the license. We believe that to achieve a fair comparison between the two medicines, both should be treated on equal grounds and assessed in accordance with the size of the colorectal cancer population for balanced evaluation. Therefore Merck contends that head and neck cancer patients should not be included in this evaluation, for the reason outlined above. This is an unusual situation as the products in question do not share same licensed indications and therefore we ask the committee to take this into account when considering this criteria, particularly given that both agents have been studied in the H&N setting with cetuximab showing benefit in this setting and panitumumab failing to show benefit.

Merck's understanding of the EOL criteria is that they were instated to determine the maximum number of patients that could possibly be treated with a new medicine. Cetuximab received marketing authorisation in 2004 and therefore its estimated usage can be determined with some certainty.

- In mCRC cetuximab has been subject to 4302 CDF applications for mCRC in **all lines** (1st, 2nd and subsequent lines) of therapy, in the 30 month period between March 2013 and Sept 2015.
- Numbers for the last year for first line cetuximab use in the mCRC population in combination with either FOLFOX or FOLFIRI, were approximately 600 for the period of Sept 2014 to Sept 2015 on the CDF (Table 1).

Cetuximab in locally advanced (LA) or recurrent metastatic (RM) squamous cell carcinoma of the head and neck (SCCHN)

In SCCHN, NICE TA145 NICE restricted the funded population to only those locally advanced SCCHN patients with a Karnofsky score of above 90 in whom all forms of platinum based chemotherapy were contraindicated or not tolerated. The number of patients with locally advanced (LA) SCCHN eligible

for cetuximab treatment was estimated in TA145 to be 8% of the total SCCHN population. The committee were of the opinion that there are 3,000 SCCHN patients in England, therefore this equates to 240 patients (3,000 x 8%). NICE TA 172 did not recommend the use of cetuximab for SCCHN patients with recurrent or metastatic disease (RM). Cetuximab is currently available for RM SCCHN patients via the CDF and for the period of Sept 2014 to Sept 2015, there were around 150 applications in this setting. Therefore, in total it is estimated that approximately 400 patients get treated with cetuximab in England for SCCHN in both the LA and RM settings annually.

Total numbers

If this number is added to the 5,968 RAS wild type mCRC patients in England (data in TA176, updated to reflect RAS wild type subgroup), the total remains below the 7,000 limit stipulated by the end-of-life criteria. And as outlined above, only around 4,300 patients were treated with cetuximab over the period of 2.5 years (2013-2015) when cetuximab was available on the CDF in ALL lines, with approximately 600 patients treated in the first line over the course of one year, therefore it can be stated with certainty that the number of patients that would be treated with cetuximab for 1st line mCRC even combined with those treated under NICE for SCCHN would never reach 7,000. Based on real world usage, for both mCRC and SCCHN, approximately 1,000 patients would be treated annually.

Cetuximab is well established in the UK, it has been available since 2011 and so has been used in clinical practice for a long period of time, and it is unlikely that treatment patterns would now change.

Merck would also urge the commitee to consider the recent publication of the newly launched NICE/NHSE CDF consultation that proposes a change to the EOL criteria in the Guide to the Methods of Technology Appraisal 2013 that removes the requirement for the size of the eligible population to be less than 7,000 in England[16]. If this proposal is accepted through the consultation, this change is planned to be effective from 1st April 2016. Therefore, this would then mean that when the Final Guidance for this MTA is published, cetuximab will meet the EOL criteria and qualify for the higher threshold.

Table 1. Cetuximab use for first line treatment of mCRC and RM SCCHN use in England (CDF), Sept 2014-2015

CDF indication	Oct-14	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Total
1st Line treatment of metastatic colorectal cancer in combination with the following regimens: FOLFOX4 or FOLFOX6 or OxMdG Chemotherapy (From 13/02/2014)	7	3	5	4	7	8	4	6	10	9	7	10	46
1st line treatment of metastatic colorectal cancer in combination with Irinotecan based chemotherapy (From 13/02/2014)	48	27	34	53	79	83	69	79	104	110	80	117	559
2nd or 3rd line treatment of metastatic colorectal cancer in combination with Chemotherapy (From 13/02/2014)	53	48	50	40	55	21	0	0	0	0	0	0	0
2nd or 3rd line treatment of metastatic colorectal cancer in patients not treated to progression under NICE TA176 (From 13/02/2014)	1	4	7	3	2	4	0	0	0	0	0	0	0
3rd and subsequent line treatment of metastatic colorectal cancer as a single agent (From 13/02/2014)	29	20	16	29	38	33	29	34	37	32	31	64	227
3rd and subsequent line treatment of metastatic colorectal cancer as a single agent in patients not treated to progression under NICE TA176 (From 13/02/2014)	0	4	2	2	7	1	9	3	5	3	5	10	35
1st line treatment of metastatic and/or recurrent squamous cell carcinoma of the head and neck	18	18	19	23	21	21	23	18	20	28	31	30	150
												Total	**1017**

Liver Resection Rates

Resection rates In the LLD Population

The LLD population is a preselected subset of patients with metastatic disease confined only to the liver. Data for this preselected population supports a resection rate of between 9% (Ye et al[17]) and

12.5% (Adam) for chemotherapy alone, compared to a resection rate of between 28% and 31% for cetuximab plus chemotherapy (Folprecht et al[13], Ye et al.[17] RESECT[18]).

These data likely underestimate cetuximab effect in this setting as analysis was conducted on the KRAS patient subset and not the more refined RAS wild-type population, where outcomes would be expected to be improved. We do not have RAS wild-type data from these studies. The resection rates for the broad first line mCRC population are inappropriate to consider in the context of the LLD subset of patients. The advancement of treatments and the specialisation of management of patient care through multi-disciplinary teams (MDTs) will likely also mean that these rates in reality would be higher in current practice.

In support of this information Merck would like to draw the panel's attention to the following paragraph from TA176:

NICE TA176 (2008) Section 4.5 states:

> *"It [the Appraisal Committee] heard from the clinical specialists that the number of patients receiving potentially curative liver resection in the CRYSTAL and OPUS trials was lower than that seen in UK clinical practice, which is based on management by multidisciplinary teams involving highly specialised liver surgical services. The clinical specialists stated that a more realistic rate for potentially curative resection with chemotherapy in general was approximately 12–15%, which could rise to approximately 30–35% with the addition of cetuximab."*

Resection rates in the broad mCRC population

As outlined above the LLD patient population is a different group of patients to the broad first line mCRC population and there are different clinical trials and clinical data which reflect this. In this submission, the studies that support the clinical evidence are CRYSTAL and OPUS. These are studies that included patient with broad metastatic disease and not the LLD population. Therefore, resection rates reported in these studies are lower than they would be if these studies had focussed on LLD patients: CRYSTAL RAS wt resection rates - cetuximab/FOLFIRI 7.3% vs FOLFIRI alone 2.1%; OPUS KRAS wt - cetuximab/FOLFOX 9.8% vs 4.1% with FOLFOX alone. As mentioned earlier, it is also worth noting that resection rates are continuously improving over time with advancing clinical practice, patient care and surgical techniques and therefore these rates may be higher in current practice.

Liver limited disease mCRC population

Patients with metastatic disease confined to the liver (liver-limited disease, LLD), require different clinical considerations to patients with widespread metastatic disease, as the goal of treatment in the LLD setting is to shrink tumours to the point at which a patient is able to undergo surgical liver resection, rather than treatment until progression of disease.

As the committee heard from the clinical experts at the first appraisal committee meeting, the duration of cetuximab/chemotherapy treatment in LLD patients is approximately 8-12 weeks, and no more than the 16 weeks currently recommended in TA176.

The clinical rationale for limiting treatment duration for LLD patients is to maximise the potential for patients receiving cetuximab with chemotherapy to get an effective response to treatment, with sufficient shrinkage to allow liver resection to proceed, while minimising the duration of treatment with irinotecan or oxaliplatin containing regimens, which can both make surgical liver resection more complicated potentially compromising the effectiveness of the procedure.

The numbers quoted by the Assessment group in the ACD are incongruous with both current NICE guidance in TA176, or with the evidence provided by the experts at the ACD meeting. This can be attributed to flawed modelling assumptions made by the Assessment Group in relation to the subgroup of patients with metastases confined to the liver. These assumptions are:

1. Patients remain on treatment following surgical resection of the liver, which is not the case
2. Patients continue treatment for more than 16 weeks. This is contrary to the view of the clinical experts who advised NICE during the Initial Appraisal Meeting that the duration of treatment when using cetuximab in LLD patients should be 8-12 weeks, and no more than the 16 weeks currently recommended in TA176.

Applying a 16 week stopping rule in the Assessment Group's model for the liver-resection patient subgroup with the corrected administration costs and under the conditions of TA176 Patient Access Scheme (16% rebate off cetuximab NHS price when combined with FOLFOX), appropriate resection rates of 12.5% for chemotherapy and 28% for cetuximab/chemo, reduces the ICERs from £130,000/QALY to £27,581/QALY for cetuximab/FOLFIRI and from £186,000/QALY to £30,268/QALY for cetuximab/FOLFOX. This demonstrates the importance of applying this stopping rule in the model in order to appropriately reflect UK clinical practice and corresponding costs.

Under current NICE guidance issued in TA176, cetuximab in combination with FOLFOX or FOLFIRI, within its licensed indication, has demonstrated cost-effectiveness and is recommended by NICE for use in patients with unresectable metastases confined to the liver. These key factors should be taken into consideration when comparing TA176 recommendations to the ongoing assessment of cetuximab in RAS wild type mCRC patient with metastasis confined to the liver:

i. The current assessment is based on a better defined patient population who are more likely to benefit from cetuximab, due to improved molecular targeting (all RAS wild-type patients instead of KRAS exon 2 wild-type patients)
ii. A patient access scheme that is significantly increased in patient coverage in comparison to the original offering (all first line RAS wild type mCRC patients compared to mCRC patients with liver only metastasis as in TA176)
iii. The proposed PAS for the total mCRC population applies to patients treated with either FOLFOX or FOLFIRI, rather than just those treated with FOLFOX in TA176

iv. In the current ERG model there is no stopping rule, Merck assumes that similarly to NICE guidance in TA176 for patients with LLD, maximum cetuximab treatment would be limited to 16 weeks.

A pragmatic stance taking these factors alone into consideration, vastly improves the value of cetuximab to patients meeting these criteria, compared to the previous assessment and represent increased value to the NHS.

Merck's comments on Appraisal Consultation Document (ACD)

Merck would like to offer comments under each of the following statements which are included in the ACD, as shown below in the text boxes:

ACD comment 1

Page 3 Paragraph 2.1	The 1-year survival rate in England and Wales is about 75%, and the 5-year survival rate is under 60%.

Merck comment:

This comment relates to survival rates for bowel cancer, all stages, after mentioning specific incidence of metastatic bowel cancer (Stage IV), and as a result the survival rates appear to refer to metastatic disease which is inaccurate. 5 year survival for metastatic bowel cancer are much lower at 6.6%[3], and this should be amended to reflect this. Bowel cancer is the UK's 2nd biggest cancer killer.

ACD comment 2

Page 23 Paragraph 4.26	The Committee concluded that the Assessment Group had included the appropriate comparators in its base case, and noted that a scenario analysis provided results for FOLFOX6.

Merck comment:

Merck disputes this comment. The Assessment Group acknowledged that their assessment costed FOLFOX-4, not FOLFOX-6. As previously discussed, Merck put the case that FOLFOX-6 should be costed and the clinical experts agreed that FOLFOX-6 was the preferred regimen in England. The Assessment Group should present a revised model that includes the cost for FOLFOX-6, not FOLFOX-4.

ACD comment 3

Page 24 Paragraph 4.27	The Committee discussed the place of cetuximab and panitumumab in the treatment pathway. It understood that these drugs are combined with chemotherapy with the aim of making initially unresectable tumours resectable.

Merck comment:

The goals of two distinct patient groups are not adequately captured or represented here. For patients with unresectable liver only metastases, patients receive neo-adjuvant therapy with cetuximab/chemotherapy, where high response rates and tumour shrinkage are the short term goals of treatment, to convert unresectable liver metastases to resectable. If this goal is achieved, the patient may undergo potentially curative liver resection.

For patients who have metastases not confined to the liver, or who have been treated as above and who remain unresectable, the treatment goal is palliation and to maximise their overall survival, balanced with an acceptable quality of life for the patient. In either setting, cetuximab can be combined with either FOLFIRI or FOLFOX.

ACD comment 4

Page 24 Paragraph 4.27	The Committee concluded that cetuximab and panitumumab would be offered as first-line treatments with chemotherapy to a subgroup of people with metastatic colorectal cancer: people who have symptomatic disease and high volume metastases, either inside or outside the liver, which are not initially resectable.

Merck comment:

The comment from the clinical experts that cetuximab and panitumumab would be reserved for people with high volume symptomatic disease where the treatment is to slow disease progression as quickly as possible reflects that in real clinical practice the total patient population that oncologists choose to treat with these agents is not as wide as the total eligible patient population. The committee appear to accept this. However, this is not reflected in the assessments regarding calculations for End of Life criteria.

ACD comment 5

Page 25 Paragraph 4.29	The Committee heard from clinical experts that the trial populations were younger than patients seen in clinical practice.
Page 32 Paragraph 4.40	The Committee acknowledged that the clinical experts had advised that cetuximab and panitumumab would be used only in a small subgroup of people with metastatic colorectal cancer (even smaller than the population in the marketing authorisation), but noted that it had not seen evidence in this group.

Merck comment:

Merck would like to note that the clinical experts expressed that the trial populations were younger than patients regularly seen and treated in clinical practice. Clinical experts discussed that in practice cetuximab is reserved for a subgroup of mCRC patients who are fit enough to tolerate triple therapy (cetuximab/chemo) treatment and that the patients in the supportive studies were younger, had better performance status and fewer co-morbidities than the broad metastatic CRC population. Merck agrees that the patient population represented in clinical studies indeed represents a subset of the entire mCRC patient population, and that subset corresponds with those selected for anti-EGFR treatment in clinical practice, namely those of better performance status, who can tolerate and benefit from triple therapy.

ACD comment 6

Page 26 Paragraph 4.32	It heard that there was no evidence that cetuximab plus FOLFOX was more effective than FOLFOX alone, but understood from the clinical experts that cetuximab would be given with FOLFIRI, not FOLFOX, in clinical practice (see section 4.27).

Merck comment:

There are a number of clinical trials in addition to OPUS as well as clinical usage that supports the efficacy of cetuximab in combination with chemotherapy, both FOLFOX and FOLFIRI; this should be taken into account and the equivalence of benefit seen with cetuximab/FOLFIRI with cetuximab/FOLFOX be acknowledged. The OPUS RAS wild-type analysis is affected by the limited number of samples available in the post-hoc analysis but it does not represent the overall clinical efficacy dataset supporting cetuximab/FOLFOX.

The use of cetuximab with FOLFOX is supported by additional clinical trial data including the FOLFOX arm from the CALGB-80405 study[15], the FOLFOX arm from the APEC study[10] and the CORE2 study[12] which show strong efficacy data of 28-32 months median OS for cetuximab in combination with FOLFOX. These data are consistent with the outcomes seen for cetuximab in combination with FOLFIRI.

ACD comment 7

Page 12 Paragraph 4.8	In Merck Serono's base case, it compared: • cetuximab plus FOLFOX4 with FOLFOX4 • cetuximab plus FOLFIRI with FOLFIRI • cetuximab plus FOLFIRI with bevacizumab plus FOLFIRI. Merck Serono provided results based on weekly dosing of cetuximab, the dosage recommended in the marketing authorisation, and also for fortnightly dosing of cetuximab, which is not specified in the marketing authorisation. NICE can issue guidance only within the marketing authorisation, so only results based on weekly dosing of cetuximab are relevant. The results in this document are based on weekly dosing of cetuximab unless otherwise stated. Merck Serono compared cetuximab plus FOLFOX with XELOX in a scenario analysis.

Merck comment:

Cetuximab is typically administered intravenously every two weeks in combination with chemotherapy in first line mCRC in England. This dosing schedule is a doubling of the weekly cetuximab dose administered fortnightly. This treatment schedule, whilst differing from that in the Summary of Product Characteristics (SmPC), has become treatment practice. As the committee heard from one of the clinical experts from The Christie Hospital, they have not administered cetuximab on a weekly schedule for the last 8 years. Subsequently, the National Cancer Drugs Fund in England recommended this dosing regimen (NHS England website[9]) in February 2014. Fortnightly administration is the standard of care in many territories, including in the UK via the CDF and this dosing regimen is also supported by the NCCN, which have been deemed to be the most influential guidelines[10] and the British Columbia guidelines[19].

There are a number of studies where cetuximab has been used on a fortnightly basis. The randomised CECOG-CORE II phase II study evaluated cetuximab/FOLFOX administered weekly or every two weeks in 152 patients (Brodowicz et al., 2013). The authors concluded that cetuximab administered every two weeks has comparable activity and a comparable safety profile as weekly dosing in combination with FOLFOX. In the APEC study in RAS wild-type patients, outcomes for cetuximab/FOLFOX vs cetuximab/FOLFIRI on a 2-weekly schedule were comparable; PFS 13.3 vs 12.8 months and OS 27.8 vs 28.7 months respectively[10]. These clinical results are similar to those from studies carried out with weekly dosing regimens such as CRYSTAL and OPUS, which underpin the NICE assessment. In addition, Hubbard and colleagues carried out a review of several studies assessing weekly vs. every two weeks cetuximab dosing and found that the results of dosing cetuximab fortnightly were comparable to those obtained from weekly dosing.

Fortnightly administration also means that cetuximab can be given on the same day as chemotherapy once fortnightly reducing clinic visits by half, which results in more convenience and better quality of life for the patient[11,12] and is also therefore more economical to the NHS.

The following statement is taken from the PenTAG report:

> "In the CRYSTAL and OPUS RCTs, cetuximab was given weekly. However, in our economic analysis, in common with Merck Serono, we assumed that cetuximab is administered fortnightly, to coincide with FOLFOX/FOLFIRI administration. Fortnightly administration is common clinical practice in the NHS. Further, Merck Serono argue on the basis of an open-label RCT and a literature review that 500mg/m² fortnightly administration is as effective as induction 400 mg/m² followed by weekly 250 mg/m² administration. We consider that this is justified by the clinical evidence."

Merck contends that although the dosing schedule as outlined in the cetuximab SPC is weekly, common clinical practice is fortnightly administration. Therefore to model actual costs, fortnightly administration is a more accurate reflection of the cost burden to the NHS, whereas weekly administration would artificially inflate these figures. Merck is not suggesting NICE make a recommendation for cetuximab which is outside of its license, but rather that NICE models its calculations based on the most accurate reflection of the costs in order to determine the true QALY.

ACD comment 8

Page 16 Paragraph 4.17	Drug administration unit costs. Merck Serono assumed lower costs, which reduced the ICERs, compared with the Assessment Group. During consultation of the assessment report, Merck Serono suggested that the Assessment Group's estimates included double-counting.
Page 30 Paragraph 4.37	The Assessment Group estimated drug administration costs appropriately; double-counting of costs was unlikely and would not substantially affect the ICERs.

Merck comment:

The drug administration costs used by the Assessment Group remain unfeasibly high. Alongside the length of treatment, the cost of administration has the largest impact on model results and therefore it is important to highlight the errors made by the Assessment Group in estimating these costs. Merck continues to disagree with the costs used due to the following reasons:

1. The Assessment Group have overestimated the cost of administration (£4,714 for Cetuximab+FOLFOX-4 and £4,000 for cetuximab+FOLFIRI) because they have unnecessarily duplicated HRG costs and added extra costs that should be fully absorbed by the HRG. The

Assessment Group estimation contradicts with the 2014-2015 NHS reference costs guide which states the following:

"Unbundled HRGs for a number of services: These costs are generally high and only relate to a limited number of patients. Including them as an overhead on treatments and procedures would significantly distort costs and lead to wide variations. Trusts therefore report them separately as:

• Chemotherapy – drug costs for cancer patients, split between procurement of regimens and delivery, with other costs included in the relevant admitted patient or outpatient setting"

Furthermore, it contradicts with the costs used in estimating the cost effectiveness of cetuximab in combination with chemotherapy for mCRC in NICE TA176, in which the ERG accepted that the cost of administration used absorbed pharmacy, infusion pump and line maintenance costs.

To ensure accurate estimation of administration costs, Merck have sought the advice of NHS Reference Costs directly since they are the source of the HRGs used in both the Assessment Group and Merck economic models (see accompanied letter from NHS Reference Costs Team for further confirmation). The following table illustrates the difference between the Assessment Group and Merck calculations according to NHS Reference Cost advice:

	Merck		PENTAG			
Cost element	**Day 1**	**Day 8**	**Day 1**		**Day 8**	
	Cet + FOLFIRI or FOLFOX-6	Cetuximab only	Cetuximab	FOLFIRI or FOLFOX-6	Cetuximab	FOLFIRI or FOLFOX-6
1. HRG	£383	£302.58	**£302.58**	£383	£302.58	£0
2. Extra Nurse time	£8.8	£0 – absorbed by HRG	£8.8		£8.8	
3. Pharmacy cost	£0 – absorbed by HRG	£0 – absorbed by HRG	£246		£246	
4. Line maintenance	£0 – absorbed by HRG	£0 – absorbed by HRG	£133		£133	
5. Infusion pump	£0 – absorbed by HRG	£0 – absorbed by HRG	£41		£41	
Total per visit	£392	£302.6	£1,114.6		£731.5	
Total per cycle (days 1+ 8)	£694		£1,846			
Total per month (2.17 cycles)	**£1,505**		**£4,000**			

It is clear from this table that the Assessment Group added the administration cost of cetuximab on day 8 (£302.58) in error to the administration cost of day 1 of each cycle; there were two day 8 administration costs present in both day 1 and day 8 when it should only apply to day 8. In addition, the Assessment group applied the additional costs of pharmacy, line maintenance and infusion pump equally between day 1 (cetuximab + FOLFOX) and day 8 (single cetuximab infusion) when these costs should be fully absorbed by the HRG, as NHS Reference Costs have confirmed in the accompanied letter.

2. The Assessment Group have identified several administration costs used in previous NICE publications, including previous NICE assessment of cetuximab, and chose to use the highest costs published because the cost of administering monoclonal antibodies is generally higher than chemotherapy. We find this assumption to be unfounded given the cost of administration outlined above as advised by NHS Reference Costs. By way of comparison, the same assessment group (PENTAG) have estimated an average monthly administration cost per person of £1,480 in NICE TA242 which assessed cetuximab + chemotherapy for the

treatment of metastatic colorectal cancer after first-line chemotherapy [2011]. This cost is more consistent with the cost of administration calculated using NHS Reference Cost advice (£1,505) and therefore proves that the Assessment Group have overestimated the administration costs.

As advised by NHS reference costs, the HRGs used in the model fully absorb the additional costs added by the Assessment Group to these HRGs (Pharmacy costs, infusion pump and line maintenance cost). If these costs are added to the HRGs, the administration costs will be more expensive than the acquisition cost of cetuximab + chemotherapy per month. In which case the acquisition cost is secondary to the administration cost in terms of impact on cost effectiveness. The statement that these costs do not substantially affect the ICERs is not correct. The Assessment Group and Merck have stated that the duration of treatment, with all the costs associated with it, are the most crucial and impactful factor in the estimation of the ICER. Since cetuximab + chemotherapy mean treatment duration is longer than that with chemotherapy only, the additional PFS in the chemotherapy arm accrues more treatment costs than chemotherapy only. Therefore, any change in the administration cost should have a great impact on the model. By using £1,505 per month for cetuximab + FOLFIRI/FOLFOX-6 instead of £4,000 per month as calculated by the Assessment Group, the ICER for this combination is reduced from £227k/QALY to £141k/QALY. This is without changing any of the Assessment Group assumptions and using the model they developed for this assessment. This demonstrates that administration costs have a large impact on ICERs, if not the largest out of all model parameters.

ACD comment 9

Page 23 Paragraph 4.26	The Committee heard that FOLFOX4 and FOLFOX6 are equally effective, but that FOLFOX6 costs more than FOLFOX4.

Merck comment:

This statement is incorrect. We suspect this may be a typing error as the experts clearly stated during the appraisal meeting that FOLFOX-4 administration costs are higher than FOLFOX-6. FOLFOX-4 requires the patient to visit the clinic on 2 consecutive days, and therefore requires double the administration costs FOLFOX-6. FOLFOX-6 requires just one clinic visit for each patient, requires one cost for pharmacy time to make up the infusion, and is therefore less costly than FOLFOX-4. The clinical experts stated that the preferred regimen administered in the UK is FOLFOX-6.

ACD comment 10

Page 16 Paragraph 4.17	Drug acquisition costs per month. Merck Serono assumed lower costs for cetuximab, and therefore lower ICERs, than the Assessment Group. Merck Serono used higher costs for FOLFOX and FOLFIRI than the Assessment Group, which does not impact cost effectiveness because both treatment arms are affected similarly.

Merck comment:

Drug acquisition costs. Merck used the NHS price for cetuximab, rather than the list price, which was used by the Assessment Group. Merck used the BNF prices for both irinotecan & oxaliplatin, not the NHS acquisition prices. Consistent process should reflect the real cost to the NHS for all drugs.

We noted the use of significantly lower chemotherapy acquisition costs using the CMU eMit tool to reflect true cost to the NHS. We believe that following this approach should allow for the use of actual cost of cetuximab to the NHS for fair comparison. We have indicated in our evidence submission that "Cetuximab has been offered at a guaranteed discounted price to the NHS in agreement with the Department of Health since 2008. This agreement is not limited to a time period. The NHS acquisition prices are £136.50 (100mg/20ml vial); £682.50 (500mg/100ml vial)."

However, we followed the NICE methodology in using List prices for all comparators, including cetuximab to allow for a like-to-like comparison. Therefore, the use of CMU eMit cost for chemotherapy without the use of true NHS cost of cetuximab overestimates the cost difference between cetuximab in combination with chemotherapy and chemotherapy alone. Using the model developed by the Assessment Group, the cost of cetuximab acquisition is reduced to £2,665.85 per month using the actual NHS price. Therefore, outside the consideration of cetuximab's patient access scheme price, the cost effectiveness of cetuximab should be based on the actual price to the NHS; i.e. £136.50 per 100mg vial.

Table 1: List price and eMit/NHS prices for cetuximab and chemotherapy

Price used in calculating cost	Cetuximab acquisition cost	FOLFIRI acquisition cost	FOLFOX-6 acquisition cost
List price	£3,859	£1,797	£2,120
eMit/NHS price	£2,666	£128	£91

ACD comment 11

Page 30 Paragraph 4.37	The Assessment Group's estimate for average body surface area (1.85m^2) was plausible.

Merck comment:

Merck have commented on the use of 1.85 m2 in our response to the Assessment Groups report. The use of such body surface area implicitly assumes that all patients treated would be in the highest dose banding which does not take into account patients with a lower body surface area and does not reflect the actual distribution of body surface area amongst patients. In practice, there is special consideration for this variation though dose banding where the link between body surface area and costs of the drug is a step function with steps at 1.60, 1.70 and 1.80 m2 and so a weighted average should be applied.

ACD comment 12

Page 30 Paragraph 4.37	The Assessment Group's estimate for the cost of resection surgery (£10,440) was more plausible than Merck Serono's estimates of £2707 in its original submission.
Page 16 Paragraph 4.17	Cost of a resection operation. Merck Serono assumed a lower cost, which resulted in lower ICERs, compared with the Assessment Group.

Merck comment:

Cost of a resection. Merck accepts that the original company submission incorrectly costed the cost of resection. It should be noted that although using a lower cost of surgical resection lowered the ICERs, it did not lower them significantly.

ACD comment 13

Page 4 Paragraph 2.2	When possible, surgically removing (resecting) the primary tumour and metastases is considered, but usually only when there are no metastases outside of the liver.

Merck comment:

In patients with metastatic disease, surgical resection of the primary tumour is common even when metastases are not confined to the liver and are more widespread. For patients with metastatic disease confined to the liver, the best chance of long-term survival is through resection of both the primary bowel tumour and the liver metastases.

ACD comment 14

Page 22 Paragraph 4.25	The Committee heard that patients with small numbers of resectable metastases confined to the liver (about 1–3 metastases) may proceed to surgery without any chemotherapy.

Merck comment:

This is the case if the liver metastases are "upfront resectable" and can be surgically removed without the need for any down-sizing therapy. These patients wouldn't be treated with cetuximab as they are already resectable and therefore don't require tumour shrinkage.

ACD comment 15

Page 22 Paragraph 4.25	Clinical experts explained that they use first-line chemotherapy for 8–12 weeks, at which point they assess whether the patient is eligible for resection.
Page 28 Paragraph 4.35	The clinical experts stated that people who have resection generally have treatment for between 8 and 12 weeks.
Page 30 Paragraph 4.38	Duration of treatment with cetuximab was shorter in the original appraisal when the company applied a 16-week stopping rule. In the current appraisal, treatment duration ranged from 38–46 weeks in the Assessment Group's model and 25 weeks in the Merck Serono model, which the Committee had concluded were overestimates (see section 4.35). The Committee noted that a stopping rule had not been explored as part of the current modelling.

Merck comment:

Merck agrees that patients with LLD get treated for 8-12 weeks (up to 16 weeks as in NICE TA176 guidance) to provide tumour shrinkage to allow successful resection of liver metastases.

ACD comment 16

Page 28 Paragraph 4.34	The Committee heard that the Assessment Group had modelled an average of 1.6 resection operations per patients, which the clinical experts noted reflected clinical practice. The Committee concluded that the model included uncertainties, but was an adequate basis for its decision-making.

Merck comment:

The statement that clinical experts agreed with the Assessment Group that 1.6 resection operations per patient reflects clinical practice is not correct. Clinical experts stated that the risk of operation failure is likely to be lower than 60% in practice and hence the cost of surgery calculated by the Assessment Group is overestimated.

ACD comment 17

Page 29 Paragraph 4.36	The Committee discussed the Assessment Group's estimates of the proportion of people who have resection of liver metastases after first-line treatment. It heard from clinical experts that, for patients whose tumours are initially unresectable, chemotherapy with or without cetuximab or panitumumab could shrink the metastases enough to be resected in about 15% of people.

Merck comment:

The LLD population is a preselected subset of patients with metastatic disease confined only to the liver. Data for this preselected population supports a resection rate of between 9% (Ye et al) and 12.5% (Adam) for chemotherapy alone, compared to a resection rate of between 28% and 31% for cetuximab plus chemotherapy (Folprecht et al[13], Ye et al.[17], RESECT[18]).

Merck would like to draw the panel's attention to the following paragraph from TA176

TA176 in 2008. Section 4.5 in NICE TA176 states:

> "It [the Appraisal Committee] heard from the clinical specialists that the number of patients receiving potentially curative liver resection in the CRYSTAL and OPUS trials was lower than that seen in UK clinical practice, which is based on management by multidisciplinary teams involving highly specialised liver surgical services. The clinical specialists stated that a more realistic rate for potentially curative resection with chemotherapy in general was approximately 12–15%, which could rise to approximately 30–35% with the addition of cetuximab."

ACD comment 18

Page 31 Paragraph 4.38	Resection rates were higher in the original appraisal, ranging from 30–43% compared with about 7–31% in the current appraisal. These were based on clinical expert opinion and the results of an open-label phase II trial comparing cetuximab plus FOLFOX with cetuximab plus FOLFIRI (the CELIM trial). The Committee heard that the CELIM trial studied a specific subgroup of people with KRAS wild-type metastatic colorectal cancer who had metastases confined to the liver, good performance status and who were fit for surgery. It considered that the population in the CELIM trial was narrower than the population relevant to the current appraisal.

Merck comment:

In this submission, the studies that support the clinical evidence are CRYSTAL and OPUS. These are studies that included patient with broad metastatic disease. As the patient population in these trials wasn't selected for those with LLD, resection rates are lower than they would be if they were LLD studies: CRYSTAL RAS wt resection rates - cetuximab/FOLFIRI 7.3% vs FOLFIRI alone 2.1%; OPUS KRAS wt - cetuximab/FOLFOX 9.8% vs FOLFOX alone.

ACD comment 19

Page 12 Paragraph 4.9	In Merck Serono's deterministic base case of all patients, using the list price for cetuximab, the incremental cost-effectiveness ratios (ICERs) were £61,894 per quality-adjusted life year (QALY) gained for cetuximab plus FOLFOX and £74,212 per QALY gained for cetuximab plus FOLFIRI, compared with chemotherapy alone. Cetuximab plus chemotherapy produced approximately 0.3 extra QALYs compared with chemotherapy alone. Merck Serono did not provide estimates of cost effectiveness for the subgroup of people with metastases confined to the liver who have cetuximab weekly.

Merck comment:

Under the current NICE guidance issued in TA176, cetuximab in combination with FOLFOX or FOLFIRI, within its licensed indication, has demonstrated cost-effectiveness and is recommended by NICE for use in patients with unresectable metastases confined to the liver. As a result Merck did not provide an initial cost-effectiveness assessment in this appraisal, as the understanding was that the cost-effectiveness had already been established and would be improved beyond the current guidance in TA176 based on 2 key facts:

a) This assessment is based on a better defined patient population who are more likely to benefit from cetuximab, due to improved molecular targeting (all RAS wild-type patients instead of KRAS exon 2 wild-type patients);

b) A patient access scheme that is significantly increased in patient coverage in comparison to the original offering (all first line RAS wild type mCRC patients compared to mCRC patients with liver only metastasis as in TA176).

A pragmatic stance taking these factors alone into consideration, and applying the same disease management assumptions in TA176, should vastly improve the value of cetuximab to patients meeting these criteria, compared to the previous assessment and represent increased value to the NHS.

ACD comment 20

Page 18/19 Paragraph 4.20	In the Assessment Group's base-case analysis of the subgroup of people with metastases confined to the liver, cetuximab and panitumumab produced more incremental QALYs than chemotherapy alone (0.40–0.57) and the ICERs were lower than for the full population. The ICERs for cetuximab (using the discounted price) plus chemotherapy were about £130,000 per QALY gained compared with chemotherapy alone. The ICER for panitumumab (using the confidential discounted price) plus chemotherapy was substantially above £30,000 per QALY gained compared with chemotherapy alone. NICE cannot report the exact ICERs for panitumumab because the patient access scheme is confidential.
Page 32 Paragraph 4.39	The ICERs for cetuximab and panitumumab were lower in the subgroup of people with metastases confined to the liver. The ICER for cetuximab was about £127,000 per QALY gained when it was combined with FOLFOX and £129,000 per QALY gained when combined with FOLFIRI, both compared with chemotherapy alone. The ICER for panitumumab plus FOLFOX remained substantially above £30,000 per QALY gained compared with FOLFOX. NICE cannot report the exact ICERs for panitumumab because the patient access scheme is confidential.

Merck comment:

The numbers quoted here are an inaccurate reflection of the true ICERs for the LLD patient population. This can primarily be explained by the fact that in the ERG model patients continue to get treated beyond 16 weeks, whereas in actuality patients in this group get treatment for 8-12 weeks, and up to 16 weeks, as was noted by the clinical experts. In addition, in the Assessment Groups model patients remain on treatment following surgical resection of the liver.

Applying a 16 week stopping rule in the Assessment Group's model for the liver-resection patient subgroup with the corrected administration costs and the TA176 assumptions, and resection rates of 12.5% for chemotherapy and 28% for cetuximab/chemo, reduces the ICERs from £130,000/QALY to £27,581/QALY for cetuximab/FOLFIRI and from £186,000/QALY to £30,268/QALY for cetuximab/FOLFOX. This demonstrates the importance of applying this stopping rule in the model.

ACD statement 21

Page 9 Paragraph 4.3	The Assessment Group stated that the clinical evidence was limited because it reflected subgroup analyses. The trials were analysed post-hoc after re-evaluating tumour samples from people with KRAS wild-type exon 2 tumours, and reclassifying them by RAS wild-type status as currently defined. The Assessment Group noted that there were few samples available for re-analysis and missing data further reduced the power of some studies. The Assessment Group stated that the trial populations were generally balanced with respect to baseline characteristics, which lessened confounding bias.

Merck comment:

The paragraph makes reference to the fact that the RAS wild-type data under consideration to represent the clinical evidence for both cetuximab and panitumumab are post-hoc sub-group analyses. While Merck do not contest this, it should be noted that modern science moves faster than clinical trials. Much research has been undertaken to understanding the molecular and genetic pathways that play a role in identifying those patients that are likely to benefit from anti-EGFR therapies such as cetuximab and panitumumab and to exclude those patients that do not benefit. These data were considered robust enough to have warranted amends to the marketing authorisations of both drugs in 2013 and increasing the personalisation of medicines such as cetuximab means that patients who gain no clinical benefit are not exposed to unnecessary side-effects for no treatment gain.

ACD comment 22

Page 25 Paragraph 4.29	The Committee discussed the clinical trial evidence for cetuximab and panitumumab in people with RAS wild-type metastatic colorectal cancer. It heard that the Assessment Group considered that survival data were not sufficiently mature, and that the size of the effect was confounded by the use of different second and subsequent lines of treatment across the trial arms.
Page 28 Paragraph 4.33	The Committee would have preferred to see a model based on survival data from trials, but understood that the trial data for cetuximab and panitumumab may have been confounded by second-line drugs that are not commonly used in the NHS.

Merck comment:

With regards to data maturity, PFS and OS data from CRYSTAL and OPUS are mature and no further data is expected from these studies. In addition, as science has progressed since these studies were conducted and the benefit seen when combining cetuximab with chemotherapy in this patient population is well accepted, it is unlikely that any further clinical trials would be undertaken comparing cetuximab/chemotherapy to chemotherapy alone in patients fit for triplet therapy. Therefore, funding decisions should be made on the available data.

In the CRYSTAL trial [redacted] of patients in the cetuximab/FOLFIRI group and [redacted] of patients in the FOLFIRI alone group received subsequent chemotherapy treatment in the ITT population. Of this only [redacted] in the cetuximab/FOLFIRI group and [redacted] in the FOLFIRI alone group received a subsequent anti-EGFR therapy.

As can be seen there was a low level of personalised medicine use in later lines of treatment. In the case of bevacizumab use, it is balanced between the two arms and so wouldn't be expected to cause an imbalance in the outcomes. Regarding subsequent anti-EGFR use, there was approximately three times the use in the FOLFIRI alone arm compared to the cetuximab/FOLFIRI arm which may have improved outcomes for those patients in the FOLFIRI alone group. Even with this, the benefits seen when adding cetuximab to FOLFIRI were still significantly better than the FOLFIRI alone group.

There were similar findings in the OPUS trial with [redacted] of patients receiving a subsequent anti-cancer therapy in either arm. EGFR-targeted subsequent therapies were received by [redacted] of patients in the cetuximab/FOLFOX arm and [redacted] in the FOLFOX alone arm.

ACD comment 23

Page 27 Paragraph 4.32	The Committee concluded that the clinical evidence surrounding the degree to which cetuximab and panitumumab are effective in RAS wild-type metastatic colorectal cancer was subject to considerable uncertainty.

Merck comment:

In the context of the head to head clinical trial data under consideration here (CRYSTAL, OPUS), There is an evidence base beyond that under consideration in this appraisal that suggests that cetuximab can extend median overall survival to in excess of 30 months, which is a step change to that observed across many studies that have investigated the efficacy of multiple lines of chemotherapy, where median survival durations are in the region of 20 months.

ACD comment 24

Page 35 Paragraph 4.41	The Committee recalled hearing from the clinical experts that patients in the clinical trials of cetuximab and panitumumab were younger and fitter than patients in clinical practice in England, so patients in clinical practice may not achieve the level of survival benefit estimated. The Committee considered that these estimates were not sufficiently robust.

Merck comment:

The committee expressed reservations regarding the applicability to the UK population of the clinical trial data used to support these submissions. Clinical experts discussed that in practice cetuximab is reserved for a subgroup of mCRC patients who are fit enough to tolerate triple therapy treatment and that the patients in the supportive studies were younger, had better performance status and fewer co-morbidities than the broad metastatic CRC population. Merck agrees that the patient population represented in clinical studies indeed represents a subset of the entire mCRC patient population, and that subset corresponds with those selected for cetuximab treatment in clinical practice, namely those of better performance status, who can tolerate and benefit from triple therapy. Therefore the clinical data findings should be considered relevant to UK practice.

ACD comment 25

Page 15 Paragraph 4.17	Duration of first-line treatment. The Assessment Group considered that Merck Serono underestimated the mean duration of treatments. This resulted in lower drug acquisition costs and lower ICERs than the Assessment Group's estimates. The Assessment Group noted that treatment duration was the most important issue explaining the difference between the results of the Merck Serono model and the Assessment Group's model.

Merck comment:

Duration of first line treatment. Merck provided the mean values for treatment duration from the OPUS & CRYSTAL trials, in the response to the Assessment Group report, sent to NICE on 21st September 2015, having initially used median values, which were inconsistent with a mean calculated value from the Assessment Group. Merck notes that the Assessment Group model used a mean value extrapolated from the median using an unconventional method as opposed to using the actual uncensored mean values of treatment duration reported in the clinical trial reports provided by Merck.

The panel noted uncertainty around length of treatment with cetuximab/chemo, and that the real world treatment duration estimated by experts was far shorter, around 6 months, than that modelled by the ERG, which was 10.7 months for cetuximab/FOLFIRI and 14.4 months for cetuximab/FOLFOX. Merck has analysed real world data from [redacted] that have completed 1st line treatment with cetuximab plus either FOLFIRI or FOLFOX between 2012 & 2015, and the mean treatment duration in the real world was [redacted] (Appendix 5), which supports clinical expert estimate. This data is based on chart reviews conducted through market research for the period between March 2013 to October 2015 corresponds to approximately [redacted] of the CDF applications in this period and therefore can be considered to be a more accurate reflection of cetuximab treatment duration in the UK.

As outlined, real world cetuximab/chemotherapy treatment durations are around [redacted], whereas treatment duration with chemotherapy alone is estimated to be approximately [redacted] for FOLFIRI and slightly shorter for FOLFOX due to neuropathy at [redacted] based on expert clinical opinion.

ACD comment 26

Page 24 Paragraph 4.28	The Committee understood that, in clinical trials, first-line cetuximab or panitumumab is given until disease progression. But, it heard from clinical experts that clinical practice in the UK includes treatment holidays and so patients are not treated continuously until disease progression. The Committee concluded that treatment duration with cetuximab or panitumumab in clinical trials may not reflect clinical practice in England.

Merck comment:

Merck would like to reinforce the comments made by the clinical experts. The understanding should be that the intention in clinical trials is that treatment with either cetuximab in combination with chemotherapy would be continued until disease progression. In reality, the CRYSTAL, OPUS & FIRE-3 trials that used cetuximab in combination with either FOLFIRI or FOLFOX, the mean treatment duration was significantly shorter than the progression free survival that was observed. This is can occur due to many reasons, including of the side of effects of combination treatment and the desire of patients to have breaks from treatment. Patients in clinical trials are also more likely to have longer treatment due to wider support available while in the study.

ACD comment 27

Page 24 Paragraph 4.28	The Committee understood that, in clinical trials, first-line cetuximab or panitumumab is given until disease progression. But, it heard from clinical experts that clinical practice in the UK includes treatment holidays and so patients are not treated continuously until disease progression. The Committee concluded that treatment duration with cetuximab or panitumumab in clinical trials may not reflect clinical practice in England.
Page 29 Paragraph 4.35	The Committee noted that the estimates of the duration of first-line treatment differed in the models from Merck Serono and the Assessment Group. It understood from clinical experts that, in England, first-line treatment does not continue uninterrupted until disease progression.
Page 29 Paragraph 4.35	The Committee concluded that the Assessment Group's estimates of treatment duration may not reflect clinical practice, and would have preferred to see the model validated with observational data.

Merck comment:

In developing its model the Assessment Group utilised modelled estimates of mean treatment durations for cetuximab in combination with FOLFOX or FOLFIRI using exponential extrapolation of the median treatment durations report in the clinical trials rather than using actual mean treatment durations from studies or real world data.

The panel noted uncertainty around length of treatment with cetuximab/chemo, and that the real world treatment duration estimated by experts was far shorter, around 6 months, than that modelled by the ERG, which was 10.7 months for cetuximab/FOLFIRI and 14.4 months for cetuximab/FOLFOX. These figures were based on a flawed and unconventional extrapolation of median treatment periods as reported in the respective clinical trials. As there is no evidence to support these overestimated treatment lengths, and in response to the Appraisal Committee's recommendation for investigating real-world treatment length in England, Merck has analysed real world data from [redacted] that have completed 1st line treatment with cetuximab plus either FOLFIRI or FOLFOX between 2012 & 2015, and the mean treatment duration in the real world was [redacted] (Appendix 5), which supports clinical expert estimate. This data is based on chart reviews conducted through market research for the period between March 2013 to October 2015 corresponds to approximately [redacted] of the CDF applications in this period and therefore can be considered to be a more accurate reflection of cetuximab treatment duration in the UK.

As outlined, real world cetuximab/chemotherapy treatment durations are around [redacted], whereas treatment duration with chemotherapy alone is estimated to be approximately [redacted] for FOLFIRI and [redacted] for FOLFOX based on expert clinical opinion. Merck has supplied both the real world data and the actual mean clinical trial treatment durations.

ACD comment 28

Page 18 Paragraph 4.19	In the Assessment Group's base-case analysis of all patients, both cetuximab plus chemotherapy and panitumumab plus chemotherapy generated more QALYs than for chemotherapy alone: 0.15–0.35 more QALYs compared with FOLFOX and 0.30 QALYs compared with FOLFIRI. However, the additional costs using list prices were substantial: up to about £69,000 for cetuximab or panitumumab compared with FOLFOX or FOLFIRI. When the Assessment Group used the list prices for panitumumab and cetuximab, the ICERs compared with chemotherapy alone were £239,007 per QALY gained for panitumumab plus FOLFOX, £165,491 per QALY gained for cetuximab plus FOLFOX, and £227,381 per QALY gained for cetuximab plus FOLFIRI. When the Assessment Group used the discounted price for panitumumab (discount commercial in confidence), the ICER was substantially above £30,000 per QALY gained compared with FOLFOX. When the Assessment Group used the discounted price for cetuximab, the ICERs were about £135,000 per QALY gained for cetuximab plus FOLFOX and £183,000 per QALY gained for cetuximab plus FOLFIRI, both compared with chemotherapy alone.
Page 32 Paragraph 4.39	In the overall population, the ICER for cetuximab was about £135,000 per QALY gained when it was combined with FOLFOX and £183,000 per QALY gained when combined with FOLFIRI, both compared with chemotherapy alone. The Committee noted that the ICER for panitumumab plus FOLFOX was also substantially above £30,000 per QALY gained compared with FOLFOX.

Merck comment:

The statements above show the impact of price discounts on ICERs as estimated by the Assessment Group. Given that Merck offered a substantial PAS to the value of 35.6% off cetuximab list price, the ICERs based on the PAS discount highlight the fact that cetuximab would not be cost-effective even at zero price, which shows the flaws in the methodology applied in this assessment, and that the price is not the main driver for cost effectiveness in this case. The main driver, as identified by both Merck and the Assessment group, is the length of treatment in the first line setting and the associated cost of NHS provision of healthcare. Therefore, the current methodology penalises cetuximab-chemotherapy for extending patients' survival compared to chemotherapy alone.

ACD comment 29

Page 20

Table 3

	CET+FOLFOX compared with FOLFOX	CET+FOLFIRI compared with FOLFIRI	PAN+FOLFOX compared with FOLFOX
Short life expectancy, normally <24 months	Months, mean: 22.3 (AG model) 26.7 (PRIME)	Months, mean: 21.0 (AG model) 24.9 (CRYSTAL)	Months, mean: 22.3 (AG model) 26.7 (PRIME)
Extension to life, normally ≥3 months	Months, mean: 6.6 (AG model) 0.5 (OPUS)	Months, mean: 5.5 (AG model) 8.8 (CRYSTAL)	Months, mean: 2.6 (AG model) 5.7 (PRIME)
Licensed for <7000 people in England (all indications)	• 8,807 (data in TA176, incl other indications and updated to reflect RAS wt subgroup) • 7,567 (Merck Serono data, updated to reflect England only and incl all indications) • 11,349 (data cited in assessment report)	• 5,968 (data in TA176, updated to reflect RAS wt subgroup) • 4,728 (Merck Serono data, updated to England only) • 8,511 (data cited in assessment report)	
Note that the indications for cetuximab and panitumumab differ; cetuximab is also approved for treating squamous cell cancer of the head and neck. Abbreviations: AG, Assessment Group; CET, cetuximab; FOLFIRI, folinic acid+fluorouracil+irinotecan; FOLFOX, folinic acid+fluorouracil+oxaliplatin; incl, including; PAN, panitumumab; TA, NICE technology appraisal guidance; wt, wild-type.			

Merck comment:

The table above shows that cetuximab has met 2 of the 3 criteria of end of life conditions for the broad mCRC population. The third criteria refers to the number of patients that are eligible for cetuximab in all indications.

In relation to the size of the population for all licensed indications in England, we noted that NICE differentiated between cetuximab and panitumumab based on the indications under the license. We believe that to achieve a fair comparison between the two medicines, both should be treated on equal grounds and assessed in accordance with the size of the colorectal cancer population for balanced evaluation. Therefore Merck contends that head and neck cancer patients should not be included in this evaluation, for the reason outlined above. This is an unusual situation as the products in question do not share same licensed indications and therefore we ask the committee to take this into account when considering this criteria, particularly given that both agents have been studied in the H&N setting with cetuximab showing benefit in this setting and panitumumab failing to show benefit.

Merck's understanding of the EOL criteria is that they were instated to determine the maximum number of patients that could possibly be treated with a new medicine. Cetuximab received marketing authorisation in 2004 and therefore its estimated usage can be determined with some certainty.

- In mCRC cetuximab has been subject to 4302 CDF applications for mCRC in **all lines** (1st, 2nd and subsequent lines) of therapy, in the 30 month period between March 2013 and Sept 2015.

- For first line mCRC in combination with either FOLFOX or FOLFIRI, there were approximately 600 patients treated with cetuximab for the period of Sept 2014 to Sept 2015 on the CDF.

In SCCHN, NICE TA145 NICE restricted the funded population to only those locally advanced SCCHN patients with a Karnofsky score of above 90 in whom all forms of platinum based chemotherapy were contraindicated or not tolerated. The number of patients with locally advanced (LA) SCCHN eligible for cetuximab treatment was estimated in TA145 to be 8% of the total SCCHN population. The committee were of the opinion that there are 3,000 SCCHN patients in England, therefore this equates to 240 patients (3,000 x 8%). NICE TA 172 did not recommend the use of cetuximab for SCCHN patients with recurrent or metastatic disease (RM). Cetuximab is currently available for RM SCCHN patients via the CDF and for the period of Sept 2014 to Sept 2015, there were around 150 applications in this setting. Therefore, in total it is estimated that approximately 400 patients get treated with cetuximab in England for SCCHN in both the LA and RM settings annually.

If this number is added to the 5,968 RAS wild type mCRC patients in England (data in TA176, updated to reflect RAS wild type subgroup), the total remains below the 7,000 limit stipulated by the end-of-life criteria. And as outlined above, only around 4,300 patients were treated with cetuximab over the period of 2.5 years (2013-2015) when cetuximab was available on the CDF in ALL lines, with approximately 600 patients treated in the first line annually, therefore it can be stated with certainty that the number of patients that would be treated with cetuximab for 1st line mCRC even combined with those treated under NICE for SCCHN would never reach 7,000. Based on real world usage, for both mCRC and SCCHN, approximately 1,000 patients would be treated annually.

Cetuximab is well established in the UK, it has been available since 2011 and so has been used in clinical practice for a long period of time, and it is unlikely that treatment patterns would now change.

Merck would also urge the commitee to consider the recent publication of the newly launched NICE/NHSE CDF consultation that proposes a change to the EOL criteria in the Guide to the Methods of Technology Appraisal 2013 that removes the requirement for the size of the eligible population to be less than 7,000 in England. If this proposal is accepted through the consultation, this change is planned to be effective from 1st April 2016. Therefore, this would then mean that when the Final Guidance for this MTA is published, cetuximab will meet the EOL criteria and qualify for the higher threshold.

References

1. Cancer Research UK – 2nd biggest cancer killer. http://www.cancerresearchuk.org/health-professional/cancer-statistics/mortality/common-cancers-compared#heading-Zero
2. ONS Cancer Survival in England: adults diagnosed in 2009 to 2013, followed up to 2014. http://www.ons.gov.uk/ons/rel/cancer-unit/cancer-survival/cancer-survival-in-england--adults-diagnosed--2009-to-2013--followed-up-to-2014/stb-cancer-survival.html
3. NCIN Cancer Statistics for England. http://www.ncin.org.uk/publications/data_briefings/colorectal_cancer_survival_by_stage
4. Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang X-S, et al. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). The Lancet. 2015;385:977–1010.
5. Walters S, Benitez-Majano S, Muller P, Coleman MP, Allemani C, Butler J, et al. Is England closing the international gap in cancer survival? British Journal of Cancer. 2015;113(5):848-60.
6. National Comprehensive Cancer Network Guidelines: Colon Cancer. Available at http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf
7. European Society for Medical Oncology. Metastatic Colorectal Cancer: ESMO Clinical Practice Guidelines. http://www.esmo.org/Guidelines/Gastrointestinal-Cancers/Metastatic-Colorectal-Cancer
8. NICE TA242 (2012): Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy: 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. https://www.nice.org.uk/guidance/ta242
9. National Cancer Drugs Fund List, Ver6.0. https://www.england.nhs.uk/wp-content/uploads/2015/11/ncdf-list-nov-15.pdf
10. Cheng A-L, Cornelio GH, Shen L, et al. Final analysis of the phase 2 APEC study: Overall survival (OS) data and biomarker subanalyses for first-line FOLFOX or FOLFIRI with cetuximab (cet) once every 2 weeks in patients (pts) with KRAS or RAS (KRAS and NRAS, exons 2-4) wild-type (wt) metastatic colorectal cancer (mCRC). Journal of Clinical Oncology, 2015; Gastrointestinal Cancers Symposium, 33(3): 566.
11. Hubbard JM and Alberts SR. Alternate dosing of cetuximab for patients with metastatic colorectal cancer. Gastrointest Cancer Res. 2013; 6(2): 47-55.
12. Brodowicz T et al. FOLFOX4 plus cetuximab administered weekly or every two weeks in first-line treatment of patients with KRAS and NRAS wild-type (wt) metastatic colorectal cancer (mCRC). Abstract No: LBA391. Citation: J Clin Oncol 32, 2014 (suppl 3; abstr LBA391^)
13. Folprecht G, Gruenberger T, Bechstein WO, et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. Lancet Oncol. 2010; 11(1): 38-47.
14. Stintzing et al. Independent radiological evaluation of objective response, early tumor shrinkage, and depth of response in FIRE-3 (AIO KRK-0306) in the final RAS evaluable population. Oral Presentation and abstract LBA11, 2014 ESMO Congress.
15. Lenz H-J, et al. Oral Presentation and abstract 5010, ESMO 2014
16. Consultation on proposals for a new Cancer Drugs Fund (CDF) operating model from 1st April 2016. https://www.engage.england.nhs.uk/consultation/cdf-consultation/supporting_documents/cdfconsultationdoc.pdf
17. Ye *et al.* Randomized Controlled Trial of Cetuximab Plus Chemotherapy for Patients With KRAS Wild-Type Unresectable Colorectal Liver-Limited Metastases. JCO 2013. 31(18): 1931-1939.
18. Malik *et al.* Liver resection rate following downsizing chemotherapy with cetuximab in metastatic colorectal cancer: UK retrospective observational study. EJSO 41 (2015) 499-505

19. British Columbia Guidelines: Use of Cetuximab. http://www.bccancer.bc.ca/health-professionals/professional-resources/cancer-drug-manual/drug-index#c-content

Appendices

Appendix 1 – Treatment administration costs

Appendix 2 – Letter from Reference Costs Team, Department of Health

Appendix 3– Post-study anti-cancer treatments in CRYSTAL and OPUS studies

Appendix 4 – Clinical trial mean treatment durations in first line setting from CRYSTAL and OPUS studies

Appendix 5 – Real-world length of treatment in the first line setting in the United Kingdom

Appendix 1: Treatment Administration costs

The following tables explain the differences between administration costs estimates between Merck and the Assessment groups and highlight the errors in the Assessment group's method of calculation:

The Assessment Group have overestimated the cost of administration (£4,714 for Cetuximab+FOLFOX-4 and £4,000 for cetuximab+FOLFIRI) because they have unnecessarily duplicated HRG costs and added extra costs that should be fully absorbed by the HRG.

Since clinical expert advised that FOLFOX-6 is the used clinical practice instead of FOLFOX-4, the cost of FOLFOX-6 has been estimated in this document. Both Merck and the Assessment Group agree that the administration cost of FOLFOX-6 is equal to the cost of FOLFIRI as evident in their economic models and reports.

Table 1. Merck and PenTAG reference costs (based on <u>weekly</u> cetuximab administration)

	Merck		**PENTAG**			
Cost element	**Day 1**	**Day 8**	**Day 1**		**Day 8**	
	Cet + FOLFIRI or FOLFOX-6	Cetuximab only	Cetuximab	FOLFIRI or FOLFOX-6	Cetuximab	FOLFIRI or FOLFOX-6
6. HRG	£383	£302.58	**<u>£302.58</u>**	£383	£302.58	£0
7. Extra Nurse time	£8.8	£0 – absorbed by HRG	£8.8		£8.8	
8. Pharmacy cost	£0 – absorbed by HRG	£0 – absorbed by HRG	£246		£246	
9. Line maintenance	£0 – absorbed by HRG	£0 – absorbed by HRG	£133		£133	
10. Infusion pump	£0 – absorbed by HRG	£0 – absorbed by HRG	£41		£41	
Total per visit	£392	£302.6	£1,114.6		£731.5	
Total per cycle (days 1+ 8)	£694		£1,846			
Total per month (2.17 cycles)	**£1,505**		**£4,000**			

It is clear from this table that the Assessment Group added the administration cost of cetuximab on day 8 (£302.58) in error to the administration cost of day 1 of each cycle; there were two day 8 administration costs present in both day 1 and day 8 when it should only apply to day 8. In addition, the Assessment group applied the additional costs of pharmacy, line maintenance and infusion pump equally between day 1 (cetuximab + FOLFOX) and day 8 (single cetuximab infusion) when these costs should be fully absorbed by the HRG, as NHS Reference Costs have confirmed in the accompanied letter.

Table 2 also illustrates the significant difference between the Assessment Groups estimation of administration costs and Merck's estimation when considering fortnightly administration of cetuximab as practiced in the UK. The Assessment Group estimated nearly double the administration cost as Merck due to the addition of costs that are fully absorbed by the HRG as advised by the NHS Reference Costs team.

Table 2. Merck and PenTAG reference costs (based on <u>fortnightly</u> cetuximab administration)

	Merck	**PENTAG**
Cost element	Cet + FOLFIRI or FOLFOX-6	Cet + FOLFIRI or FOLFOX-6
11. HRG	£383	£383
12. Extra Nurse time	£8.8	£8.8
13. Pharmacy cost	£0 – absorbed by HRG	£246
14. Line maintenance	£0 – absorbed by HRG	£133
15. Infusion pump	£0 – absorbed by HRG	£41
Cost per cycle	£392	£812
Total per month (2.17 cycles)	**£849**	**1,759**

Appendix 2: Letter from Reference Costs Team, Department of Health

Department of Health

Reference costs team
Department of Health,
Quarry House,
Leeds, LS2 7UE

www.dh.gov.uk

Ahmed Hnoosh
Health Economist, Merck,
Brentford Cross Stanwell Road
Feltham, Middlesex TW14 8NX

27 November 2015

Dear Ahmed

[Reference]

Thank for your recent enquiry regarding the method for estimating the cost of chemotherapy administration.

'In Table 10 (p41) of the Department of Health Reference costs guidance 2013-14, the cost of "Deliver complex chemotherapy, including prolonged infusional treatment" was defined as "Overall time of 60 minutes nurse time and over two hours chair time for the delivery of a complete cycle.". Does this cost cover any of the following costs:

- Pharmacy preparation costs for chemotherapy injections/infusions
- Cost of infusion pumps
- Cost of infusion line maintenance'

I can confirm all costs reported against a currency (healthcare resource groups (HRG's) mental health clusters) are fully absorbed costs. Therefore HRG SB14Z - Deliver complex chemotherapy, including prolonged infusional treatment" and SB13Z - Deliver more complex Parenteral Chemotherapy at first attendance would include

- Pharmacy preparation costs for chemotherapy injections/infusions
- Cost of infusion pumps
- Cost of infusion line maintenance
- Acquisition cost of chemotherapy agents except high cost drugs
- Any overhead costs.

Kind Regards
Nisha Mistry
Reference Costs Collection Manager
Nisha.Mistry@dh.gsi.gov.uk

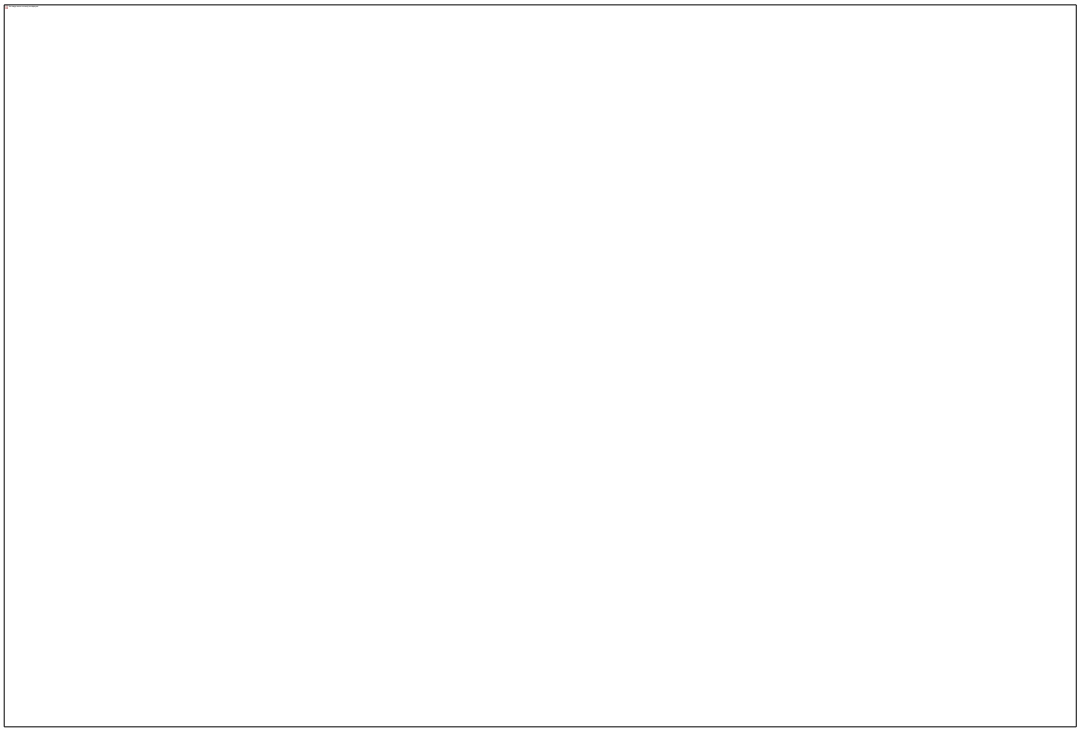
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

	W1 March 2013			W2 Oct 2013			W3 March 2014			W4 Oct 2014			W5 March 2015			W6 October 2015		
	1st line (30)	2nd line (49)	3rd line (23)	1st line (28)	2nd line (33)	3rd line (24)	1st line (56)	2nd line (14*)	3rd line (29)	1st line (44)	2nd line (18)	3rd line (35)	1st line (68)	2nd line (19)	3rd line (16)	1st line (37)	2nd line (27)	3rd line (22)
Mean	17	26	24	17	21	23	27	26	22	27	17	20	23	19	13	27	19	25
Median	15	26	22	13	17	17	22	24	26	25	17	21	22	17	13	26	17	26
Range	3-47	8-95	4-82	1-65	4-69	4-86	4-122	8-43	9-43	4-73	2-30	4-103	< 1 month -57	9-43	<1 month -22	4-65	4-39	4-48

[redacted]

[redacted]

[redacted]

[redacted]

Response to NICE Appraisal Consultation Document assessing cetuximab and panitumumab for the first line treatment of colorectal cancer

About Beating Bowel Cancer
Beating Bowel Cancer is the support and campaigning charity for everyone affected by bowel cancer. We provide practical and emotional support for the growing number of people affected by bowel cancer. We bring people with bowel cancer together to share experiences and create a powerful voice for change. We promote early diagnosis of bowel cancer, and campaign for the highest quality treatment and care for bowel cancer patients.

Our response

We would firstly like to thank NICE for giving us the opportunity to respond to its Appraisal Consultation Document (ACD) on cetuximab and panitumumab for the first line treatment of colorectal cancer. In particular we thank the Committee for its recognition that cetuximab and panitumumab "appear be more effective for treating tumours without mutations (known as 'wild-type')"

However, we are disappointed by the Appraisal Committee's decision not recommend the use of cetuximab and panitumumab on the NHS; a decision we feel will compromise doctors' ability to provide the best international standards of care for advanced bowel cancer patients in England and will cruelly deny hundreds of eligible people with advanced bowel cancer the chance of spending valuable extra time with the loved ones

We believe it to be misguided and in our opinion brings into question the methodology used to assess targeted, end of life treatment in patients with advanced cancer. As a charity supporting patients we are acutely aware of the impact that this negative decision will have on the lives of the patients and families we support. A final negative NICE appraisal will have an impact on the psychological state of patients and their families; as there will be no options available to them at a very advanced stage.

We are gravely concerned for the future of patients with advanced bowel cancer and also for the doctors that treat them. The interaction between doctor and patient will be compromised by being unable to offer all the drugs which are standard elsewhere in the Europe, and enabling patients to participate in international trials which mandate the use of these agents.

The ability of NICE to give a positive assessment would have been seen as a test case for how a new, more flexible NICE methodology could work for cancer drugs, in particular flexibility around the assessment of End of Life drugs and their affordability to the NHS. While recognising their clinical effectiveness, the Committee concluded that even if they were provided for free they would still not be cost-effective, as the methodology used takes into account all the associated treatment costs, including the partner chemo regimens and hospital expenses.

Beating Bowel Cancer
Harlequin House | 7 High Street | Teddington | TW11 8EE | Main Tel 08450 719 300 | Nurse Advisor 08450 719 301 info@beatingbowelcancer.org | beatingbowelcancer.org
Registered Charity Nos. 1063614 (England & Wales) SCO43340 (Scotland) | Registered Company Number 3377182

We run the risk of treatment for advanced bowel cancer in this country going backwards with patients diagnosed in 2016 facing worse care than patient diagnosed in 2015

The decision means that both drugs will now only be available to NHS patients in England via the Cancer Drugs Fund, but this comes to an end in March next year, after which patients with metastatic bowel cancer will no longer be able to access a personalised therapy in the country.

With the uncertainty around the Cancer Drugs Fund, we need NICE to reconsider its decision not to approve these drugs before the UK slips behind the rest of Europe and the world. Otherwise, we will be back to square one, with thousands of patients not getting the drugs they need and deserve—drugs which over the past four years have been proved to make an immense difference to patients' and their families' and friends' lives.

In closing, as a patient-focused charities we are committed to doing all we can to make the drug available to people on the NHS in England. NICE must also continue to talk with the manufacturers Merck and Amgen work towards finding a solution urgently to ensure the future of advanced bowel treatments does not grind to a halt. We need to find a solution now before bowel cancer patients start having their lives cut short.

Appendix 1

Feedback on NICE ACD for cetuximab and panitumumab for the first line treatment of colorectal cancer

Has all of the relevant evidence been taken into account?
No.

We are concerned that appraisal committee has adopted an overcautious attitude towards uncertainty. The treatments have contributed significantly to improving outcomes and increasing Quality of Life for patients with advanced bowel cancer. There is clear evidence, through the Cancer Drugs Fund / SACT data that survival depends on receiving as many drugs as possible during the patient 'journey', with each new treatment adding incremental gains. Survival rates for advanced bowel cancer were a median of only 8 months 20 years ago. The most recent trials reveal median survival for patients with RAS wild type tumours to be in excess of 30 months[i]– a striking improvement in a relatively short period of time. Adding almost 2 years to median survival (with 50% of patients living longer than 30 months) is of enormous clinical impact and of great benefit to patients and their family.

1 European Journal of Cancer July 2015Volume 51, Issue 10, Pages 1243–1252 FOLFOX4 plus cetuximab treatment and RAS mutations in colorectal cancer C. Bokemeyer C.-H. Köhne F. Ciardiello H.-J. Lenz V. Heinemann U. Klinkhardt F. Beier K. Duecker J.H. van Krieken S. Tejpar

We would urge the Committee to reconsider the full patient expert testimony it heard directly from Ben Ashworth, 36, a terminally-ill father of three from Preston. In its consideration of the evidence we feel the committee has not taken fully into account the full extent of the benefits for patients and their families in terms of extension of life. In the document it states that *"the key benefit of cetuximab treatment was that the adverse reactions (such as skin reactions) were much more manageable than the adverse reactions they had previously experienced with chemotherapy alone (including debilitating fatigue and neuropathy."* The adverse effects of the treatment were the least relevant.

We believe that this vastly understates the real value of this treatment delivered to Ben and his family. In 2013 Ben who was given a terminal prognosis and life expectancy of just 6-12 months. The most important outcome of his treatment has been the precious extra time that he has been able to have with his family, watching his young daughters grow up. Also, Ben explained the vast improvement in his quality of life, which has seen him leading a very active. To help cope with his chemotherapy Ben embarked on a mission to run a marathon a month. To date he has participated in over 16 marathons despite the fact that he is currently in active treatment.

I would also bring the Committee's attention to a second patient who also submitted written evidence of his experience of receiving cetuximab as a first line treatment for bowel cancer. Barry Murphy, aged 70 was diagnosed in 2012 when his bowel cancer had spread to his liver. Barry was put on a FOLFOX in combination with cetuximab. Surgery and folfox/cetuximab delivered the best results giving him a complete year without symptoms or further treatment.

Barry said: *"I am very grateful that my first line treatment included Cetuximab. Because of that I believe my prospects for beating the disease were greatly improved and my confidence in the team treating me and the NHS in general was firmly strengthened."*

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The Assessment Group noted that treatment duration was the most important issue explaining the difference between the results of the Merck model and the Assessment Groups model. The mean

time on 1st-line drug treatment is extremely important because it affects the total mean cost of drug acquisition and administration per person. Differences in assumptions for duration of treatment will add knock on costs, which in turn will push up the cost per QALY (ICER) further beyond the NICE threshold.

In the current appraisal, treatment duration ranged from 38– 46 weeks in the Assessment Group's model and 25 weeks in the Merck model, which the Committee had concluded were overestimates.

Clinical experts who gave evidence to the Committee advised that Merck's estimates of treatment duration better reflected clinical practice in England than the Assessment Group's. Our Medical Advisory Board has advised us that clinical practice is 24-30 weeks at most. This shorter duration will impact greatly on the cost of ongoing treatment.

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
No

We feel this decision is particularly short-sighted given the fact that bowel cancer is the UK's second biggest cancer killer and the fourth most common cancer. Almost 16,000[ii] people die each year in the UK – a life every 32 minutes. A higher number of bowel cancers are diagnosed at a more advanced stage in England, compared to other countries. Patients with advanced bowel cancer have among the worst survival rates, with only 7% surviving more than 5 years.

These represent two of the few treatments options left for advanced bowel cancer, which have been the standard of care for ten years or more. This decision will mean that patients with advanced bowel cancer will be offered nothing other than standard treatments. Recently bowel cancer doctors came together to warn of a return the "dark ages" cancer treatment. We cannot go back to a time of the original postcode lottery when patients in England were denied medicines that are routinely available in other parts of the UK and Europe and where patients diagnosed with advanced bowel cancer in 2016 will receive a worse standard of care than those diagnosed in 2014.

We feel that this would be unfair.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?

No

Are there any equality -related issues that need special consideration and are not covered in the appraisal consultation document?

The NHS Constitution makes it clear that a core duty of the NHS is to promote equality. As leading bowel cancer charities supporting patients we have long campaigned to allow greater access to drugs where there is clear, clinical evidence that a patient would benefit. Although the clinical evidence for the use of these treatments is clear, not all patients will be able to access the treatments that their clinicians wish to prescribe if this appraisal received a final negative recommendation, resulting in a widening disparity in accessing cancer drugs for patients across the UK.

We are concerned that the UK, including Scotland, still lags behind Europe in terms of survival and access to medicines[iii]. The resulting final guidance from this ongoing appraisal will supersede any previous positive NICE guidance in first-line which means that there will be no targeted treatment options available in England and Wales. Also, importantly, given that this is a MTA it is highly likely that it will apply in Scotland and supersede the current (restricted) positive guidance for cetuximab

for first-line in Scotland. There is a real risk that there will be no targeted treatments available in England, Wales and Scotland.

Most of these drugs are already licensed for use in the UK and we run the risk that future access will mean they will only be obtained only through private health care. This will result in patients facing a two-tier health system. While some cancer patients may be able to afford these drugs, others will not. This raises the prospect of inequality in health care which many people will see as cruel and would damage the long-term confidence in the NHS.

In terms of achieving age equality we would question how NICE deals with age when making decisions about which treatments to fund at the end of life. NICE use of the QALY in assessing overall relative cost effectiveness of treatments that are mainly for older people means that there is an inequality in treatment of individuals with cancer which is predominantly a disease of older age

Bowel cancer mortality is strongly related to age, with the highest mortality rates being in older men and women. In the UK between 2010 and 2012, an average of 57% of bowel cancer deaths were in men and women, aged 75 years and over. England and Wales have the worst five-year survival rates for cancer in Europe among the over 75s[iv]. We want to make sure older people are offered cancer treatment based on their needs, not on their age. Regardless of age, everyone should get the treatment that's right for them.

December 2015

[i] European Journal of Cancer July 2015Volume 51, Issue 10, Pages 1243–1252 FOLFOX4 plus cetuximab treatment and RAS mutations in colorectal cancer C. Bokemeyer C.-H. Köhne F. Ciardiello H.-J. Lenz V. Heinemann U. Klinkhardt F. Beier K. Duecker J.H. van Krieken S. Tejpar

[ii] Key Facts about bowel cancer. Cancer Research UK CancerStats:

[iii] Department of Health, *Extent and causes of international variations in drug usage: a report for the Secretary of State for Health by Professor Sir Mike Richards CBE*, July 2012

[iv] Bowel cancer mortality statistics provided by Cancer Research UK

Royal College of Physicians
11 St Andrews Place
Regent's Park
London NW1 4LE
Tel: +44 (0)20 3075 1560

www.rcplondon.ac.uk

From The Registrar
[redacted]

National Institute for Health and Care Excellence
10 Spring Gardens
London
SW1A 2BU
TACommB@nice.org.uk

7 December 2015

Dear Mr Powell

Re: ACD - Consultees & Commentators: (Colorectal cancer (metastatic) - cetuximab (review TA176) and panitumumab (part review TA240) (1st line)) [794]

The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 31,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

I write on behalf of the NCRI/RCP/RCR/ACP who wish to jointly respond to the above consultation. We are grateful for the opportunity to submit the following comments:

1. Factual corrections

We believe that both clinical experts stated that FOLFOX 4 is a more expensive regimen than FOLFOX6, due to the need for attendance for a bolus dose of 5FU on day 2 in FOLFOX4, but this appears to have been transcribed incorrectly in the ACD.

Secondly, on page 23, the report states that patients who develop disease progression following liver resection may be offered further surgery followed by chemotherapy. The majority of patients in this situation are likely to progress with inoperable and incurable disease and so proceed straight to palliative chemotherapy.

2. Concern over the generalisability of the trial data to the English metastatic colorectal cancer population.

In the CRYSTAL and PRIME trials the median age of patients was 60 and 62 and over 90% were of performance status 0-1. In routine clinical practice within the NHS our patients with metastatic colorectal cancer are older and often of poorer performance status. However, due to the potential toxicity of the combination of a biological agent in addition to chemotherapy the vast majority of patients offered this treatment option will be of a performance status of 0-1, so will more closely reflect the population recruited within the clinical trials.

These decisions are based on the patient's performance status and symptoms, the extent of disease and the patient's wishes including their potential tolerance of specific toxicities and the importance to them of prolonged progression-free and overall survival. Published SACT data from January 2014 to December 2014 show that only 278 first cycles of FOLFIRI plus cetuximab were given, with a total number of 2224 cycles given. Although the data is not complete, the majority of NHS Trusts were submitting data at this point.

3. Robustness of trial data

The management of colorectal cancer has remained the same for many years, with little improvement in outcomes for patients with widespread metastatic disease. The introduction of the biological agents, in particular the anti-EGFR antibodies, has transformed the management of some of these patients with rapid improvement of symptoms and both statistically and clinically significant improvements in survival. The colorectal oncology community believe the robustness of the trial data and in particular the overall survival data from CRYSTAL and PRIME in the relevant biomarker-selected subgroups.

In 2004 Tournigand et al published a trial in which patients were randomised to receive FOLFIRI followed by FOLFOX on disease progression, or FOLFOX followed by FOLFIRI. The overall survival in this study was 21.5 months compared to 20.6 months. These survival figures are almost identical (in the RAS wild type population) to the chemotherapy only arm in the CRYSTAL study (20.2 months) and the PRIME trial (19.7 months). We feel that the concerns raised over the effect of subsequent treatments (that are not funded by the NHS after NICE approval or through the Cancer Drugs Fund) on overall survival should be considered as minimal. Over a 10 year period the addition of cetuximab and panitumumab has been the only major advance in the first line treatment of colorectal cancer.

4. End of life criteria

We believe that panitumumab and cetuximab should fall within the end of life criteria. The committee agreed that for both drugs the only field that fell outside the set criteria was the number of patients who would be eligible for treatment.

The PenTag model suggest that 95% of the population of England, Wales and Scotland live within England, Merck suggests this figure is 84% and our calculations based on mid 2014 population data suggests this is 87%, so altering the calculations on the model.

The end of life criteria states the treatment is licensed or otherwise indicated for small patient populations and will take into account the cumulative population for each licensed indication. It seems extraordinary that the patient population with head and neck cancers are included within this current calculation, as the indication for the use of cetuximab in this population is either with radiotherapy in locally advanced disease or in combination with platinum based chemotherapy in metastatic disease and therefore should be considered distinct from the indication in the metastatic colorectal cancer population.

5. Methodological issues

The conflation (described in the section above) of the use of the targeted agents under review in entirely separate cancers, in this case in a much more co-morbid population, and with different combination of systemic therapies and/or radiotherapy is incomprehensible to our patients and to the clinical community. The use of survival statistics (eg mean overall survival) which are never used by clinicians and the use of modelled data (eg mean overall survival modelled from mean progression-free survival abstracted from trial data) rather than actual data is also inappropriate in our view.

We believe that these methodological flaws significantly undermine the validity of the NICE process as regards the use of these drugs in the view of both patients and clinicians.

Our experts believe that the addition of the anti-EGFR antibodies to chemotherapy has made a significant advance in the treatment of metastatic colorectal cancer, for a relatively small group of patients selected based on their performance status and extent of disease. The SACT data demonstrates that use of cetuximab with FOLFIRI has been modest.

Our experts have concerns over many of the assumptions made by PenTAG in their modelling and feel that both cetuximab and panitumumab should meet end of life criteria if the head and neck indication is excluded and the correct population of England used.

Overall, our experts believe that if the ACD is upheld, patients with metastatic colorectal cancer will return to limited options of treatment. This will not only have an impact on outcomes but will also severely affect the ability of patients in England to have access to international studies of new treatments; which will expect the use of anti-EGFR antibodies in previous lines of treatment. This would clearly have a detrimental effect on patients, clinicians and the national targets set for trial recruitment. Our experts note that these agents are deeply embedded into the guidelines for the management of metastatic colorectal cancer written by the American Society of Clinical Oncology and the European Society of Medical Oncology, after due consideration of the published data. The UK will therefore be alone amongst the developed world, if this ACD is upheld.

Yours sincerely

[redacted]

Firstly, I would again like to thank you for inviting me as one of the clinical experts during the NICE appraisal for use of anti-EGFR agents in colorectal cancer on the 15th October 2015.

I note with huge regret that NICE is minded to decline the funding for cetuximab & panitumumab for stage IV colorectal cancer. I think this is a hugely retrograde step that the NHS will take in the management of one of the most common cancers in the country. The omission of these targeted drugs will take back management of this condition by more than a decade. This decision appears to have been taken despite the consistent overall survival that has been demonstrated in multiple clinical trials. There are other trials such as FIRE3 which understandably could not be considered as they did not contain a non-antibody arm in the trial design; nevertheless have shown significant clinically and statistically relevant improvement in overall survival.

These are ubiquitously considered as standard drugs in management of this cancer in the Ras wild type population. Clinical trial participation in experimental trials is likely to be jeopardised if our patients have not received all standard therapies possible and anti-EGFR is certainly recognised worldwide as being an essential class of drugs in Ras wild type CRC patients.

There are certain comments/reservations I would like to point out in the document and which you may wish to consider. I appreciate they may well not make a huge difference in the economic models but nevertheless feel strongly enough to highlight them below.

2.1 5 year survival is under 60%. Should read under 5-10%

4.14 Assessment Group are reluctant to use overall survival endpoints from clinical trials ostensibly in light of perceived use of second line dugs not commonly used in the NHS. This has been mentioned a few times in the document. I am not entirely sure or clear of the robustness of this assumption. Overall survival has to be considered the gold standard in clinical trials and has to be rated above other end points. The arms actually were quite balanced in my opinion in the well conducted trials that were discussed.

4.17 I am unclear as to how the mean duration of treatment estimation has affected the economic modelling but suggest the one obtained from clinical trials would be more reliable and be the one that is used.

4.18 Note comment above. Again would suggest using OS directly from randomised controlled trials

4.25 ''Resection is successful in about 90% patients.'' Just to clarify by this we did not mean 90% of patients receiving these drugs went for resection. In various databases about 13-15% of patients with previously unresectable liver disease became resectable courtesy systemic treatments. **Resection rates** are proportional to **response rates** from treatment regimens which in turn are increased by use of **anti-EGFR agents**. In good MDTs vast majority of patients deemed resectable on basis of post treatment scans are indeed successfully able to have a liver resection (in personal practice 80-90%). Our sentiments above are more clearly & accurately summarised in section 4.36

4.28 Treatment holidays with cetuximab. In England we have been using the cetuximab within CDF guidelines which do not allow treatment breaks (in excess of 4 weeks) unless there are exceptional circumstances. This clinical practice is therefore in line with what transpires in clinical trials.

4.29 Note 4.14 above. Also in clinical trials the population was relatively younger; this is not unique solely in the trials in question. This is universally true for almost all colorectal trials and infact non CRC oncological trials and should have no bearing on real life practice. We would take biological age into consideration when using drugs rather than the chronological age; in practice therefore the age factor is not relevant and should not be cited as a source of uncertainty.

4.41 'from clinical experts that life expectancy is longer when mets confined to the liver.' I don't think this is true at all. We must have been misconstrued here; patients with disease confined to the liver do not necessarily fare better (unless they have been able to have resectional surgery). Infact in absence of liver surgery (prospects of which are enhanced by anti-EGFR use) they do much worse compared to patients with little or no liver affliction from disease.

Comments on the ACD Received from the Public through the NICE Website

Role	Healthcare Other
Organisation	IntegraGen SA
Conflict	IntegraGen SA jointly holds the patent for the miR-31-3p biomarker referred to in this comment in conjunction with Paris Descartes University, INSERM, the Centre National de la Recherche Scientifique, and the Assistance Publique - Hopitaux de Paris. IntegraGen also owns the exclusive license for the worldwide rights for this biomarker.
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	"Dear Sirs, We have recently reviewed the National Institute for Health and Care Excellenceâ€™s (NICE) appraisal consultation document for the use of cetuximab and panitumumab in patient with previously untreated metastatic colorectal cancer (mCRC) and are interested in receiving your guidance prior to submitting comments by the December 8, 2015 deadline based on newer information we have available. Our understanding after reviewing the above mentioned document is that NICE has determined that the use of both cetuximab and panitumumab in the patient population described above is not recommended and that this decision is primarily due to the lack of demonstrated cost-effectiveness of EGFR inhibitors in KRAS/RAS wild-type mCRC patients. IntegraGen has recently discovered and validated a biomarker, miR-31-3p, which identifies a specific subpopulation of KRAS wild-type mCRC patients who are more likely to benefit from cetuximab and panitumumab therapy (approximately 70% of the total patient population). We believe the use of this biomarker would enable a more targeted utilization of anti-EGFR inhibitors in this patient population improving the cost utility of these agents. In conjunction with the principal investigators of several large randomized studies, we have recently validated the ability of miR-31-3p to identify a population of patients who gain more benefit from cetuximab and panitumumab with regard to both survival and response. This conclusion is based on separate analyses of miR-31-3p expression in tumor samples obtained from patients enrolled in the New EPOC, PICCOLO, and FIRE-3 studies. While the initial discovery and validation studies with miR-31-3p in KRAS wild-type mCRC patients have been published (http://goo.gl/kB4TIv), the results from the New EPOC and PICCOLO studies have only recently been presented at ASCO and ESMO with a manuscript submission for the former planned for the near future. Our initial analysis of the miR-31-3p expression in tumor samples from the FIRE-3 study has only recently been completed and we plan to complete the full statistical analysis in the very near future and then submit the results to ASCO 2016.

	Since results from our studies to date from 8 separate patient cohorts have been consistent in regards to the ability of miR-31-3p to identify a specific subpopulation of KRAS wild-type mCRC patients who are more likely to benefit from cetuximab and panitumumab, we believe these results would be of value to NICE since this biomarker could be utilized to better target the use of cetuximab and panitumumab for patients more likely to respond to therapy, improving the cost-effectiveness of these drugs. Prior to submitting a response to the preliminary guidance document, we were interested in feedback from NICE relative to the Appraisal Committeeâ€™s willingness to review late-breaking data which is relevant to the focus on their review. If there is indeed willingness to review such data, we would plan to compile a detailed response which thoroughly reviews the clinical data obtained to date from studies and analyses of miR-31-3p in KRAS/RAS WT mCRC patients. Thank you for your efforts and we appreciate your willingness to provide us with guidance. Sincerely, Francois Liebaert, M.D. "

Role	NHS Professional
Other role	Consultant Medical Oncologist
Location	England
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	"The ACD is extremely worrying for any patient with bowel cancer in the UK and any oncologist involved in the treatment of metastatic colorectal cancer (mCRC). This proposed guideline will remove the availability of a targeted biological therapy from patients with RAS wild type mCRC. This is a proven, licensed and accepted strategy for treating this disease internationally. This guideline will therefore result in the earlier death of thousands of patients with mCRC in the UK annually. The whole way the assessment group has made assumptions and calculations appears fundamentally flawed. The use of PFS over OS seems bizarre given that final OS data have been presented and over 80% of survival events had occured in PRIME. The importance of a 5.6 month increase in OS seems to have been lost on the assessment group. Moreover, removal of EGFR targeted therapy in the neoadjuvant setting for operable liver mets is a disaster. The incremental extra patients that would have been cured by such a response are now going to die of mCRC and suffer the indignity and cost of multiple lines of chemotherapy for advanced disease.

	Everyone in the oncological community is looking to see how NICE rises to the challenge of taking over from the CDF. This is a very, very bad sign and raises serious questions over NICE's ability to be involved in the commissioning of cancer drugs in the future. "

Role	NHS Professional
Other role	Consultant Medical Oncologist
Organisation	Kent Oncology Centre
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	On behalf of my clinical Colleagues at the Kent Oncology Centre, one of the busiest in the country, I have been asked to share our view that the removal of either of the EGFR inhibitors from the list of options for advanced colorectal cancer patients would be a mistake.

Role	NHS Professional
Other role	Associate Specialist Oncologist and Chair of the North of England colorectal cancer network
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	"We are writing, names and titles at the end of this document, in response to your ACT on anti EGFR therapy for metastatic bowel cancer patients in England. We would like the committee to consider the following points before reaching a final decision: 1) With colorectal cancer being the third most common cancer in England and with poor overall 5-year survival. Removing these two drugs will have a significant impact on all Pan RAS WT patients which represents half the colorectal cancer patient population. 2) We feel data is mature enough to allow usage of median OS rather than PFS to calculate QUALYs. We feel this will have potentially a significant impact on the calculations 3) We feel that the accepted mature data has shown the following: a. Kohne et al Presented a pooled analysis (ASCO GI 2010) of the OPUS and CRYSTAL data showing a significant improvement in median OS for K-RAS WT patients receiving Cetuximab and Folfiri vs Folfiri alone (23.5 vs 19.5 months) HR 0.82 p-value 0.0062 as well a significant improvement in PFS (9.6 vs 7.6 months) HR 0.66 and p-value of < 0.0001 and an improvement in over al l response rate (57.3% vs 38.5%) Odds ratio 2.16 p-value <0.0001 b. CRYSTAL showed an improvement in median OS in K-RAS WT patients receiving Cetuximab plus Folfiri vs folfiri (23.5 vs 20 months) HR = 0.796 snd a p-value of 0.0093 c. PRIME updated data demonstrated a 5 months improvement in OS for the Pantimumab + Folfox compared to folfox alone with a HR of 0.83 and a p-Value of 0.03 in WT KRAS patients d. Almost all of the studies looking at anti-EGFR plus chemotherapy vs chemotherapy alone have reported significant

	improvement in overall response rates. 4) We feel with more up to date and comprehensive RAS testing will allow better patient selection and usage of personalised medicine which can only improve outcomes. 5) We also feel that end of life criteria should be applied to this group of patients, given their severely limited life expectancy and the relative significant improvement in median overall survival seen with the use of anti-EGFR therapy and whilst colorectal cancer is a common cancer, we feel selecting patients using robust RAS testing would enforce end of life criteria application to this group of patients 6) The UK in general and England in particular has been the seat for excellent world class clinical research and innovation. Taking this stance on innovative and effective treatment options will not only lead to a decline in our research ability 7) As a group we have an extensive experience in treating metastatic bowel cancer and feel that losing the use of anti-EGFR drugs will negatively impact on our patientâ€™s wellbeing, quality of life, and overall survival and this is something we find unacceptable. "

Role	NHS Professional
Other role	Locum Consultant Oncologist
Location	England
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	"Firstly my thanks to the Cancer Drug Fund to allow clinicians to use Panitumumab and Cetuximab in the first line management of RAS wild metastatic colorectal cancers. Also the flexibility to use them either with Folfox or Folfiri is welcome. As targetted biological agents these are the only drugs that are currently available for use. They remain truly targetted drugs as they are selected only for RAS wild population. Hence they offer these patients a great advantage in disease control both in terms of OS and PFS. With regards to Panitumumab, it is widely used in the Continent. As a humanised mono clonal antibody it is easier to use with lesser allergic reactions. PRIME Trial reinforces the 5.6 months gained in OS and PFS when Panitumumab is added to the chemotherapy back bone. As a practising clinician I would request for these agents to be

	continued to be available for use and request NICE to support. As RAS testing has become more robust and accurate, there is , in my opinion, a strong case for antibodies to benefit this small group of patients. "

Role	NHS Professional
Other role	consultant medical oncologist
Location	England
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	i agree anti-egfr treatments should be standard of care on Nice not on cdf since it is biomarker driven and has good evidence base.

Role	NHS Professional
Other role	Consultant in Medical Oncology
Location	England
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	As a medical oncologist with sub-speciality practise in colorectal cancer, it is a huge concern that this class of drugs which have a proven track record of disease reduction and survival advantage would be denied to appropriate molecularly defined patient population

Role	NHS Professional
Other role	Consultant Clinical Oncologist
Location	England
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	The role of EGFR inhibitors (cetuximab, panitumumab) has been studied in multiple studies. There is a robust data for OS in both 1st and 3rd line both with chemoterapy and versus best supportive care. The most recent studies PRIME and FIRE3 has defined the patient selection further and this has improved the OS further. Adopting PFS as the end point for the appraiasl is ignoring the results that has changed practice for this group of patients. The OS has imporved by 7 months in the FIRE3 study and by 5.6 months in the PRIME study. This is the largest improvement in OS in mCRC and th edata appears mature as more than 80% of events had taken place. This should be taken in consderation. The ACD states that these drugs do not the end of life criteria in 3rd line. This group of patients are highly selected by the RAS status and have progressed on previous therapy. There life expectancey is usually less then 6 months at best and therefore the statment ought to be reconsidered.

Role	NHS Professional
Other role	Consultant in Medical Oncology
Location	England
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary	The treatments being assessed are valuable and clinically effective toold for the management of patients with incurable

recommendations)	colorectal cancer. The trials included in the analysis of which the largest and most informative are the CRYSTAL and PRIME studies are Phase 3 trials with mature follow-up. Patients with resectable liver only or predominant metastatic disease were not eligible for these studies. Patients in this sub-group have already been assessed in previous NICE guidance and the value of reviewing this group again within the context of this analysis is uncertain. As is described in the analysis only ~10% of patients will have a "successful" liver resection and then atleast half of these patients will relapse with disease which is not amenable to further surgery. The value of EGFR mAb treatment is the extension to progression free but more importantly overall survival which they provide. Not considering these agents as end of life treatments is a perverse decision given the context of treatment even if you feel the analysis in that context would not change the final cost-effectiveness decision. The panel should consider re-assessing the data based on Overll Survival being the main endpoint. Concerns regarding the quality of the trial data and the generalisability to the overall population of cancer patients are noted. Patients in these studies were younger than the overall population with advanced colorectal cancer but this has also been the case for every significant colorectal cancer trial evaluated previously including those supporting the use of standard chemotherapeutic agents such as oxaliplatin, irinotecan and capecitabine. This is not a unique factor associated with research into these agents but is a general problem with the assessment of systemic treatments in patients with a range of malignancies. The survival of patients with colorectal cancer is 20-30 months. The follow-up for all the trials considered is sufficient to demonstrate a difference is overall survival with confidence. The statement that the survival data is insufficiently true is incorrect. The reviewers correctly point to the fact that these trials have been subjected to post-hoc analyses which raise concerns regarding their statistical power and the risk of confounding factors. However, the post-hoc analyses reflect the rapid changes that have occured in our knowledge of the biology of colorectal cancer. All of the clinical trials recruited over the last decade have needed to undego analyses based on RAS and BRAF mutation status. Whilst some of these analyses from recent trials have been planned prospectively many have been performed retrospectively. Although the critique is in-part valid the evidence base will not be significantly enhanced through further follow-up. . Additional trials such as FIRE3 and the CALGB study include additional agents in their randomisation which would not be available through the NHS so I assume these studies have not been chosen for analysis based on these factors. Nevertheless these studies provide an insight into the prolongation of overall survival with the incorporation of these drugs (and other) into standard practice.

	From a broader context the debate about the clinical effectiveness rather than cost-effectiveness of these agents has been settled and internationally both of these agents are considered to be standard drugs which are available for patients with advanced colorectal cancer to receive. A decision not to fund these drugs sets the UK health system apart from those in other developed countries. Additionally it will significantly affect the ability of the UK to participate in international trials investigating systemic treatment for colorectal cancer. This has already been affected by the lack of availability of VEGF targeting mAbs and will be further undermined by the inability of UK clinicians to administer EGFR mAb therapy. Finally there is also an issue about whether the processes used to evaluate drugs in TA are fit for purpose as the UK system and the international standard practice has diverged. Inevitably some of the overall survival advantages seen with the use of the EGFR mAb agents is due to the subsequent use of additional agents each having an incremental effect. Internationally cetuximab, panitumumab, bevacizumab, aflibercept and regorafenib are all considered standard agents. In all on-going and future international studies there will be widespread use of these agents. In this context the assessment of new drugs for colorectal cancer appears to be futile in the current TA system as no evidence will be admissable given the difference between the studies and "real world" UK practice. I appreciate the difficult decisions regarding cost effectiveness which need to be made but the current system does not appear to be working for colorectal cancer patients and based on the rationale provided for the decisions its difficult to have any confidence that I will be able to offer patients under my care any of the treatments which are in development currently or have demonstrated improvements in PFS or OS over the last few years.

Role	NHS Professional
Other role	Consultant Clinical Oncologist
Location	England
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	"Re: Response to NICE preliminary negative Appraisal Consultation Document (ACD) on Panitumumab in first line metastatic colorectal cancer. I am writing on behalf of my colleagues as the colorectal cancer clinical lead at Weston Park Hospital in Sheffield, in response to the recent consultation document issued by NICE. Colorectal cancer is the 3rd most common cancer in England. Despite advances in the treatment of advanced disease the prognosis remains poor with a 5 year overall survival rate of only 5-10%. The development of the anti-EGFR antibodies cetuximab and panitumumab represents a significant advance in the management of metastatic colorectal cancer, which has led to a clinically meaningful improvement in overall survival (OS).

	Tumour analysis for RAS and BRAF mutations represents a clear move towards personalized treatment of colorectal cancer that enables the rational selection of patients most likely to respond to therapy, and prevents unnecessary treatment of those patients unlikely to respond. The use of anti-EGFR antibodies in RAS wild-type patients is standard of care in other European countries, and is recommend by clinical guidelines of the European Society of Medical Oncology and the National Cancer Institute. Without access to these drugs, there is a clear unmet need for patients with advanced colorectal RAS wild-type tumours. These patients will have no access to these drugs despite robust evidence of clinically meaningful improvements in OS with the addition of anti-EGFR antibodies to first line chemotherapy. Furthermore, the recent removal of cetuximab and panitumumab as 3rd line therapy from the Cancer Drug Fund (CDF) means these patients now have limited lines of active treatment. The recent changes to the CDF have resulted in inferior outcomes for a number of our patients, and have complicated clinical decision making. Overall this has had a negative impact on the treatment options available for patients. Having read the consultation documents it is apparent that not all of the available evidence has been taken into account. We note that the CALGB-80405 trial, which compared cetuximab plus FOLFOX or FOLFIRI with bevacizumab plus FOLFOX or FOLFIRI, was excluded from the analysis as it did not randomly allocate patients to FOLFOX or FOLFIRI and the trial results were available only in abstract form. The Fire-3 phase III trial (AIO KRK-0306) published in the Lancet Oncology1 in 2014 was also not included. This was a head to head comparison of FOLFIRI plus either cetuximab or bevacizumab as first-line treatment in patients with metastatic colorectal cancer (who had KRAS wild-type disease). Whilst patients were not allocated to a chemotherapy alone arm, the median OS in the FOLFIRI and cetuximab arm of 33 months represents a significant advance on historical controls. In this large study of 752 enrolled patients, KRAS wild-type tumours were confirmed in 592 patients, who were then randomised 1:1 to receive first-line FOLFIRI every two weeks plus either cetuximab at 400 mg/m2 on day 1 followed by 250 mg/m2 weekly (arm A) or bevacizumab at 5 mg/kg every 2 weeks (arm B). The results from the overall study population favoured arm A, with median OS in cetuximab treated patients nearly four months longer than in the bevacizumab arm. The results presented were from a preplanned analysis that evaluated the effect of KRAS mutations in exons 2, 3 & 4 exon 4 and NRAS exon 2,3, & 4 and BRAF (V600E) on the overall response rate (ORR), progression-free survival (PFS) and OS on treatment arms A and B of the FIRE-3 trial. A total of 444 (75%) patients had available tumour tissue; of these, sequencing of all known RAS mutations was possible in 396 patients. Greater benefit was demonstrated with FOLFIRI plus cetuximab in the overall intention to treat population of 592 patients with KRAS wild type disease; ORR was 62.0% and 58.0% in arm A and B,

	respectively (p = 0.183 [FisherÂ´s one-sided test]). "

Role	NHS Professional
Conflict	No
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	whilst I appreciate both drugs are expensive (and we can debate cost effectiveness) there is no doubt regarding the efficacy of both cetuximab and panitumumab on the basis of CRYSTAL/PRIME trials and the subsequent data from FIRE3/CALGB where OS was over 30 months in both studies with chemo + cetuximab.

Role	NHS Professional
Other role	Consultant in Medical Oncology
Location	England
Conflict	No
Notes	I have received funding to attend European & American Society of Medical Oncology meetings from Merck Serono & Amgen. I have received honoraria for speaking at meetings sponsored by Amgen.
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	The results of the PRIME trial analysis (following an updated analysis of RAS status) clearly demonstrate the superiority of combination treatment with FOLFOX and Panitumumab versus FOLFOX alone. Patients receiving FOLFOX-Panitumumab have a median overall survival that is over 5 months greater (26.0 vs. 20.2) than the FOLFOX alone arm. To deny such an effective treatment to patients with a significantly limited life-expectancy will only cause the gap in cancer survival rates between the UK and our comparable European neighbours to widen.

Role	NHS Professional
Other role	Medical Oncologist & Clinical Research Fellow in GI Oncology
Organisation	Royal Marsden Hospital
Location	England
Conflict	No
Notes	[redacted] is a medical oncologist at the Royal Marsden Hospital and has published multiple practice changing trials in gastrointestinal oncology including colorectal cancer. [redacted] is a clinical research fellow in gastrointestinal oncology
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	"The use of anti-EGFR therapy is well defined in multiple setting in mCRC, and following withdrawal of funding for anti-angiogenic therapy (bevacizumab and aflibercept) these remain the sole biological agents used for patients with this disease. Notably, in contrast to anti-angiogenic therapy, for anti-EGFR therapy there is a biomarker selected patient population for whom treatment with anti-EGFR therapy is more likely to yield benefits in survival thus limiting the financial impact of the use of these drugs. I would like to make the following comments with respect to the ACD which has been

	published. Concerns were raised regarding the lack of robustness of the overall survival (OS) data for anti-EGFR therapies as: Subsequent treatments used post-progression may have prolonged the overall survival gain for anti-EGR therapy In PRIME study 18% of patients who were treated with FOLFOX alone received anti-EGFR therapy second line as did 8% who had been treated with FOLFOX-panitumumab. Twelve and 15% of patients treated with FOLFOX and FOLFOX-P received bevacizumab respectively. Firstly, as treatment was continued until progression in PRIME, rechallenge with an anti-EGFR therapy for patients previously treated with panitumumab (and therefore resistant to EGFR inhibition) is unlikely to have significantly affected survival outcomes. Secondly, if patients who had not previously received an EGFR inhibitor(FOLFOX treated patients) were treated subsequently with panitumumab then this would reduce the survival benefit demonstrated in the trial to panitumumab. Thirdly, the proportion of patients who received second line chemotherapy was higher (62% vs 53%) in patients treated with FOLFOX alone first line which would also negatively influence survival outcomes for panitumumab treated patients (and not extend the survival benefit). Finally, as anti-angiogenic therapy was used in approximately equivalent proportions of patients in each arm this can be assumed to have a negligible differential effect. In the CRYSTAL study post progression anti-EGFR therapy was used in 6.2% of patients in the cetuximab-FOLFIRI group and 25.4% of patients in the FOLFIRI alone group. Therefore the same argument applies â€“ this could only potentially attenuate the survival benefit of cetuximab. Similarly, in line with PRIME, the proportion of patients who were treated with chemotherapy second line was higher in patients who did not receive cetuximab first line (63.9% vs 68.8% respectively). Therefore it is not clear to us how the effects of post progression therapy can be used as a rationale for rejecting the use of the robust overall survival data for either cetuximab or panitumumab in these first line studies. . Treatments used post progression in the CRYSTAL and PRIME studies are no longer used in the NHS Regarding the comment that treatments used post progression in CRYSTAL and PRIME are no longer used in the NHS and that the overall survival data for this study should not be used for this reason, this may also be solidly refuted. Firstly, anti-angiogenic therapies are no longer funded foir NHS patients (although continue to be used worldwide) , but were used in equivalent numbers of patients in each arm in PRIME. Secondly, anti EGFR therapy may not be used beyond first line, but in each trial this was used in more patients in the control arm (and would have been ineffective in the smaller number of patients in the experimental arms). Controlling for this would only extend the survival benefit due to first line use of anti-EGFR therapy. Immature survival data The survival data are commented to be immature. In the

	original CRYSTAL publication almost 70% of patients had died, whereas in the updated analysis of PRIME 82% of patients had died which we believe is sufficient to make a robust assessment of the efficacy of the experimental arm in either study. " "Further concerns were raised regarding: Uncertainties in the clinical evidence base for anti-EGFR therapies given subgroup analysis and small sample size The committee considered that the clinical evidence was limited as it represented subgroup analysis, and that there were â€œfew samples available for re-analysisâ€ . While it is certainly true that this does represent a post-hoc subgroup analysis we do not believe that this in itself is a reason to reject this evidence. Evidence from subgroup analysis of phase III randomised trials is accepted as sufficiently robust to determine licensing indications as extended RAS testing is now mandatory before administration of anti-EGFR therapy for patients with mCRC (FDA and EMA regulations). It is difficult to understand how the requirement evidence of subgroup activity for funding could be so much more stringent that which guides assessment of patient safety and benefit from a regulatory perspective. The comment stating that â€œfew samples were available for analysisâ€ is simply untrue; in PRIME the rate of ascertainment of RAS and BRAF status was 89%, and was assessed in 1047 of 1183 patients. This is a very high proportion of patients in any trial to have available for biomarker assessment. To draw an important parallel, NICE approval was granted for the BRAF inhibitor dabrafenib based on the results of the BREAK 3 trial, which randomised 250 patients with BRAF mutant melanoma to dabrafenib or chemotherapy. In PRIME, 512 RAS wild type patients were randomised to FOLFOX vs FOLFOX panitumumab. Similarly in the CRYSTAL trial 367 RAS wild type patients are evaluable for survival assessment. Together these numbers equate to almost nine hundred patients. Although this hypothesis was not pre-specified for either study, these numbers mean that these are practice changing analyses as evidenced by the subsequent licensing changes and therefore survival data should not be ignored an untrue claim of â€œsmall sample sizeâ€ . Lack of generalisibility of the clinical trial population in the relevant clinical trials While concerns regarding the external validity of clinical trials are common, this is not a valid reason to withhold anti-EGFR therapy for NHS patients. To further this argument one could argue that no treatment based on a clinical trial should be extended to NHS patients, which is clearly not credible. Eligibility criteria are necessary for clinical trials to protect the patient and the scientific value of the trial. However, when extending treatments to a broader patient population oncologists (who are both responsible and liable) will consider what the eligibility criteria were for a trial, and are unlikely to extend treatment to patients who do not meet those criteria. In this setting, the key question is whether patients will tolerate doublet chemotherapy and not the addition of anti-EGFR

	antibody treatment which is associated with limited additional toxicity compared to chemotherapy alone. If a fit patient is appropriate for doublet chemotherapy, then they are very likely to tolerate combination chemotherapy plus anti-EGFR treatment and the results of the study are generalisable to those patients. It is relevant to state at this point that of course many NHS patients (including my own) participated in these studies and that clearly this population exists in the UK. " "Anti-EGFR therapies do not meet the End of Life (EoL) criteria overall as it does not meet the criterion of small patient population Firstly, if end of life criteria entail that less than 7000 patients per year in England may be treated with a drug, it is likely that either cetuximab or panitumumab will meet this goal. Approximately 15000 patients per year in the UK will die from advanced colorectal cancer. Of these approximately half will have a RAS mutation which will render them unsuitable for anti-EGFR therapy. However there will be another proportion (relating the previous point above) who have co-morbidities or a performance status which renders them unsuitable for doublet chemotherapy (and therefore an anti-EGFR inhibitor). If we conservatively estimate this to be 10-15% (and it is likely to be higher), then the absolute number of patients treated with anti-EGFR therapy is likely to be less than 7000. This is notwithstanding the fact that recently the â€œsmall populationâ€ criterion for EoL criteria has been challenged as valid reason not to extend the possibility of treatment to patients with cancer. Why should patients with a more common cancer be disadvantaged by this fact? This is underlined by the revision of the CDF application of NICE EoL criteria as proposed in the document â€œConsultation on proposals for a new cancer drugs fund (CDF) operating model from 1st April 2016â€ (https://www.nice.org.uk/Media/Default/About/what-we-do/our-programmes/technology-appraisals/cdf-consultation-document.pdf) which proposes to exclude this as a relevant criterion from future assessments. " "A final and pertinent point which is not addressed in the NICE appraisal is that withdrawal of anti-EGFR therapy for patients with advanced colorectal cancer will significantly impact on the capacity of the UK oncologists and their patients to participate in clinical trials. The UK has a research infrastructure which is world renowned, and in which academic research is part supported by a symbiotic relationship with the pharmaceutical industry through participation in commercial clinical trials. As many clinical trials recruit patients to â€œProduct Xâ€ plus the standard of care which in this case worldwide is chemotherapy plus an anti-EGFR inhibitor, the UK will no longer be an attractive destination for pharmaceutical companies wishing to perform such research. This has knock-on effects for patients in the later stages of treatment too because if they have not received a full complement of available treatments in the first line setting then they are ineligible for studies in second and third line. The implications

	of this for patients are devastating in terms of access to promising new drugs. However the implications for UK research may be equally profound, lack of funding investment may lead to decreased academic activity, loss of research jobs and a decline in the UKâ€™s standing as an academic powerhouse for gastrointestinal oncology trials. Whilst we acknowledge that this does not directly impact on the economic cost-benefit analysis for individual patients it may have economic effects on society as whole. In conclusion, survival for patients with advanced colorectal cancer in the UK was previously significantly inferior to other comparable countries however in recent years the UK has narrowed the gap in this regard (Walters et al, Br J Cancer. 2015 Sep 1; 113(5): 848â€“860). As median overall survival for patients with advanced colorectal has is improved significantly with the use of anti-EGFR therapy it would very regretful to limit access to these life extending drugs and revert UK gastrointestinal oncology to an era more than a decade ago. We therefore urge the committee to reconsider this evaluation. "

The clinical effectiveness and cost-effectiveness of cetuximab (review of TA176) and panitumumab (partial review of TA240) for previously untreated metastatic colorectal cancer: a systematic review and economic evaluation

Addendum in response to comments on NICE ACD from Amgen and Merck Serono

4th January 2016

Confidential information that is commercial-in-confidence is [redacted]

On 7th August 2015, we submitted our final report for this MTA to NICE, and on 9th October 2015, the first Addendum to our report.

In December 2015, we received comments on the NICE ACD from Merck Serono and Amgen.

In this Addendum, we respond to these comments.

Changes to our base case

In response to comments from Amgen and Merck Serono, we have made two changes to our base case.

First, we incorporate the **revised PAS for panitumumab**, a [redacted] discount on the list price.

Second, in response to comments from Merck Serono, we have substantially reduced our estimated **unit costs of drug administration**. For details, please refer to our full response document to Merck Serono and Amgen (4th January 2016). In summary, we concede that we made three errors. First, we double counted the costs of cetuximab and FOLFOX administration. Second, we double counted the costs of pharmacy, line maintenance and infusion pump. Third, we have made the minor correction to the administration cost applied to Day 8 of cetuximab so that it now refers to the subsequent, rather than the first, attendance in a treatment cycle. As a result, our estimated unit costs of drug administration have fallen substantially, by between 34% and 61%.

"PFS" vs. "OS" model structure. In our original submission, in our base case, we used only PFS from the RCTs of 1st-line drugs. OS from these RCTs was discarded. This is the "PFS" model structure. In an important scenario analysis, we instead modelled both PFS and OS from the RCTs. This is the "OS" model structure (Section 6.2.3.3, p379 our report). See p243 of our original report for a full description of these two methods, and our justification for choosing the "PFS" method in our base case.

Amgen now argue that, at the first NICE appraisal meeting, the committee preferred our "OS" model structure. However, as we explain in detail our responses to the comments on the ACD from the companies, we argue that it is not clear which, if any, of the two methods were preferred by the committee.

For this reason, the "PFS" method remains in our base case, but we also give results using the "OS" method. The NICE committee is then free to select their preferred method.

In our first response to the companies (9th October 2015), we explained that we amended the "OS" method compared to the version of the analysis presented in our original report. The amendments are as following:

- We do not cost for subsequent monoclonal antibody treatments.
- We consider the resulting ICERs for PAN+FOLFOX vs. FOLFOX and CET+FOLFOX vs. FOLFOX as upper bounds, to reflect our belief that that the OS benefit of PAN+FOLFOX vs. FOLFOX and CET+FOLFOX vs. FOLFOX would probably have been slightly greater than that achieved in PRIME and OPUS if no patients had received monoclonal antibodies as subsequent treatments.

Merck Serono originally assumed far shorter **mean treatment durations** than us (see table below). They have now substantially [redacted] their estimated durations with, what they claim, is data from OPUS and CRYSTAL, but these are [redacted] than our estimated durations (table below).

Table 1. Mean treatment durations (months)

	PenTAG base case modelled	Merck original submission (p202 our report)	Merck revised estimates (based on means from RCT, Appendix 4, Merck response document)
Cetuximab+FOLFIRI	[redacted]	[redacted]	[redacted]
FOLFIRI	[redacted]	[redacted]	[redacted]
Cetuximab+FOLFOX	[redacted]	[redacted]	[redacted]
FOLFOX	[redacted]	[redacted]	[redacted]

As explained in detail in our response document, Merck Serono now give figures which they claim are the mean treatment durations from CRYSTAL and OPUS. They cite the source of these as the Addenda to the Clinical Trial Reports for CRYSTAL and OPUS. In summary, we believe that the means from the CRYSTAL Study Report are plausible. But given that (a) we do not find these figures in the Study Report and (b) we are concerned that censoring may not have been considered, we retain our mean treatment durations in our base case. However, we use Merck Serono's means in scenario analyses, see below. Next, as explained in detail in our response document, we do not find the estimated duration of

cetuximab+FOLFOX that Merck Serono claim to have taken from OPUS to be credible. Once again, we retain our estimated mean durations in our base case, and use Merck Serono's means in scenario analyses. In further scenario analyses, we assume a reduced mean treatment duration of 6 months for all treatments both in the whole patient population, and in the liver metastases subgroup.

We now present our key cost-effectiveness results under these revisions. Results that have changed from our original base case are highlighted in black.

1. Base case results

1.1 All patients

Our revised base case results for all patients for the FOLFOX and FOLFIRI networks are given in Table 2 and Table 3 below.

Table 2. PenTAG base case summary cost-effectiveness results: All patients, FOLFOX network, weekly CET dosing, revised unit costs of drug administration

				CET+FOLFOX vs.	PAN+FOLFOX vs.
	CET+FOLFOX	**PAN+FOLFOX**	**FOLFOX**	**FOLFOX**	**FOLFOX**
Life years (mean, undiscounted)	2.41	2.08	1.86	0.55	0.22
QALYs (mean, discounted)	**1.61**	**1.41**	**1.26**	**0.35**	**0.15**
Total costs (mean, discounted)	**£73,639**	**£64,177**	**£30,585**	**£43,054**	**£33,592**
ICER (Cost / QALY) vs. FOLFOX				**£123,000**	**£224,000**
ICER (Cost / QALY) on efficiency frontier		**Extended dominated**	**Reference**		

Key: CET = cetuximab; FOLFOX = folinic acid + fluorouracil + oxaliplatin; ICER, incremental cost-effectiveness ratio; PAN = panitumumab; QALYs, quality-adjusted life years

Table 3. PenTAG base case summary cost-effectiveness results: All patients, FOLFIRI network, weekly CET dosing, revised unit costs of drug administration

			CET+FOLFIRI vs.
	CET+FOLFIRI	**FOLFIRI**	**FOLFIRI**
Life years (mean, undiscounted)	2.21	1.75	0.46
QALYs (mean, discounted)	**1.53**	**1.23**	**0.30**
Total costs (mean, discounted)	**£80,018**	**£29,668**	**£50,350**
ICER (Cost / QALY)			**£166,000**

Key: CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; ICER, incremental cost-effectiveness ratio; PD = progressive disease; PFS = progression free survival; QALYs, quality-adjusted life years

The probability that the following treatments are most cost-effective for all patients combined at a willingness to pay threshold of £30,000 per QALY are:

- CET+FOLFOX: 19%.
- PAN+FOLFOX: 0%.
- CET+FOLFIRI: 0%

1.2 Liver metastases subgroup

Our revised base case results for the liver metastases subgroup for the FOLFOX and FOLFIRI networks are given in Table 4 and Table 5Table 3 below.

Table 4. PenTAG base case summary cost-effectiveness results: Liver mets subgroup, FOLFOX network, weekly CET dosing, revised unit costs of drug administration

				CET+FOLFOX vs.	PAN+FOLFOX vs.
	CET+FOLFOX	**PAN+FOLFOX**	**FOLFOX**	**FOLFOX**	**FOLFOX**
Life years (mean, undiscounted)	2.98	2.86	2.21	0.76	0.65
QALYs (mean, discounted)	1.97	1.89	1.49	0.49	0.40
Total costs (mean, discounted)	£90,223	£69,515	£34,598	£55,625	£34,917
ICER (Cost / QALY) vs. FOLFOX				**£115,000**	**£87,000**
ICER (Cost / QALY) on efficiency frontier	**£249,000 (vs. PAN+FOLFOX)**	**£87,000 (vs. FOLFOX)**	**Reference**		

Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab;ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

Table 5. PenTAG base case summary cost-effectiveness results: Liver mets subgroup, FOLFIRI network, weekly CET dosing, revised unit costs of drug administration

			CET+FOLFIRI vs.
	CET+FOLFIRI	FOLFIRI	FOLFIRI
Life years (mean, undiscounted)	2.69	1.83	0.86
QALYs (mean, discounted)	1.83	1.26	0.57
Total costs (mean, discounted)	**£94,941**	**£29,809**	**£65,132**
ICER (Cost / QALY)			**£115,000**

Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years

The probability that the following treatments are most cost-effective for the liver mets subgroup at a willingness to pay threshold of £30,000 per QALY are:

- CET+FOLFOX: 2%.
- PAN+FOLFOX: 0%.
- CET+FOLFIRI: 0%

2. PAS prices of CET and PAN

In the tables below, we present our ICERs given the Patient Access scheme (PAS) price of CET and the PAS price for PAN, which was revised in December 2015.

For cetuximab, the list price of a 20 ml vial (5 mg/ml) is £178.10, and of a 100 ml vial (5 mg/ml) is £890.50. Under Merck Serono's PAS, the cost of a 20 ml vial becomes £114.66. This is a 35.6% discount.

For panitumumab, the list price of a 5 ml vial (20 mg/ml) is £379.29, and of a 20 ml vial (20 mg/ml) is £1,517.16. Under Amgen's revised PAS, these figures become [redacted] and [redacted]. This is a [redacted] discount.

Table 6. ICERs for base case and scenario analyses given PAS pricing for CET and PAN: all patients, weekly CET dosing, revised unit costs of drug administration

	CET+FOLFOX vs. FOLFOX	PAN+FOLFOX vs. FOLFOX	CET+FOLFIRI vs. FOLFIRI
Base case (with CET & PAN PAS)	**£93,000**	[redacted]	**£122,000**
Overall survival from RCTs, assume no costs for subsequent treatment	**<£399,000**	[redacted]	**<£84,000**
OPUS as baseline RCT in FOLFOX network	**£106,000**	[redacted]	**Unchanged from base case**
FOLFOX 6	**£90,000**	[redacted]	**£123,00**
List prices for FOLFOX and FOLFIRI	**£105,000**	[redacted]	**£133,000**
Mean treatment durations from OPUS and CRYSTAL from Merck Serono	**Unchanged from base case**	**Unchanged from base case**	**£107,000**
Overall survival from RCTs, assume no costs for subsequent treatment & Mean treatment durations from OPUS and CRYSTAL from Merck Serono	**<£282,000**	**Unchanged from OS scenario analysis above**	**<£75,000**
Mean treatment durations 6 months for all treatments	**£64,000**	[redacted]	**£70,000**
Overall survival from RCTs, assume no costs for subsequent treatment & Mean treatment durations 6 months for all treatments	**<£139,000**	[redacted]	**<£52,000**

Table 7. ICERs for base case and scenario analyses given PAS pricing for CET and PAN: liver mets patients, weekly CET dosing, revised unit costs of drug administration

	CET+FOLFOX vs. FOLFOX	PAN+FOLFOX vs. FOLFOX	CET+FOLFIRI vs. FOLFIRI
Base case (with CET & PAN PAS)	£87,000	[redacted]	£86,000
Overall survival from RCTs	Not calculated	[redacted]	Not calculated
OPUS as baseline RCT in FOLFOX network	£79,000	[redacted]	unchanged from base case
FOLFOX 6	£83,000	[redacted]	£87,000
List prices for FOLFOX and FOLFIRI	£100,000	[redacted]	£99,000
Mean treatment durations 6 months for all treatments	£49,000	[redacted]	£41,000

BEV+FOLFOX and BEV+FOLFIRI as comparators

Table 8. ICERs for scenario analysis allowing for bevacizumab as a comparator with PAS pricing for cetuximab and panitumumab, weekly CET dosing, revised unit costs of drug administration

	CET+FOLFOX vs. BEV+FOLFOX	PAN+FOLFOX vs. BEV+FOLFOX	CET+FOLFIRI vs. BEV+FOLFIRI
All patients	£62,000	[redacted]	£212,000
Liver mets subgroup	BEV+FOLFOX dominates CET+FOLFOX	[redacted]	£523,000

XELOX as comparator

Table 9. ICERs for scenario analysis allowing for XELOX as a comparator with PAS pricing for cetuximab and panitumumab, weekly CET dosing, revised unit costs of drug administration

	CET+FOLFOX vs. XELOX	PAN+FOLFOX vs. XELOX
All patients	£115,000	[redacted]
Liver mets subgroup	£105,000	[redacted]

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Assessment Group response to comments on the Appraisal Consultation Document provided by companies

Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer

4th January 2016

Due to the limited time available to the Assessment Group, written responses have been provided for some but not all of the consultee comments received.

Confidential information that is academic-in-confidence is highlighted and underlined

Confidential information that is commercial-in-confidence is highlighted and underlined

We first consider comments from Amgen, then comments from Merck Serono, and finally comments from other consultees.

Text concerning a change to our base case, or any additional scenario analyses or amendments to existing scenario analyses is shown in bold. Specifically, these relate to (a) changes in our base case estimates of the unit costs of drug administration, as suggested by Merck Serono, and inclusion of scenario analyses using Merck Serono's estimates of treatment durations from the CRYSTAL and OPUS RCTs.

Comments from Amgen

Comment from consultee	Response from assessment group
Executive summary The key clinical evidence for panitumumab comes from a pre-specified subgroup analysis of 512 WT RAS mCRC patients from the pivotal head-to-head randomised controlled trial (RCT) (PRIME) which compared panitumumab plus FOLFOX with FOLFOX. This robust set of evidence for panitumumab plus FOLFOX in WT RAS mCRC patients contrasts with the uncertainties associated with the evidence base for cetuximab plus FOLFOX which relate to low sample size and missing data. However these should not be attributed to panitumumab.	In the PRIME study, extended subgroup analysis was noted alongside a protocol amendment restricting the analysis of the ITT population to compare PFS and OS according to KRAS status. The PEAK trial however was prespecified. As this was not the ITT population and not originally prespecified the power of the PRIME trial to demonstrate statistical significance was reduced. We agree the PRIME trial was the largest available and was chosen to inform the base case of the economic model on this basis.
Generalisability of the trial population in PRIME to patients treated in the NHS The ACD concluded that the population studied in the PRIME RCT was younger and fitter than patients seen in clinical practice in England and that this was a source of uncertainty in the clinical and cost effectiveness results. It is generally expected that RCTs recruit younger and fitter patients than the broader populations treated in the NHS, and PRIME is no exception. We think it reasonable to assume that the results from PRIME can be generalised to the NHS population and note that NICE have taken a similar, pragmatic, stance on this in other appraisals	The trials available are currently the only evidence for the effectiveness of panitumumab. However this does not negate that that the population is likely to differ from what is seen in practice and therefore this must be taken into consideration when making decisions on effectiveness in practice.
Robustness of the OS gain for panitumumab Although the ACD states that the NICE preferred approach would be to use OS data (4.33, pg 27), this disappointingly has not informed the base case incremental cost effectiveness ratio (ICER) for panitumumab. Instead, PFS data has been used, which in turn is a surrogate marker for OS. The Appraisal Committee deemed "*that survival data were not sufficiently mature, and that the size of the effect was confounded by the use of different second*	We agree that the PRIME data is mature compared to reported results from many RCTs. However, as stated in our response to comments on our Assessment Report provided by companies (9th Oct 2015): "*for this HTA, we would like to see PFS and OS that is even more mature. This is because both Merck and we believe that a small proportion of patients (about 10%), those that receive a successful resection, are expected to live substantially longer, and spend substantially longer progression-free, than the*

Comment from consultee	Response from assessment group
and subsequent lines of treatment across the trial arms" and "these treatments are associated with prolonged survival and are also not widely available in the NHS". Amgen believes that the OS data for panitumumab is robust and should be used in the economic model, in preference to PFS data, to inform the base case ICER: The OS data from PRIME is sufficiently mature, since the majority of patients (82%) had died by the time of the analysis. Robust analysis of the impact of subsequent treatments on OS in WT RAS patients confirms previously presented analyses in WT KRAS patients: They consistently demonstrate that the impact of subsequent therapies would have been to attenuate the OS gain for panitumumab. They also address ACD concerns regarding second-line therapies not commonly used in the NHS, by demonstrating that they do not prolong OS gain for panitumumab. Therefore the OS gain observed in PRIME (a median 5.6 months) should be considered conservative. This was recognised by the Assessment Group who acknowledged the use of OS to be highly plausible and considered the resulting ICER for panitumumab to be an upper bound, given that survival could have been greater. Critically, the face validity of the PFS-based model, used as the base case by the Assessment Group, is questionable, since OS results generated from the PFS model are highly inconsistent with those from the PRIME and OPUS trials. The use of OS is the preferred approach and was indeed recognised as such in the ACD. Therefore in using PFS, instead of robust OS data from a large multicentre international RCT to inform the base case ICER, the Appraisal Committee has not taken into account all relevant evidence from clinical trials in estimating the base case ICER for panitumumab. Therefore the ensuing recommendations contained in the ACD do not form a sound and suitable basis for guidance to the NHS.	*remaining patients.* *We already say words to this effect on p60 of our report.* *Indeed, Merck have implicitly agreed that the PFS from PRIME does not capture PFS for resected patients, as they instead use PFS for the patients from a different study (Adam 2004). We agree with this*." As we explained in our response document of 9th Oct 2015, on p243 of our original report, we justified our choice of model structure based on just PFS from the 1st line trials. Our reading of Section 4.33, p27 of the ACD is that it is not clear whether the committee prefer the PFS or OS model structure. However, it appears that they have a slight preference for the OS structure. • "*The Committee would have preferred to see a model based on survival data from trials, but understood that the trial data for cetuximab and panitumumab may have been confounded by second-line drugs that are not commonly used in the NHS*." • "*The Committee concluded that, in general, it would prefer to see trial-based survival modelled, but it recognised the limitations associated with using trial data in this instance*.". We believe that the above two quotes could be read either as: • The committee prefer the OS method, or • The committee would in general prefer the OS method, but only if the trial data is not confounded by 2nd-line drugs not commonly used in the NHS. Given that there was confounding by 2nd-line drugs in this MTA, the committee are not expressing a preference for either

Comment from consultee	Response from assessment group
	method. Given this ambiguity, throughout our responses to the comments to the ACD, we present the cost-effectiveness results based separately on both model structures. The NICE committee can then select the results according to their preferences. Next, we agreed in our response document of 9th Oct 2015, p15, that the impact of subsequent therapies would have been to attenuate the OS gain for panitumumab and that the resulting ICER for panitumumab under the OS method is an upper bound. Below, we discuss the consistency of our estimated OS results with the results of the PRIME and OPUS trials.
Consideration of the EoL criteria for panitumumab It is noteworthy that the Committee was presented with 3 estimates of population size, of which two fell well within the 7,000 threshold. Consequently, the conclusion that panitumumab does not meet this EoL criterion is not a balanced one, given that it is driven by the one estimate (of 8,511) that exceeded the threshold. Further, this higher estimate is incorrect and likely to be an overestimate, since it is based on a population broader than that licensed for panitumumab; in our response we estimate the eligible licensed population to be 5,123, which is well below the 7,000 threshold. Therefore panitumumab meets all three EoL criteria and as such should qualify as life-extending, end of life treatment.	Please see our response to EoL below.
Assessment of the ICER for panitumumab using the robust OS data and assuming EoL criteria are met The Committee state in the ACD that "even if the end-of-life criteria were met, an unacceptably large weighting would need to be put on the QALY to bring the ICERs for cetuximab and panitumumab into the range representing a	In our original report, we did indeed estimate the ICER for PAN+FOLFOX vs. FOLFOX based on OS data and the previous PAS as [redacted] per QALY. However, we later revised this estimate to an upper bound of [redacted] per QALY, as explained on p16 of our response document of 9th Oct 2015. In this revision, we no longer cost for any subsequent treatments from the 1st-line trials, and the ICER is an upper bound to reflect our belief that it is

Comment from consultee	Response from assessment group
cost-effective treatment". (4.41, pg 35) This conclusion is misleading for panitumumab. Whilst this may be true for a base case using suboptimal survival data, i.e. PFS data, it is not correct when using OS data. Indeed, the Assessment Group estimated the ICER for panitumumab based on OS data (and including the previous confidential PAS) to be [redacted], which although not within the threshold considered when appraising EoL treatments (£50K), [redacted]. It is also noteworthy that this estimate is based on the lower resection rate of 12.6% for panitumumab, whilst use of the 15% resection rate advised by the clinical experts (and acknowledged in the ACD) would have improved the ICER for panitumumab to below [redacted].	plausible that the OS benefit of PAN+FOLFOX vs. FOLFOX would have been slightly greater than that achieved in PRIME if no patients had received 2nd-line CET, PAN or BEV. As discussed below, we disagree with the assumption of a resection rate of 15% for PAN+FOLFOX.
Strength of the clinical evidence base for panitumumab Uncertainties regarding the clinical evidence base The PRIME WT RAS evidence was based on a pre-specified subgroup analysis that was accepted by the EMA, with baseline patient characteristics similar to the WT KRAS population and the intent to treat (ITT) population. The size of the WT RAS subgroup (n=512) compares favourably with that of the previously licensed WT KRAS population (n= 656 in PRIME) and the width of confidence intervals around the hazard ratios (HRs) for PFS and OS are similar in the 2 populations, suggesting that loss of precision is not an issue when moving from the WT KRAS population to the WT RAS population (**Error! Reference source not found.**). It should also be noted that a subgroup analysis was unavoidable since the ability of RAS mutation status to predict response to treatment was unknown when the PRIME trial was designed. Regarding maturity of the OS data, 82% of patients with WT RAS tumours in PRIME had died at the time of the updated analysis of OS compared with 72% of patients in OPUS (**Error! Reference source not found.**). We would	As previously mentioned, we do not believe the *RAS* WT population was prespecified in the PRIME trial and therefore is subject to the concerns surrounding retrospective analysis. As before, we agree that PRIME was the largest of the studies, hence why we chose it as the base RCT in the FOLFOX network in our economic model. Please see our response above concerning the maturity of OS in PRIME.

Comment from consultee	Response from assessment group
argue that the PRIME data are sufficiently mature and that NICE have been pragmatic and regularly have recommended therapies based on OS data that are not fully mature, e.g. TA319 (National Institute for Health and Care Excellence, 2014a). In summary, we believe that there is robust clinical evidence comparing panitumumab plus FOLFOX versus FOLFOX in WT RAS patients which demonstrates a statistically significant and clinically meaningful median OS gain of 5.6 months. Therefore the uncertainties raised in the ACD, regarding low sample size and missing data relate specifically to the evidence base for cetuximab plus FOLFOX and should not be attributed to panitumumab.	
Generalisability of the trial population in PRIME to patients treated in the NHS The ACD queried the relevance of the trial population in the pivotal phase 3 clinical trial (PRIME) to patients treated in the NHS. *"The Committee heard from clinical experts that the trial populations were younger than patients seen in clinical practice. The Committee concluded that the populations in the clinical trials of cetuximab and panitumumab differed from patients in clinical practice in England, and that this difference was a source of uncertainty in the clinical- and cost-effectiveness results". (Page 25, 4.29)* RCTs are considered the gold standard for assessing new interventions due to control of bias, however it is acknowledged that entry criteria can lead to populations that differ from those seen in routine clinical practice (Ballman et al, 2014). We think it is reasonable to assume that results from PRIME can be generalised to the wider NHS patient population and are not aware of any evidence to suggest otherwise. NICE have taken a pragmatic stance on this in other appraisals, e.g. TA221 (National Institute for Health and Care Excellence, 2011).	It is important to acknowledge the limitations of an RCT that selected patients that are younger than those seen in clinical practice. However, we are sympathetic to Amgen's appeal to pragmatism.

Comment from consultee	Response from assessment group
Robustness of the OS gain for panitumumab The ACD noted concerns regarding the robustness of the OS gain for panitumumab "The Assessment Group assumed in its base-case analysis that the duration of survival after first-line treatment was independent of first-line treatment (that is, any treatment effect from first-line drugs stopped when disease progressed). By contrast, in the randomised controlled trials, overall survival reflected response to both first and subsequent lines of treatment. However, the Assessment Group considered it inappropriate to assume this in its model because the trials included second-line drugs that are not commonly used in the NHS (including second-line panitumumab, cetuximab and bevacizumab) and may prolong survival. It also noted that second-line treatments were imbalanced across the trial arms. In addition, it considered that the survival data from trials were not mature enough. Therefore the Assessment Group modelled only progression-free survival from the randomised controlled trials, not overall survival". (Page 14, 3.13) We believe that the economic model should be based on OS which is widely recognised as the "gold standard" endpoint in oncology trials from a clinical and patient perspective (Driscoll et al, 2009). It is common for patients to move on to subsequent lines of treatment (which may prolong survival) post-progression in oncology trials and we note that NICE has previously accepted economic models based on OS in this situation, e.g. TA319, TA268 and TA269 (National Institute for Health and Care Excellence, 2014a; National Institute for Health and Care Excellence, 2012a; National Institute for Health and Care Excellence, 2012b). We acknowledge that subsequent treatments may prolong survival (in particular second-line anti-EGFR therapy and bevacizumab which are not commonly used in the NHS) and that these were not balanced across treatment arms in PRIME. It should be noted that the proportion of WT RAS patients receiving any subsequent anti-tumour therapy was slightly higher in the FOLFOX arm compared with the panitumumab arm (67% vs 58%): Use of traditional chemotherapy agents was slightly higher in the FOLFOX arm (64% vs 54%), whilst use of bevacizumab was broadly	Amgen now present an analysis of the *RAS* wild-type OS data from PRIME adjusting for imbalances in second line treatment. The conclusion is consistent with their earlier analysis of the *KRAS* wild-type data adjusting for imbalances. We agree with their conclusion that the observed OS benefit of PAN+FOLFOX vs. FOLFOX in PRIME is an under estimate of the benefit if there had been no imbalance in second line treatment. We have some sympathy with Amgen's comment that the validity of a PFS-based model for the base case is questionable given that the OS benefit of PAN is greater than the PFS benefit of PAN and that a smaller proportion of patients in the PAN+FOLFOX arm received active 2nd-line treatments than in the FOLFOX arm. However, we disagree with their corresponding argument for the OPUS trial. In this case, the OS benefit of CET+FOLFOX is less than the PFS benefit of CET+FOLFOX, and a smaller proportion of patients in the CET+FOLFOX arm received active 2nd-line treatments than in the FOLFOX arm. Anyhow, as discussed above, we leave it to the NICE committee to choose whether to consider the PFS or OS method in the base case.

Comment from consultee	Response from assessment group
similar for the FOLFOX and panitumumab plus FOLFOX arms respectively (13% vs 16%). However subsequent anti-EGFR therapy was more commonly received in the FOLFOX arm than in the panitumumab plus FOLFOX arm (19% vs 7%). In our response to the Assessment Report, we presented analysis which used a variety of recognised statistical methods to explore the impact of subsequent anti-EGFR therapy on the OS benefit in PRIME in WT KRAS patients (Douillard et al, 2012). We now present further analysis in the WT RAS population of interest, using the inverse probability of censoring weighted (IPCW) method; the OS HR for panitumumab plus FOLFOX versus FOLFOX is 0.69 (95% CI 0.50 to 0.95) compared with the ITT analysis HR of 0.77 (95% CI 0.64 to 0.94) (Table 1). The results from the WT RAS analysis confirms those presented for KRAS and suggest that the true OS benefit for panitumumab plus FOLFOX versus FOLFOX is larger than that observed in the PRIME trial (Table 1). The Assessment Group acknowledged this during the first Appraisal Committee meeting and stated likewise in their response to consultee comments that the ICER for panitumumab plus FOLFOX versus FOLFOX can be considered an upper bound (in OS scenario analysis). In addition, the ACD concerns about the use of second-line drugs that are not commonly used in the NHS are only relevant if they serve to prolong the OS gain for panitumumab. The results presented in the table below show that these concerns are unfounded, as they do not inflate the OS gain for panitumumab. Table 1. Impact of subsequent anti-EGFR therapy on OS in PRIME	

	OS HR (95% CI) Panitumumab plus FOLFOX vs FOLFOX	
	WT KRAS[a]	WT RAS[b]

Comment from consultee	Response from assessment group

Intent to treat analysis	0.88 (0.73, 1.06)	0.77 (0.64, 0.94)
Statistical model for influence of subsequent anti-EGFR therapy		
Branson & Whitehead, 2002	0.84 (0.68, 1.05)	
Robins & Tsiatis, 1992	0.83 (0.66, 1.04)	
Allison, 1995	0.68 (0.55, 0.83)	
Inverse probability of censoring weighted (IPCW)	0.74 (0.56, 0.97)	0.69 (0.50, 0.95)

CI, confidence interval; HR, hazard ratio; OS, overall survival; WT, wild-type.

[a] Based on final analysis (data cut-off 02 August 2010).

[b] Based on OS update analysis (data cut-off 24 January 2013).

Source: WT KRAS: (Douillard et al, 2012); WT RAS: (Peeters et al, 2013).

The validity of a PFS-based model for the base case is questionable given that OS results generated from the model are not consistent with results from the PRIME and OPUS trials: In Table 3 of the ACD the base case model mean OS gain for panitumumab plus FOLFOX versus FOLFOX is 2.6 months, which is substantially lower than the mean OS gain of 5.7 months in PRIME. Similarly, the base case model mean OS gain for cetuximab plus FOLFOX versus FOLFOX is 6.6 months, which is much higher than the mean OS gain of 0.5 months in OPUS.

In summary, we do not accept that an OS model is inappropriate and indeed the Assessment Group have stated that OS is an important scenario analysis in their response to consultee comments. Analysis of the impact of subsequent therapies on OS suggests that the OS benefit observed is an underestimate of the true benefit of panitumumab plus FOLFOX compared

Comment from consultee	Response from assessment group
with FOLFOX. This also addresses ACD concerns regarding second-line therapies not commonly used in the NHS, by demonstrating that they do not prolong OS gain for panitumumab. Therefore we consider OS data in PRIME is robust and should be used in the economic model, in preference to PFS data, to inform the base case ICER.	
Consideration of the EoL criteria for panitumumab The Appraisal Committee considered the evidence presented on the EoL criteria and concluded that the while panitumumab fulfilled the criteria of short life expectancy and extension to life, there was uncertainty around the criterion of small patient population (< 7000 people) and therefore it deemed that EoL status was "probably not met" for panitumumab. The Assessment Report included three population estimates for the RAS WT mCRC population: 5,968, 4,728 and 8,511, the first two being Merck Serono estimates and the last the Assessment Group's estimate of the population. The decision that panitumumab does not meet EoL criteria was based solely on the one estimate that exceeded 7,000 and consequently is unbalanced. More importantly, the Assessment Group's estimate of 8,511 is an overestimate as it is based on a population that is broader than the population licensed for treatment with panitumumab: The license for panitumumab is limited to WT RAS patients who are eligible for certain chemotherapy regimens (FOLFOX or FOLFIRI in the first-line setting and FOLFIRI in the second-line setting for patients who have received first-line fluoropyrimidine-based chemotherapy excluding irinotecan) The estimate of 8,511 is based on the total (instead of the licensed) wild type RAS population, regardless of the type of chemotherapy regimen these patients would be eligible for. Using the IMS Oncology Analyser (an oncology patient-record database based on clinician-reported case histories from UK patients and considered the most established and robust data source of market share data) we	We agree that, for all patients combined, the NICE ACD states that panitumumab fails to meet the EoL criteria solely based on the patient population size (p36 ACD). The NICE committee also concluded that panitumumab does not meet the EoL criteria for the subgroup of patients with metastases confined to the liver for several reasons, one of which being the total patients population size (p36 ACD). First, we understand that eligibility for EoL must be assessed based solely on the current criteria, not criteria that may apply in the future. The three values presented were different estimates for the total population. The plausibility of each is not necessarily equal and as such, the conclusion that 2/3 were below 7,000 so that must be where the true number lies is incorrect. The current EMA licence for panitumumab (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000741/WC500187313.pdf) reads: "Vectibix is indicated for the treatment of adult patients with wild-type RAS metastatic colorectal cancer (mCRC): • in first-line in combination with FOLFOX or FOLFIRI. • in second-line in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan). • as monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and

Comment from consultee	Response from assessment group
demonstrate that the population size falls well below the criterion of 7,000 when considering the patients eligible for panitumumab as per its license indication in different lines of therapy. The number of patients treated with FOLFOX or FOLFIRI in the first- line setting who would be eligible for panitumumab first-line therapy, in accordance with its license, was estimated to be 3,250 (**Error! Reference source not found.**). The number of patients eligible for panitumumab second-line therapy, in accordance with its license, was estimated to be 1,693 (**Error! Reference source not found.**). The number of patients eligible for panitumumab third-line monotherapy (after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens), in accordance with its license, was estimated to be 180 (**Error! Reference source not found.**). This was based on the Tappenden algorithm (Tappenden et al, 2007), where 5% of the total second-line chemotherapy population goes on to receive third line chemotherapy. Therefore a total of 5,123 patients are eligible for panitumumab across the first, second and third-line settings, which is well below the suggested population limit for EoL criteria. It is highly likely that this estimate of population size is an overestimate. In the first-line setting, the market share of patients previously treated with FOLFOX/FOLFIRI regimens (45.2%, **Error! Reference source not found.**) also included regimens in combination with a biologic. In the second-line setting, the market share of patients previously treated with fluoropyrimidine combination therapy without irinotecan (47.1%, **Error! Reference source not found.**), included cetuximab treatment (although in practice retreatment with an anti-EGFR inhibitor would be highly unlikely). It is also noteworthy that in the previous NICE assessment of aflibercept in TA307 (National Institute for Health and Care Excellence, 2014b), the total second-line chemotherapy population in mCRC accepted by the Committee was 4,000 patients (Wade et al, 2013). This is again much smaller than the estimate of total second-line	irinotecan-containing chemotherapy regimens. first-line fluoropyrimidine-based chemotherapy (excluding irinotecan). • as monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. Amgen now make the claim that the patient population relevant for the EoL criteria for 1st-line treatment is comprised of patients who are sufficiently fit for FOLFIRI or FOLFOX. We agree that only patients who are sufficiently fit for FOLFIRI or FOLFOX will be treated with PAN+FOLFIRI or PAN+FOLFOX. However, we are unsure whether the 1st-line population relevant for the EoL criteria is the whole 1st-line RAS wild-type population (as assumed in the NICE ACD), or just the subset who are eligible for FOLFIRI or FOLFOX. If the former is true, then the size of the eligible population (for EoL consideration) according to Amgen's figures is approximately equal to our estimate of 8,500 patients. If the latter is true, the size of the eligible population is about 5,100, as stated by Amgen.

Comment from consultee	Response from assessment group
chemotherapy population of 7,190 in **Error! Reference source not found.**. The Appraisal Committee's conclusion that panitumumab does not meet the population size EoL criterion is also inconsistent with previous EoL determinations where NICE have placed less importance on this criterion and accepted treatments whose estimates of patient numbers were less certain and exceeded the threshold (<7000). Examples include TA309 (National Institute for Health and Care Excellence, 2014c) and TA208 (National institute for Health and Care Excellence, 2010). The ongoing consultation jointly published by NHS England and NICE for the future of the CDF proposes the removal of the restriction of cumulative patient population from the current EoL criteria, recognising that "this criterion has rarely been engaged". Although the NHS England / CDF consultation is ongoing and is expected to be published in April 2016, it is important for the Committee to be aware of the impending changes to the EoL criteria, since panitumumab would certainly qualify for EoL under the new proposals. Importantly, the current considerations of the Committee that panitumumab does not meet EoL criteria would no longer be relevant when guidance on this appraisal (ID794) comes to be published in April next year. We have demonstrated that when using the current EoL criteria (which include the criterion on small patient population size), the panitumumab licensed population falls well within the upper bound of 7,000 patients and should therefore qualify as an EoL treatment. In addition, panitumumab will also meet the revised changes to the EoL criteria proposed under the ongoing CDF consultation, with the removal of the criterion for small patient population size.	
Assessment of the ICER for panitumumab using the robust OS data and assuming the EoL life criteria are met The Assessment Group estimated the ICER for panitumumab to be [redacted], based on OS data and including the previous confidential PAS.	Please see our earlier response. In particular, our revised ICER for PAN+FOLFOX vs. FOLFOX based on OS data and including the previous PAS is [redacted] per QALY, not [redacted] per QALY, as Amgen say here. We assume resection rates of [redacted] for PAN+FOLFOX and [redacted] for

Comment from consultee	Response from assessment group
This is not substantially above the threshold considered when appraising EoL treatments (£50K). Further, the use of the higher resection rate advised by the clinical experts (and acknowledged in the ACD) would improve the ICER for panitumumab to below [redacted]. The Committee state in the ACD that "even if the end-of-life criteria were met, an unacceptably large weighting would need to be put on the QALY to bring the ICERs for cetuximab and panitumumab into the range representing a cost-effective treatment". (Page 35, 4.41) This conclusion is misleading for panitumumab. Whilst this may be true for a base case using suboptimal survival data, i.e. PFS data, it is incorrect when using OS data from the PRIME study to inform the base case model. Indeed, the Assessment Group estimated the ICER for panitumumab based on OS data and including the previous [redacted] confidential PAS to be [redacted], which although is not within the threshold considered when appraising EoL treatments, is close to it. It is also noteworthy that the ICER is expected to decrease further when a resection rate of 15%, as advised by experts, is applied instead of the current lower resection rate of 12.6% for panitumumab.	FOLFOX, which were taken directly from *RAS* wild-type patients in PRIME. Amgen now suggest a resection rate of 15% for PAN+FOLFOX, "*as advised by experts*." We assume the quote comes from the ACD, p29: "*It heard from clinical experts that, for patients whose tumours are initially unresectable, chemotherapy with or without cetuximab or panitumumab could shrink the metastases enough to be resected in about 15% of people.*" However, if we were to use this advice, then we should assume a resection rate of 15% for both PAN+FOLFOX and FOLFOX, whereas Amgen advise the higher rate for PAN+FOLFOX only. In this case, the ICER for PAN+FOLFOX vs. FOLFOX would increase. Further on p29 of the ACD: "*The clinical experts advised that the resection rates for cetuximab and panitumumab chosen by the Assessment Group in its model were too high in both the overall population (in which, after first-line treatment, up to 20.7% of people had resection) and the subgroup of people with metastases confined to the liver (in which, after firstline treatment, up to 31.3% of people had resection). The Committee concluded that the Assessment Group had overestimated resection rates associated with cetuximab and panitumumab*." This contradicts the early statement from the clinicians that we have underestimated the resection rates for PAN+FOLFOX and FOLFOX. Next, it would be very poor practice to estimate the resection rate for PAN+FOLFOX from clinicians, and for FOLFOX from PRIME, a completely different source. This is because cost-effectiveness is most affected by the difference in resection rates between treatment arms. For these reasons, we do not accept Amgen's recommendation to estimate the resection rate for PAN+FOLFOX as 15%, whilst leaving the rate for

Comment from consultee	Response from assessment group
	FOLFOX as [redacted]
Consideration of a revised base case ICER for panitumumab using robust OS data, assuming EoL criteria are fulfilled, and applying the increased confidential PAS for panitumumab We would strongly recommend that the Committee consider a more plausible revised base case analysis based on the use of robust and highly plausible OS data and the fulfilment of current EoL considerations (including policy considerations around the removal of the EoL criterion on small patient population size), specifically: Use a model structure based on OS • Apply EoL considerations to panitumumab • Apply the increased confidential discount of [redacted] to the drug cost of panitumumab • Assume a resection rate of 15% as advised by experts We believe this more plausible revised base case, considering all the factors above, would bring the ICER for panitumumab into a range representing a cost-effective treatment.	As explained in our previous answer, we disagree with Amgen's suggestion to use a resection rate of 15% for PAN+FOLFOX. In a separate Addendum, we present our revised cost-effectiveness results given (1) the new PAS for panitumumab and (2) revised unit costs of drug administration (in response to comments from Merck Serono). Results are given based on the (a) PFS and separately the (b) OS modelling methods.

Factual inaccuracies identified by Amgen

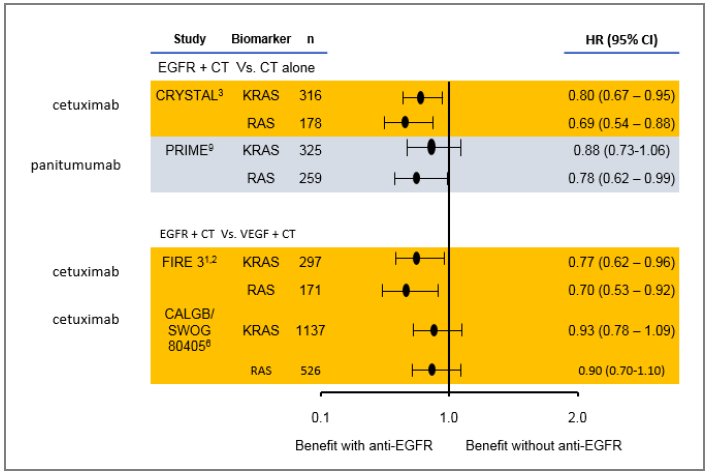
Section	Assessment report text	Comment from consultee	Response from assessment group
2.1	The 5-year survival rate for mCRC is stated as 'under 60%'	The value stated in the NICE final scope document is 6.6% so this should be corrected to 'under 10%'	
4.39	The ACD states 'The Committee understood from the clinical experts that the Assessment Group had overestimated resection rates. The Assessment Group had not presented ICERs using lower resection rates, but informed the Committee **that lower resection rates would increase the ICERs and worsen cost effectiveness'**	This statement is not correct for panitumumab. The resection rate used in the model for panitumumab is 12.6% which is below the 15% rate recommended by the clinical experts (section 4.36 of ACD) and therefore is not an overestimate. Using the 15% rate advised would decrease the ICER for panitumumab and improve cost effectiveness.	Please see our response previously

Comments from Merck Serono

Comment from consultee	Response from assessment group
Drug Administration Costs **The drug administration costs used by the Assessment Group remain unfeasibly high. Merck has uncovered that the Assessment group have indeed made errors regarding administration costs and included costs in the model that are already included in the HRG, thereby double-counting costs. This has been confirmed by Department of Health, Reference Costs Team as outlined in the attached letter (Appendix 2). Alongside the length of treatment, the cost of administration has the largest impact on model results and therefore it is important to highlight the errors made by the Assessment Group in estimating these costs. These erroneous costs are a key factor driving divergence between the ERG model and the reality of colorectal cancer treatment costs in England and Wales.** **The Assessment Group have overestimated costs through both duplication of costs and the unnecessary addition of costs which are in fact fully absorbed by the HRG. Based on the actual costs confirmed by NHSE, Merck have recalculated the administration costs involved. The model should be corrected, with chemotherapy administration cost at £830 per month, and cetuximab plus chemotherapy administration cost at £849 per month when using fortnightly dosing (or £1,505 per month if administered weekly).** **These costs are robust and are in line with other assessments in this therapy area, including one by the same Assessment group8, and should be the costs utilised for modelling going forward within this assessment. A full analysis of the errors identified, corrections applied, and NHS reference costs confirmation can be found in appendices 1 & 2.**	**We would like to thank Merck Serono for investigating this matter. We have now updated our unit costs of drug administration on the basis of their correspondence with the NHS Reference costs team (where pharmacy, line maintenance and infusion pump costs are included in the HRG codes) and have corrected for the wiring error which was double counting the cetuximab cost on Day 1 of the weekly dosing.** **We have also corrected the administration cost applied to the Day 8 cost of cetuximab as this was based on first attendance in a cycle, rather than being a subsequent element in a cycle. The difference in these costs is minimal (£330 rather than £303).** **As a result, our estimated monthly administration costs have fallen substantially, by between 34% and 61%:** • **FOLFOX4: from £2,348 to £1,544.** • **CET+FOLFOX4: from £4,714 to £2,277 (weekly admin CET).** • **PAN+FOLFOX4: from £2,473 to £1,563.** • **BEV+FOLFOX4: from £2,473 to £1,563.** • **FOLFIRI: from £1,634 to £830.** • **CET+FOLFIRI: from £4,000 to £1,563 (weekly**

Comment from consultee	Response from assessment group
	admin CET). • **BEV+FOLFIRI: from £1,759 to £849.**
Fortnightly cetuximab administration	Whilst we understand that fortnightly dosing is common practice and recommended by the CDF, we understand that NICE must make recommendations on the licensed use of cetuximab, namely weekly dosing. We assume that this also implies that the underlying economic evaluation should be based on assumptions that are consistent with the licence.

Comment from consultee	Response from assessment group
Applicability of clinical trial data to the UK population The committee expressed reservations regarding the applicability to the UK population of the clinical trial data used to support this submission. Clinical experts discussed that in practice cetuximab is reserved for a subgroup of mCRC patients who are fit enough to tolerate triple therapy (cetuximab/chemo) treatment and that the patients in the supportive studies were younger, had better performance status and fewer co-morbidities than the broad metastatic CRC population. Merck agrees that the patient population represented in clinical studies indeed represents a subset of the entire mCRC patient population, and that subset corresponds with those selected for cetuximab treatment in clinical practice, namely those of better performance status, who can tolerate and benefit from triple therapy (cetuximab plus FOLFOX or FOLFIRI). Therefore the clinical data findings should be considered relevant to UK practice.	
RAS wt analysis of cetuximab in combination with chemotherapy in the broad metastatic disease CRC population Concern has been expressed by the NICE committee that the RAS wild-type data under consideration to represent the clinical evidence for both cetuximab and panitumumab have limitations due to being post-hoc sub-group analyses. Merck do not contest this, and acknowledge that it increases uncertainty around results. However, it should be noted that modern science moves faster than clinical trials. Much research has been undertaken to understand the molecular and genetic pathways that play a role in identifying those patients that are likely to benefit from personalised medicines such as cetuximab and to exclude those patients that do not benefit. These data were considered robust enough to have warranted amendment of the marketing authorisation from the European Medicines Agency (EMA) in 2013 and have been accepted by the clinical panel of the CDF and the Scottish Medicines Consortium in their appraisal of first-line cetuximab (guidance 1012/14). In situations such as these, where biomarkers are identified subsequent to the completion of a clinical trial, conducting analysis of archived samples is the only viable option. Increased understanding of these biological pathways and improved personalisation of medicines such as cetuximab, means that patients who gain no clinical benefit are not exposed to unnecessary side-effects for no treatment gain. With the increased focus on personalised medicines in the advancement of oncology treatments, this phenomenon is	We agree that the best available evidence has been presented for this assessment, but this does not negate the concerns of using post-hoc subgroup analyses. We are not sure what Merck Serono are intending with their description of the 'improved hazard ratios' but would caution that with the overlap and widening of confidence intervals (as the population size decreases) that the 'improvement' is not statistically significant. That being said the decision to narrow from *KRAS* to *RAS* WT is outside the scope of this project and we are unclear what relevance it has to the committee's decision. We caution the interpretation of the results of the CALGB study. This is currently only reported in abstract and patients were not randomised to background chemotherapy, which may bias the results.

Comment from consultee	Response from assessment group
likely to be more frequently observed with emerging new therapies which will continue to be a challenge for NICE in the future. Notably the treated population has been successively restricted, first from all patients (the original intent to treat (ITT) population) to KRAS wild-type patients only, then from KRAS wild-type patients to All RAS (KRAS and NRAS wild-type patients). As the targeted population was restricted, so the hazard ratio improved (Figure 1). Figure 1. Improved hazard ratios in studies when population refined from KRAS to RAS wild-type  Merck contends that the clinical data presented supports the efficacy of cetuximab in combination with either FOLFOX or FOLFIRI chemotherapy backbones. In the large CRYSTAL study, superiority of cetuximab plus FOLFIRI compared to FOLFIRI alone was demonstrated across endpoints. The smaller phase 2 OPUS study was affected by the limited number of RAS wild-type samples available for analysis. Despite this, in the OPUS study the PFS improved when the population was refined from KRAS wild-type to RAS wild-type. The overall survival data demonstrated in the KRAS wild-type population became non-significant in the RAS wild-type patient population due to limited patient numbers, but as	

Comment from consultee	Response from assessment group
discussed earlier, the economic models developed by Merck and the Assessment Group are based on PFS. In this context, the ERG approach of modelling data seems the most appropriate way to address these uncertainties. Moreover these studies may underestimate the magnitude of impact on survival. [redacted] The confounding effect of later line anti-EGFR therapy is likely to have led to understatement of the true survival benefit of 1st line cetuximab. Examination of first line studies beyond that under consideration in this appraisal suggests that cetuximab in combination with FOLFOX or FOLFIRI can extend median overall survival to in excess of 30 months (FIRE3 – 33.1 months[14], CALGB-80405 - 32 months[15], CECOG/CORE2 – 28.5 months[12]). Assuming chemotherapy only provides approximately 20 months OS, which is what has been shown in numerous clinical trials and is reinforced by expert clinical opinion, these data reinforce the benefit seen with the addtion of cetuximab to chemotherapy compared to treatment with chemotherapy alone. With regards to data maturity, PFS and OS data from CRYSTAL and OPUS are mature and no further data is expected from these studies. In addition, as science has progressed since these studies were conducted and the benefit seen when combining cetuximab with chemotherapy in this patient population is well accepted, it is unlikely that any further large clinical trials would be undertaken comparing cetuximab/chemotherapy to chemotherapy alone in patients fit for triplet therapy. As noted earlier, it would be unethical to conduct such a clinical trial denying patients cetuximab/chemo and the associated clinical benefits. Therefore, funding decisions must be made on the data that is currently available.	
Cetuximab in combination with FOLFOX Cetuximab in combination with FOLFOX has demonstrated clinical benefit compared to FOLFOX alone. In addition to the OPUS study, the use of cetuximab with FOLFOX is supported by clinical trial data including the FOLFOX arm from the CALGB-80405 study[15], the	We agree the OPUS trial was small and as such results were uncertain. The other trials were not included in the AG's review as they

Comment from consultee	Response from assessment group
FOLFOX arm from the APEC study[10] and the CORE2 study which show strong efficacy data of 28-32 months median OS for cetuximab in combination with FOLFOX. These data are consistent with the outcomes seen for cetuximab in combination with FOLFIRI reflecting similar outcomes for cetuximab/FOLFOX as cetuximab/FOLFIRI. In the CALGB-80405 study, patients were treated with cetuximab/chemotherapy vs bevacizumab/chemotherapy[15]. The choice of chemotherapy backbone was left up to the investigators discretion. In the RAS wild-type analysis, PFS for patients for cetuximab/FOLFOX was 11.3 months and 12.7 months for cetuximab/FOLFIRI and OS was 32.5 months and 32 months respectively for cetuximab/FOLFOX vs cetuximab/FOLFIRI. In the APEC study in RAS wild-type patients, outcomes for cetuximab/FOLFOX vs cetuximab/FOLFIRI on a 2-weekly schedule were comparable; PFS 13.3 vs 12.8 months and OS 27.8 vs 28.7 months respectively[10]. These studies reinforce that there are similar outcomes whether cetuximab is used in combination with either FOLFOX or FOLFIRI. The phase II OPUS study, as a relatively small data set, is most affected by sample size reductions as a result of post hoc analysis based on licence restriction. In general, when the patient population is refined from Intention-To-Treat population to the KRAS wild-type population to the RAS wild-type population, due to the exclusion of patients that do not benefit from cetuximab, there is an improvement in outcomes (Figure 1). This has been observed in multiple studies and is the rationale behind the restriction of the cetuximab indication to RAS wild-type patients. For the PFS in OPUS, this improvement in outcome was observed, with an improvement from 1.1 months to 6.2 months. Reductions in the evaluable sample size affected statistical powering. From an OS perspective, insufficient subjects could be analysed to draw a robust conclusion. Therefore, although OPUS is the study used to represent the clinical data section for cetuximab/FOLFOX in this submission due to it being the only head to head trial against FOLFOX alone, other studies support comparable outcomes are seen when cetuximab is administered with either FOLFOX or FOLFIRI.	are currently published in abstract. Furthermore, as previously stated CALGB did not randomise to the background chemotherapy regimens.
FOLFOX6 vs FOLFOX4 Following on from expert opinion, the committee acknowledged that FOLFOX6 is the regimen	Our clinical expert believed that both FOLFOX4 and FOLFOX6 were both widely used on the NHS. Administration

Comment from consultee	Response from assessment group
that is most commonly used in the UK, rather than. FOLFOX6 is less costly than FOLFOX4 and not the other way around, as is stated in the ACD, which we believe to be a typo. These costs are addressed elsewhere in this response.	of FOLFOX6 is less costly than of FOLFOX4 (we estimate £830 and £1,544 per month, respectively), but as demonstrated in our sensitivity analysis the impact this had on results was minimal.
Treatment Durations and interval **In developing its model the Assessment Group utilised modelled estimates of mean treatment durations for cetuximab in combination with FOLFOX or FOLFIRI using exponential extrapolation of the median treatment durations report in the clinical trials, rather than using actual mean treatment durations from studies or real world data. Merck have supplied the actual mean treatment durations from the clinical trials which should be used in the base case model (Appendix 4).** **The panel noted uncertainty around length of treatment with cetuximab/chemo, and that the real world treatment duration estimated by experts was far shorter, around 6 months, than that modelled by the ERG, which was 10.7 months for cetuximab/FOLFIRI and 14.4 months for cetuximab/FOLFOX. These figures were based on a flawed and unconventional extrapolation of median treatment periods as reported in the respective clinical trials. As there is no evidence to support these overestimated treatment lengths, and in response to the Appraisal Committee's recommendation for investigating real-world treatment length in England, Merck has analysed real world data from [redacted] that have completed 1st line treatment with cetuximab plus either FOLFIRI or FOLFOX between 2012 & 2015, and the mean treatment duration in the real world was [redacted] (Appendix 5), which supports clinical expert estimate. This data is based on chart reviews conducted through market research for the period between March 2013 to October 2015 corresponds to approximately [redacted] of the CDF applications in this period and therefore can be considered to be a more accurate reflection of cetuximab treatment duration in the UK.** **As outlined, real world cetuximab/chemotherapy treatment durations are around [redacted], whereas treatment duration with chemotherapy alone is estimated to be approximately [redacted] for FOLFIRI and [redacted], slightly shorter due to neuropathy) for FOLFOX based on expert clinical opinion.**	**We did indeed estimate mean treatment durations by extrapolating treatment durations in the RCTs. We maintain this is was appropriate given the information at our disposal.** **In their Appendix 4, Merck Serono cite mean treatment durations that they claim we assumed in our analysis. We agree that we do indeed assume durations of 10.7 and 8.3 months for cetuximab + FOLFIRI and FOLFIRI respectively. However, the figure corresponding to our estimate duration on cetuximab + FOLFOX, of 14.4 months is incorrect. The 14.4 months is our estimated actual treatment duration, however, under our base case "PFS" method, we modelled a duration of 8.7 months, as we cap the modelled treatment duration at the mean PFS (in this case 8.7 months) (p285 our report). Similarly, the value of 9.0 months cited by Merck Serono for the duration of FOLFOX, should read 7.0 months.** **Next, in their Appendix 4, Merck Serono now give figures which they claim are the mean treatment durations from CRYSTAL and OPUS. They cite the source of these as the Addenda to the Clinical Trial Reports for CRYSTAL and OPUS.** **However, we do not find these figures in the Addenda. Merck are billing the mean durations as relevant to the *RAS* wild type population, but the trial reports do not**

Comment from consultee	Response from assessment group
	give data for this population. Instead, they discuss the whole population and the population split by *KRAS* status only. **However, given that the *KRAS* wild-type population is similar to the *RAS* wild-type population (specifically, the *KRAS* wild-type population covers the whole *RAS* wild-type population, and is approximately 20% larger), we believe that the mean treatment durations for the *KRAS* wild-type populations in the clinical study reports are important relevant information.** **First, in the CRYSTAL RCT, the mean and median treatment durations for cetuximab for the *KRAS* wild-type population for the cetuximab arm were [redacted] weeks respectively (p 2,397 Addendum to CRYSTAL study report). Next, Merck Serono previously told us that the median treatment duration for the *RAS* wild-type population is [redacted] (Merck Serono March 2015 data submission). Based on this, we estimate (based the accelerated failure time assumption) the mean treatment duration for the *RAS* wild-type population as [redacted] = [redacted] weeks. This compares with [redacted] weeks, which Merck Serono give in Appendix 4 of their response document. Given that these figures are similar, we believe that Merck Serono's estimated mean for the *RAS* patients of [redacted] weeks is plausible. This is substantially lower than our base case estimate of [redacted] weeks (which Merck Serono correctly cite in their Appendix 4).** **Further, in the CRYSTAL RCT, the mean and median treatment durations for the *KRAS* wild-type population**

Comment from consultee	Response from assessment group
	for FOLFIRI in the FOLFIRI arm were [redacted] weeks respectively (p 2,398 Addendum to CRYSTAL study report). Next, Merck Serono previously told us that the median treatment duration for FOLFIRI in the FOLFIRI arm for the *RAS* wild-type population is [redacted] (Merck Serono March 2015 data submission). Based on this, we estimate the mean treatment duration for the *RAS* wild-type population as [redacted] = [redacted] weeks. This compares with [redacted] weeks, which Merck Serono give in Appendix 4 of their response document. Given that these figures are similar, we believe that Merck Serono's estimated mean for the *RAS* patients of [redacted] weeks is plausible. This is substantially lower than our base case estimate of [redacted] weeks (which Merck Serono correctly cite in their Appendix 4). However, we are concerned that the mean treatment durations given the Clinical Study Reports may not have allowed for any censoring of patients. If there was censoring, and this was not considered, then the mean durations will underestimate the true means. In summary, we believe that the means from CRYSTAL Study Reports of [redacted] weeks for cetuximab and [redacted] weeks for FOLFIRI in the FOLFIRI arm may be correct. But given that (a) we do not find these figures in the Study Report and (b) we are concerned that censoring may not have been considered, we retain our mean treatment durations in our base case. However, we use

Comment from consultee	Response from assessment group
	Merck Serono's means in a Scenario analysis. **We now turn to the treatment durations from OPUS.** **Merck Serono now cite the mean and median treatment durations for cetuximab for the *KRAS* wild-type population for the CET+FOLFOX arm as [redacted] weeks respectively (p1,936 Addendum to OPUS study report). Next, Merck Serono previously told us that the median treatment duration for the *RAS* wild-type population is [redacted] (Merck Serono March 2015 data submission). Based on this, we estimate the mean treatment duration for the *RAS* wild-type population as [redacted] weeks. This compares with [redacted] weeks, which Merck Serono give in Appendix 4 of their response document. Given that these figures are very different, we believe that Merck Serono's estimated mean for the *RAS* patients of [redacted] weeks is far closer to the estimate of [redacted] from the CSR.** **Further, in the OPUS RCT, the mean and median treatment durations for the *KRAS* wild-type population for FOLFOX in the FOLFOX arm were [redacted] and [redacted] weeks respectively (p1,937 Addendum to OPUS study report).** **Next, Merck Serono previously told us that the median treatment duration for FOLFOX in the FOLFOX arm for the *RAS* wild-type population is 20.0 weeks (Merck Serono March 2015 data submission). Based on this, we estimate the mean treatment duration for the *RAS* wild-type population as [redacted] weeks. This is similar to the [redacted] weeks, which Merck**

Comment from consultee	Response from assessment group
	Serono give in Appendix 4 of their response document. **We again retain our estimated mean duration in our base case, and use Merck Serono's means in Scenario analyses as follows.** **First, in our base case, we estimate the mean modelled treatment duration for CET+FOLFOX by an indirect comparison as** [redacted] **Assuming Merck Serono's quoted mean for cetuximab, we estimate a** [redacted] **Our estimated mean treatment duration for cetuximab in the FOLFIRI network is not adjusted, as no indirect comparison is performed.** **Assuming our base case analysis, amended for unit costs of drug administration, and assuming the PAS for cetuximab and revised PAS panitumumab, and assuming Merck Serono's mean treatment durations from the RCTs, the ICER for:** • **CET+FOLFOX vs. FOLFOX is unchanged at** [redacted] **per QALY. The ICER is unchanged because even after we reduce the mean treatment duration, the mean modelled treatment duration**

Comment from consultee	Response from assessment group
	remains greater than the mean PFS for unresected patients ([redacted] vs. 8.7 months), and under the "PFS" method, we cap the modelled treatment duration at mean PFS (p285 our report) (in this case, 8.7 months). • **CET+FOLFIRI vs. FOLFOX reduces from [redacted] per QALY. In this case, the mean PFS of [redacted] months is greater than our estimated base case mean treatment duration of [redacted] months, and so the cap does not bite.** **In a second important Scenario analysis, we also consider the "OS" model structure. The following ICERs correspond to the changes in the previous scenario analysis and additionally, assuming the "OS" modelling structure:** • **CET+FOLFOX vs. FOLFOX reduces from [redacted] per QALY (corresponding to the "OS" method) to [redacted] per QALY. The ICER now falls because under the "OS" method, we do not cap treatment duration at a maximum of PFS.** • **CET+FOLFIRI vs. FOLFOX reduces from [redacted] per QALY.** **Next, we turn to the "real world" treatment durations reported by Merck Serono. At the first NICE committee meeting, the clinical experts considered that we had overestimated treatment durations in our analysis (p28**

Comment from consultee	Response from assessment group
	NICE ACD). The committee concluded that treatment duration with cetuximab or panitumumab may not reflect clinical practice and would have preferred to see the model validated with observational data (p29 NICE ACD). **In response, we are prepared to accept the clinicians'' view that our estimated treatment durations are longer than those in clinical practice. However, we maintain that they are most appropriate for the economic analysis, because they are consistent with the clinical outcomes from the trials, in particular, PFS in our base case analysis and PFS and OS in our scenario analysis under the "OS" method. If instead we assume treatment durations typical of those in the real world, then we ought also to assume outcomes such as resection rates, PFS and OS from real world data.** **Merck Serono estimate "real world" duration of 1st-line cetuximab + FOLFIRI and cetuximab + FOLFOX treatment as [redacted] (Appendix 5, Merck response document). Whilst this is interesting information, we clearly cannot critique this data rigorously given the limited information available to us.** **Given this, and given that we believe that it is important that the source of our estimates of treatment duration are consistent with the source of our estimates of clinical outcomes, namely OPUS and CRYSTAL, we do not consider Merck Serono's observational evidence in our base case analysis.** **However, in our Addendum, we now present Scenario analyses in which we assume a mean treatment duration**

Comment from consultee	Response from assessment group
	of 6 months for all treatments both in the whole patient population, and in the liver metastases subgroup.
End-of-Life criteria In the ACD, the NICE committee have concluded that cetuximab meets 2 of the 3 criteria for end of life for the broad metastatic population. The third criteria refers to the number of patients that are eligible for cetuximab in all indications. In relation to the size of the population for all licensed indications in England, we noted that NICE differentiated between cetuximab and panitumumab based on the indications under the license. We believe that to achieve a fair comparison between the two medicines, both should be treated on equal grounds and assessed in accordance with the size of the colorectal cancer population for balanced evaluation. Therefore Merck contends that head and neck cancer patients should not be included in this evaluation, for the reason outlined above. This is an unusual situation as the products in question do not share same licensed indications and therefore we ask the committee to take this into account when considering this criteria, particularly given that both agents have been studied in the H&N setting with cetuximab showing benefit in this setting and panitumumab failing to show benefit. Merck's understanding of the EOL criteria is that they were instated to determine the maximum number of patients that could possibly be treated with a new medicine. Cetuximab received marketing authorisation in 2004 and therefore its estimated usage can be determined with some certainty. In mCRC cetuximab has been subject to 4302 CDF applications for mCRC in all lines (1st, 2nd and subsequent lines) of therapy, in the 30 month period between March 2013 and Sept 2015. Numbers for the last year for first line cetuximab use in the mCRC population in combination with either FOLFOX or FOLFIRI, were approximately 600 for the period of Sept 2014 to Sept 2015 on the CDF (Table 1). *Cetuximab in locally advanced (LA) or recurrent metastatic (RM) squamous cell carcinoma of the head and neck (SCCHN)* In SCCHN, NICE TA145 NICE restricted the funded population to only those locally	The EoL criteria refer to the number of patients eligible to receive a treatment overall all licensed indications. For panitumumab, this includes only metastatic colorectal cancer. For cetuximab, this includes metastatic colorectal cancer and head and neck cancer. Merck Serono now quote the numbers of patients treated with cetuximab for mCRC and head and neck cancer on the Cancer Drugs Fund. These figures are not relevant to the EoL criteria, as the total for the EoL criteria refers to the size of the eligible patient population according to the licence. Merck Serono urge the committee to consider possible changes to the EoL criteria concerning the eligible patient population size. We believe that this is not relevant – the patient population size relevant to EoL is the one given in the 2013 Methods guide.

Comment from consultee	Response from assessment group
advanced SCCHN patients with a Karnofsky score of above 90 in whom all forms of platinum based chemotherapy were contraindicated or not tolerated. The number of patients with locally advanced (LA) SCCHN eligible for cetuximab treatment was estimated in TA145 to be 8% of the total SCCHN population. The committee were of the opinion that there are 3,000 SCCHN patients in England, therefore this equates to 240 patients (3,000 x 8%). NICE TA 172 did not recommend the use of cetuximab for SCCHN patients with recurrent or metastatic disease (RM). Cetuximab is currently available for RM SCCHN patients via the CDF and for the period of Sept 2014 to Sept 2015, there were around 150 applications in this setting. Therefore, in total it is estimated that approximately 400 patients get treated with cetuximab in England for SCCHN in both the LA and RM settings annually. *Total numbers* If this number is added to the 5,968 RAS wild type mCRC patients in England (data in TA176, updated to reflect RAS wild type subgroup), the total remains below the 7,000 limit stipulated by the end-of-life criteria. And as outlined above, only around 4,300 patients were treated with cetuximab over the period of 2.5 years (2013-2015) when cetuximab was available on the CDF in ALL lines, with approximately 600 patients treated in the first line over the course of one year, therefore it can be stated with certainty that the number of patients that would be treated with cetuximab for 1st line mCRC even combined with those treated under NICE for SCCHN would never reach 7,000. Based on real world usage, for both mCRC and SCCHN, approximately 1,000 patients would be treated annually. Cetuximab is well established in the UK, it has been available since 2011 and so has been used in clinical practice for a long period of time, and it is unlikely that treatment patterns would now change. Merck would also urge the commitee to consider the recent publication of the newly launched NICE/NHSE CDF consultation that proposes a change to the EOL criteria in the Guide to the Methods of Technology Appraisal 2013 that removes the requirement for the size of the eligible population to be less than 7,000 in England[16]. If this proposal is accepted through the consultation, this change is planned to be effective from 1st April 2016. Therefore, this would then mean that when the Final Guidance for this MTA is published, cetuximab will meet the EOL criteria and qualify for the higher threshold.	

Comment from consultee	Response from assessment group
Liver Resection Rates Resection rates In the LLD Population The LLD population is a preselected subset of patients with metastatic disease confined only to the liver. Data for this preselected population supports a resection rate of between 9% (Ye et al[17]) and 12.5% (Adam) for chemotherapy alone, compared to a resection rate of between 28% and 31% for cetuximab plus chemotherapy (Folprecht et al[13], Ye et al.[17] RESECT[18]). These data likely underestimate cetuximab effect in this setting as analysis was conducted on the KRAS patient subset and not the more refined RAS wild-type population, where outcomes would be expected to be improved. We do not have RAS wild-type data from these studies. The resection rates for the broad first line mCRC population are inappropriate to consider in the context of the LLD subset of patients. The advancement of treatments and the specialisation of management of patient care through multi-disciplinary teams (MDTs) will likely also mean that these rates in reality would be higher in current practice. In support of this information Merck would like to draw the panel's attention to the following paragraph from TA176: NICE TA176 (2008) Section 4.5 states: "It [the Appraisal Committee] heard from the clinical specialists that the number of patients receiving potentially curative liver resection in the CRYSTAL and OPUS trials was lower than that seen in UK clinical practice, which is based on management by multidisciplinary teams involving highly specialised liver surgical services. The clinical specialists stated that a more realistic rate for potentially curative resection with chemotherapy in general was approximately 12–15%, which could rise to approximately 30–35% with the addition of	We have taken our estimates of resection rates from the RCTs of 1st-line drugs. Earlier in this document, we have again defended this decision. Merck Serono seem to imply that data from the 1st-line RCTs is not available for the liver limited disease subpopulation. This is not true. We have taken resection rates for this subpopulation directly from these trials. We would also not that in the current appraisal, the ACD states: "It heard from clinical experts that, for patients whose tumours are initially unresectable, chemotherapy with or without cetuximab or panitumumab could shrink the metastases enough to be resected in about 15% of people" This resection rate of 15% appears to be applicable to all treatment arms and must supersede the opinion of the clinical specialists from TA176.

Comment from consultee	Response from assessment group
cetuximab." Resection rates in the broad mCRC population As outlined above the LLD patient population is a different group of patients to the broad first line mCRC population and there are different clinical trials and clinical data which reflect this. In this submission, the studies that support the clinical evidence are CRYSTAL and OPUS. These are studies that included patient with broad metastatic disease and not the LLD population. Therefore, resection rates reported in these studies are lower than they would be if these studies had focussed on LLD patients: CRYSTAL RAS wt resection rates - cetuximab/FOLFIRI 7.3% vs FOLFIRI alone 2.1%; OPUS KRAS wt - cetuximab/FOLFOX 9.8% vs 4.1% with FOLFOX alone. As mentioned earlier, it is also worth noting that resection rates are continuously improving over time with advancing clinical practice, patient care and surgical techniques and therefore these rates may be higher in current practice.	
Liver limited disease mCRC population Patients with metastatic disease confined to the liver (liver-limited disease, LLD), require different clinical considerations to patients with widespread metastatic disease, as the goal of treatment in the LLD setting is to shrink tumours to the point at which a patient is able to undergo surgical liver resection, rather than treatment until progression of disease. As the committee heard from the clinical experts at the first appraisal committee meeting, the duration of cetuximab/chemotherapy treatment in LLD patients is approximately 8-12 weeks, and no more than the 16 weeks currently recommended in TA176. The clinical rationale for limiting treatment duration for LLD patients is to maximise the potential for patients receiving cetuximab with chemotherapy to get an effective response to treatment, with sufficient shrinkage to allow liver resection to proceed, while minimising the duration of treatment with irinotecan or oxaliplatin containing regimens, which can both make surgical liver resection more complicated potentially compromising the effectiveness of the procedure. The numbers quoted by the Assessment group in the ACD are incongruous with both current	Merck Serono claim that we assume that: • patients remain on treatment following surgical resection of the liver, and they say that this assumption is flawed. • patients continue treatment for more than 16 weeks. Merck Serono say that this is contrary to the view of the clinical experts who advised NICE during the Initial Appraisal Meeting that the duration of treatment when using cetuximab in LLD patients should be 8-12 weeks, and no more than the 16 weeks currently recommended in TA176. In fact, we make neither of these two assumptions. As we stated in our response to Merck and Amgen on our report (9th Oct 2015): "Merck say we assume that resected patients are treated for the same duration as non-resected patients, and they we

Comment from consultee	Response from assessment group
NICE guidance in TA176, or with the evidence provided by the experts at the ACD meeting. This can be attributed to flawed modelling assumptions made by the Assessment Group in relation to the subgroup of patients with metastases confined to the liver. These assumptions are: Patients remain on treatment following surgical resection of the liver, which is not the case Patients continue treatment for more than 16 weeks. This is contrary to the view of the clinical experts who advised NICE during the Initial Appraisal Meeting that the duration of treatment when using cetuximab in LLD patients should be 8-12 weeks, and no more than the 16 weeks currently recommended in TA176. Applying a 16 week stopping rule in the Assessment Group's model for the liver-resection patient subgroup with the corrected administration costs and under the conditions of TA176 Patient Access Scheme (16% rebate off cetuximab NHS price when combined with FOLFOX), appropriate resection rates of 12.5% for chemotherapy and 28% for cetuximab/chemo, reduces the ICERs from £130,000/QALY to £27,581/QALY for cetuximab/FOLFIRI and from £186,000/QALY to £30,268/QALY for cetuximab/FOLFOX. This demonstrates the importance of applying this stopping rule in the model in order to appropriately reflect UK clinical practice and corresponding costs. Under current NICE guidance issued in TA176, cetuximab in combination with FOLFOX or FOLFIRI, within its licensed indication, has demonstrated cost-effectiveness and is recommended by NICE for use in patients with unresectable metastases confined to the liver. These key factors should be taken into consideration when comparing TA176 recommendations to the ongoing assessment of cetuximab in RAS wild type mCRC patient with metastasis confined to the liver: The current assessment is based on a better defined patient population who are more likely to benefit from cetuximab, due to improved molecular targeting (all RAS wild-type patients instead of KRAS exon 2 wild-type patients) A patient access scheme that is significantly increased in patient coverage in comparison to the original offering (all first line RAS wild type mCRC patients compared to mCRC patients with liver only metastasis as in TA176) The proposed PAS for the total mCRC population applies to patients treated with either	should instead assume that resected patients are treated for 4 months. However, Merck cannot say that we assume that resected patients are treated for the same duration as non-resected patients, because neither we nor Merck model 1st-line treatment duration separately for resected vs. unresected patients. For us, this is because we do not have the data to do so. Instead, for the "all patients" analysis, we take treatment duration for all patients combined from the median and 25% and 75% percentiles given to us by Merck & Amgen. Both we and Merck base treatment durations on the durations in the trials. In the trials, it is likely that 1st-line treatment stopped at about the time of resection, about 4 months, as this appears to be normal clinical practice (as noted by the clinician in TA176). However, we cannot be sure of this, as we do not have the required data from the trials. Therefore, in the absence of data to the contrary, we defend our modelling of treatment duration. "For the liver metastases subgroup, we do indeed assume treatment durations greater than 16 weeks (e.g. 38 weeks for CET+FOLFOX). This is the data from the relevant RCTs, and reflects a proportion of patients who are resected (e.g. [redacted] for CET+FOLFOX) and a proportion who are not resected (e.g. [redacted] for CET+FOLFOX). It is quite possible that in the RCTs, treatment for resected patients stopped at the time of resection.

Comment from consultee	Response from assessment group
FOLFOX or FOLFIRI, rather than just those treated with FOLFOX in TA176 In the current ERG model there is no stopping rule, Merck assumes that similarly to NICE guidance in TA176 for patients with LLD, maximum cetuximab treatment would be limited to 16 weeks. A pragmatic stance taking these factors alone into consideration, vastly improves the value of cetuximab to patients meeting these criteria, compared to the previous assessment and represent increased value to the NHS.	

Specific comments from Merck Serono on the ACD

Section	ACD text	Comment from consultee	Response from assessment group
Page 3 Paragraph 2.1	The 1-year survival rate in England and Wales is about 75%, and the 5-year survival rate is under 60%.	This comment relates to survival rates for bowel cancer, all stages, after mentioning specific incidence of metastatic bowel cancer (Stage IV), and as a result the survival rates appear to refer to metastatic disease which is inaccurate. 5 year survival for metastatic bowel cancer are much lower at 6.6%3, and this should be amended to reflect this. Bowel cancer is the UK's 2nd biggest cancer killer.	No further comment required
Page 23 Paragraph 4.26	The Committee concluded that the Assessment Group had included the appropriate comparators in its base case, and noted that a scenario analysis provided results for FOLFOX6.	Merck disputes this comment. The Assessment Group acknowledged that their assessment costed FOLFOX-4, not FOLFOX-6. As previously discussed, Merck put the case that FOLFOX-6 should be costed and the clinical experts agreed that FOLFOX-6 was the preferred regimen in England. The Assessment Group should present a revised model that includes the cost for FOLFOX-6, not FOLFOX-4.	We presented results for FOLFOX6 in a scenario analysis and have shown that the impact upon cost-effectiveness is minimal.
Page 24 Paragraph 4.27	The Committee discussed the place of cetuximab and panitumumab in the treatment pathway. It understood that these drugs are combined with chemotherapy with the aim of making initially unresectable tumours resectable.	The goals of two distinct patient groups are not adequately captured or represented here. For patients with unresectable liver only metastases, patients receive neo-adjuvant therapy with cetuximab/chemotherapy, where high response rates and tumour shrinkage are the short term goals of treatment, to convert unresectable liver metastases to resectable. If this goal is achieved, the patient may undergo potentially curative liver resection. For patients who have metastases not confined to	No comment required

Section	ACD text	Comment from consultee	Response from assessment group
		the liver, or who have been treated as above and who remain unresectable, the treatment goal is palliation and to maximise their overall survival, balanced with an acceptable quality of life for the patient. In either setting, cetuximab can be combined with either FOLFIRI or FOLFOX.	
Page 24 Paragraph 4.27	The Committee concluded that cetuximab and panitumumab would be offered as first-line treatments with chemotherapy to a subgroup of people with metastatic colorectal cancer: people who have symptomatic disease and high volume metastases, either inside or outside the liver, which are not initially resectable.	The comment from the clinical experts that cetuximab and panitumumab would be reserved for people with high volume symptomatic disease where the treatment is to slow disease progression as quickly as possible reflects that in real clinical practice the total patient population that oncologists choose to treat with these agents is not as wide as the total eligible patient population. The committee appear to accept this. However, this is not reflected in the assessments regarding calculations for End of Life criteria.	The population relevant for the End of Life criteria is the total licensed population, not the subpopulation referred to by Merck Serono.
Page 25 Paragraph 4.29 Page 32 Paragraph 4.40	The Committee heard from clinical experts that the trial populations were younger than patients seen in clinical practice. The Committee acknowledged that the clinical experts had advised that cetuximab and panitumumab would be used only in a small subgroup of people with metastatic colorectal cancer (even smaller than the population in the marketing authorisation), but noted that it had	Merck would like to note that the clinical experts expressed that the trial populations were younger than patients regularly seen and treated in clinical practice. Clinical experts discussed that in practice cetuximab is reserved for a subgroup of mCRC patients who are fit enough to tolerate triple therapy (cetuximab/chemo) treatment and that the patients in the supportive studies were younger, had better performance status and fewer co-morbidities than the broad metastatic CRC population. Merck agrees that the patient population represented in clinical studies indeed	No comment required

Section	ACD text	Comment from consultee	Response from assessment group
	not seen evidence in this group.	represents a subset of the entire mCRC patient population, and that subset corresponds with those selected for anti-EGFR treatment in clinical practice, namely those of better performance status, who can tolerate and benefit from triple therapy.	
Page 26 Paragraph 4.32	It heard that there was no evidence that cetuximab plus FOLFOX was more effective than FOLFOX alone, but understood from the clinical experts that cetuximab would be given with FOLFIRI, not FOLFOX, in clinical practice (see section 4.27).	There are a number of clinical trials in addition to OPUS as well as clinical usage that supports the efficacy of cetuximab in combination with chemotherapy, both FOLFOX and FOLFIRI; this should be taken into account and the equivalence of benefit seen with cetuximab/FOLFIRI with cetuximab/FOLFOX be acknowledged. The OPUS RAS wild-type analysis is affected by the limited number of samples available in the post-hoc analysis but it does not represent the overall clinical efficacy dataset supporting cetuximab/FOLFOX. The use of cetuximab with FOLFOX is supported by additional clinical trial data including the FOLFOX arm from the CALGB-80405 study[15], the FOLFOX arm from the APEC study[10] and the CORE2 study[12] which show strong efficacy data of 28-32 months median OS for cetuximab in combination with FOLFOX. These data are consistent with the outcomes seen for cetuximab in combination with FOLFIRI.	As previously stated, caution should be used when interpreting the CALGB study as patients were not randomised to background chemotherapy. Also all three studies: CALGB, APEC and CORE2 are currently only available in abstract.

Section	ACD text	Comment from consultee	Response from assessment group
Page 12 Paragraph 4.8	In Merck Serono's base case, it compared: cetuximab plus FOLFOX4 with FOLFOX4 cetuximab plus FOLFIRI with FOLFIRI cetuximab plus FOLFIRI with bevacizumab plus FOLFIRI. Merck Serono provided results based on weekly dosing of cetuximab, the dosage recommended in the marketing authorisation, and also for fortnightly dosing of cetuximab, which is not specified in the marketing authorisation. NICE can issue guidance only within the marketing authorisation, so only results based on weekly dosing of cetuximab are relevant. The results in this document are based on weekly dosing of cetuximab unless otherwise stated. Merck Serono compared cetuximab plus FOLFOX with XELOX in a scenario analysis.	Cetuximab is typically administered intravenously every two weeks in combination with chemotherapy in first line mCRC in England. This dosing schedule is a doubling of the weekly cetuximab dose administered fortnightly. This treatment schedule, whilst differing from that in the Summary of Product Characteristics (SmPC), has become treatment practice. As the committee heard from one of the clinical experts from The Christie Hospital, they have not administered cetuximab on a weekly schedule for the last 8 years. Subsequently, the National Cancer Drugs Fund in England recommended this dosing regimen (NHS England website[9]) in February 2014. Fortnightly administration is the standard of care in many territories, including in the UK via the CDF and this dosing regimen is also supported by the NCCN, which have been deemed to be the most influential guidelines[10] and the British Columbia guidelines[19]. There are a number of studies where cetuximab has been used on a fortnightly basis. The randomised CECOG-CORE II phase II study evaluated cetuximab/FOLFOX administered weekly or every two weeks in 152 patients (Brodowicz et al., 2013). The authors concluded that cetuximab administered every two weeks has comparable activity and a comparable safety profile as weekly dosing in combination with FOLFOX. In the APEC study in RAS wild-type patients, outcomes for cetuximab/FOLFOX vs	No further comment required, please see our previous response

Section	ACD text	Comment from consultee	Response from assessment group
		cetuximab/FOLFIRI on a 2-weekly schedule were comparable; PFS 13.3 vs 12.8 months and OS 27.8 vs 28.7 months respectively[10]. These clinical results are similar to those from studies carried out with weekly dosing regimens such as CRYSTAL and OPUS, which underpin the NICE assessment. In addition, Hubbard and colleagues carried out a review of several studies assessing weekly vs. every two weeks cetuximab dosing and found that the results of dosing cetuximab fortnightly were comparable to those obtained from weekly dosing. Fortnightly administration also means that cetuximab can be given on the same day as chemotherapy once fortnightly reducing clinic visits by half, which results in more convenience and better quality of life for the patient[11,12] and is also therefore more economical to the NHS. The following statement is taken from the PenTAG report: "In the CRYSTAL and OPUS RCTs, cetuximab was given weekly. However, in our economic analysis, in common with Merck Serono, we assumed that cetuximab is administered fortnightly, to coincide with FOLFOX/FOLFIRI administration. Fortnightly administration is common clinical practice in the NHS. Further, Merck Serono argue on the basis of an open-label RCT and a literature review that 500mg/m² fortnightly administration is as effective as induction 400 mg/m² followed by weekly 250	

Section	ACD text	Comment from consultee	Response from assessment group
		mg/m² administration. We consider that this is justified by the clinical evidence." Merck contends that although the dosing schedule as outlined in the cetuximab SPC is weekly, common clinical practice is fortnightly administration. Therefore to model actual costs, fortnightly administration is a more accurate reflection of the cost burden to the NHS, whereas weekly administration would artificially inflate these figures. Merck is not suggesting NICE make a recommendation for cetuximab which is outside of its license, but rather that NICE models its calculations based on the most accurate reflection of the costs in order to determine the true QALY.	
Page 16 Paragraph 4.17 Page 30 Paragraph 4.37	Drug administration unit costs. Merck Serono assumed lower costs, which reduced the ICERs, compared with the Assessment Group. During consultation of the assessment report, Merck Serono suggested that the Assessment Group's estimates included double-counting. The Assessment Group estimated drug administration costs appropriately; double-counting of costs was unlikely and would not substantially affect the ICERs.	The drug administration costs used by the Assessment Group remain unfeasibly high. Alongside the length of treatment, the cost of administration has the largest impact on model results and therefore it is important to highlight the errors made by the Assessment Group in estimating these costs. Merck continues to disagree with the costs used due to the following reasons: The Assessment Group have overestimated the cost of administration (£4,714 for Cetuximab+FOLFOX-4 and £4,000 for cetuximab+FOLFIRI) because they have unnecessarily duplicated HRG costs and added extra costs that should be fully absorbed by the	As previously stated, we thank Merck Serono for going into some detail of this and our full response can be found earlier in this document. Revised ICERs can be found in our addendum.

Section	ACD text	Comment from consultee	Response from assessment group
		HRG. The Assessment Group estimation contradicts with the 2014-2015 NHS reference costs guide which states the following: *"Unbundled HRGs for a number of services: These costs are generally high and only relate to a limited number of patients. Including them as an overhead on treatments and procedures would significantly distort costs and lead to wide variations. Trusts therefore report them separately as:* *• Chemotherapy – drug costs for cancer patients, split between procurement of regimens and delivery, with other costs included in the relevant admitted patient or outpatient setting"* Furthermore, it contradicts with the costs used in estimating the cost effectiveness of cetuximab in combination with chemotherapy for mCRC in NICE TA176, in which the ERG accepted that the cost of administration used absorbed pharmacy, infusion pump and line maintenance costs. To ensure accurate estimation of administration costs, Merck have sought the advice of NHS Reference Costs directly since they are the source of the HRGs used in both the Assessment Group and Merck economic models (see accompanied letter from NHS Reference Costs Team for further confirmation). It is clear from this table that the Assessment Group added the administration cost of cetuximab on day 8 (£302.58) in error to the administration cost of day 1 of each cycle; there were two day 8 administration costs present in both day 1 and day	

Section	ACD text	Comment from consultee	Response from assessment group
		8 when it should only apply to day 8. In addition, the Assessment group applied the additional costs of pharmacy, line maintenance and infusion pump equally between day 1 (cetuximab + FOLFOX) and day 8 (single cetuximab infusion) when these costs should be fully absorbed by the HRG, as NHS Reference Costs have confirmed in the accompanied letter. The Assessment Group have identified several administration costs used in previous NICE publications, including previous NICE assessment of cetuximab, and chose to use the highest costs published because the cost of administering monoclonal antibodies is generally higher than chemotherapy. We find this assumption to be unfounded given the cost of administration outlined above as advised by NHS Reference Costs. By way of comparison, the same assessment group (PENTAG) have estimated an average monthly administration cost per person of £1,480 in NICE TA242 which assessed cetuximab + chemotherapy for the treatment of metastatic colorectal cancer after first-line chemotherapy [2011]. This cost is more consistent with the cost of administration calculated using NHS Reference Cost advice (£1,505) and therefore proves that the Assessment Group have overestimated the administration costs. As advised by NHS reference costs, the HRGs used in the model fully absorb the additional costs added by the Assessment Group to these HRGs (Pharmacy costs, infusion pump and line	

Section	ACD text	Comment from consultee	Response from assessment group
		maintenance cost). If these costs are added to the HRGs, the administration costs will be more expensive than the acquisition cost of cetuximab + chemotherapy per month. In which case the acquisition cost is secondary to the administration cost in terms of impact on cost effectiveness. The statement that these costs do not substantially affect the ICERs is not correct. The Assessment Group and Merck have stated that the duration of treatment, with all the costs associated with it, are the most crucial and impactful factor in the estimation of the ICER. Since cetuximab + chemotherapy mean treatment duration is longer than that with chemotherapy only, the additional PFS in the chemotherapy arm accrues more treatment costs than chemotherapy only. Therefore, any change in the administration cost should have a great impact on the model. By using £1,505 per month for cetuximab + FOLFIRI/FOLFOX-6 instead of £4,000 per month as calculated by the Assessment Group, the ICER for this combination is reduced from £227k/QALY to £141k/QALY. This is without changing any of the Assessment Group assumptions and using the model they developed for this assessment. This demonstrates that administration costs have a large impact on ICERs, if not the largest out of all model parameters.	
Page 23 Paragraph 4.26	The Committee heard that FOLFOX4 and FOLFOX6 are equally effective, but that FOLFOX6 costs more than FOLFOX4.	This statement is incorrect. We suspect this may be a typing error as the experts clearly stated during the appraisal meeting that FOLFOX-4 administration costs are higher than FOLFOX-6. FOLFOX-4 requires the patient to visit the clinic on	No further comment required

Section	ACD text	Comment from consultee	Response from assessment group
		2 consecutive days, and therefore requires double the administration costs FOLFOX-6. FOLFOX-6 requires just one clinic visit for each patient, requires one cost for pharmacy time to make up the infusion, and is therefore less costly than FOLFOX-4. The clinical experts stated that the preferred regimen administered in the UK is FOLFOX-6.	
Page 16 Paragraph 4.17	Drug acquisition costs per month. Merck Serono assumed lower costs for cetuximab, and therefore lower ICERs, than the Assessment Group. Merck Serono used higher costs for FOLFOX and FOLFIRI than the Assessment Group, which does not impact cost effectiveness because both treatment arms are affected similarly.	Drug acquisition costs. Merck used the NHS price for cetuximab, rather than the list price, which was used by the Assessment Group. Merck used the BNF prices for both irinotecan & oxaliplatin, not the NHS acquisition prices. Consistent process should reflect the real cost to the NHS for all drugs. We noted the use of significantly lower chemotherapy acquisition costs using the CMU eMit tool to reflect true cost to the NHS. We believe that following this approach should allow for the use of actual cost of cetuximab to the NHS for fair comparison. We have indicated in our evidence submission that "Cetuximab has been offered at a guaranteed discounted price to the NHS in agreement with the Department of Health since 2008. This agreement is not limited to a time period. The NHS acquisition prices are £136.50 (100mg/20ml vial); £682.50 (500mg/100ml vial)." However, we followed the NICE methodology in using List prices for all comparators, including cetuximab to allow for a like-to-like comparison. Therefore, the use of CMU eMit cost for chemotherapy without the use of true NHS cost of cetuximab overestimates the cost difference	We discussed acquisition costs in great detail with NICE. For comparator arms the real cost to the NHS is reflected, in line with the NICE technology appraisal methods guide. At the Pre-meeting briefing teleconference on 30th Sept 2015, NICE instructed us not to use the NHS price for cetuximab in our base case. As cetuximab is an intervention and not a comparator, we are advised by NICE to use the list price. The NHS list price is also superseded by the PAS discount for cetuximab, which is applied to the list price and for which results have been presented to the committee in a confidential appendix.

Section	ACD text	Comment from consultee	Response from assessment group
		between cetuximab in combination with chemotherapy and chemotherapy alone. Using the model developed by the Assessment Group, the cost of cetuximab acquisition is reduced to £2,665.85 per month using the actual NHS price. Therefore, outside the consideration of cetuximab's patient access scheme price, the cost effectiveness of cetuximab should be based on the actual price to the NHS; i.e. £136.50 per 100mg vial.	

Section	ACD text	Comment from consultee	Response from assessment group
Page 30 Paragraph 4.37	The Assessment Group's estimate for average body surface area ($1.85m^2$) was plausible.	Merck have commented on the use of 1.85 m2 in our response to the Assessment Groups report. The use of such body surface area implicitly assumes that all patients treated would be in the highest dose banding which does not take into account patients with a lower body surface area and does not reflect the actual distribution of body surface area amongst patients. In practice, there is special consideration for this variation though dose banding where the link between body surface area and costs of the drug is a step function with steps at 1.60, 1.70 and 1.80 m2 and so a weighted average should be applied.	As we have previously stated on p27 of our response to Merck Serono and Amgen on 9th October 2015, and as explained in p401 of our report, our estimated mean BSA of 1.85m2 is based on a database of people receiving palliative chemotherapy for CRC (Sacco and colleagues (2010), Appendix S3, http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0008933), with 66% males, 34% females, the typical sex mix in the RCTs for mCRC. By contrast, Merck Serono do not give the source of their estimate of 1.79m2. Our estimate leads to a slightly higher estimate of mean mg of CET per administration. Assuming 1.85m2, the precise dose of CET is 923mg per patient, or 1,000mg allowing for wastage. Assuming 1.79m2, the precise dose is 895mg, or 900mg allowing for wastage. Both we and Merck assume wastage. Merck are incorrect to say that we implicitly assume that all patients would be in the highest dose banding. The BSA of some patients may actually be > 2m2. These patients would actually receive more than 1,000mg. We agree that we do not model the actual distribution of patients. We decided not do this, as we found this had little impact on cost-effectiveness in 2011 in TA242. Merck also do not model the actual distribution of patients

Section	ACD text	Comment from consultee	Response from assessment group
Page 30 Paragraph 4.37 Page 16 Paragraph 4.17	The Assessment Group's estimate for the cost of resection surgery (£10,440) was more plausible than Merck Serono's estimates of £2707 in its original submission. Cost of a resection operation. Merck Serono assumed a lower cost, which resulted in lower ICERs, compared with the Assessment Group.	Cost of a resection. Merck accepts that the original company submission incorrectly costed the cost of resection. It should be noted that although using a lower cost of surgical resection lowered the ICERs, it did not lower them significantly.	No comment required
Page 4 Paragraph 2.2	When possible, surgically removing (resecting) the primary tumour and metastases is considered, but usually only when there are no metastases outside of the liver.	In patients with metastatic disease, surgical resection of the primary tumour is common even when metastases are not confined to the liver and are more widespread. For patients with metastatic disease confined to the liver, the best chance of long-term survival is through resection of both the primary bowel tumour and the liver metastases.	No comment required.
Page 22 Paragraph 4.25	The Committee heard that patients with small numbers of resectable metastases confined to the liver (about 1–3 metastases) may proceed to surgery without any chemotherapy.	This is the case if the liver metastases are "upfront resectable" and can be surgically removed without the need for any down-sizing therapy. These patients wouldn't be treated with cetuximab as they are already resectable and therefore don't require tumour shrinkage.	No comment required.
Page 22 Paragraph 4.25	Clinical experts explained that they use first-line chemotherapy for 8–12 weeks, at which point they assess whether the patient is eligible for resection.	Merck agrees that patients with LLD get treated for 8-12 weeks (up to 16 weeks as in NICE TA176 guidance) to provide tumour shrinkage to allow successful resection of liver metastases.	No further comment required

Section	ACD text	Comment from consultee	Response from assessment group
Page 28 Paragraph 4.35 Page 30 Paragraph 4.38	The clinical experts stated that people who have resection generally have treatment for between 8 and 12 weeks. Duration of treatment with cetuximab was shorter in the original appraisal when the company applied a 16-week stopping rule. In the current appraisal, treatment duration ranged from 38–46 weeks in the Assessment Group's model and 25 weeks in the Merck Serono model, which the Committee had concluded were overestimates (see section 4.35). The Committee noted that a stopping rule had not been explored as part of the current modelling.		
Page 28 Paragraph 4.34	The Committee heard that the Assessment Group had modelled an average of 1.6 resection operations per patients, which the clinical experts noted reflected clinical practice. The Committee concluded that the model included uncertainties, but was an adequate basis for its decision-making.	The statement that clinical experts agreed with the Assessment Group that 1.6 resection operations per patient reflects clinical practice is not correct. Clinical experts stated that the risk of operation failure is likely to be lower than 60% in practice and hence the cost of surgery calculated by the Assessment Group is overestimated.	Our assumption of 1.6 liver resection surgeries per mCRC patient is based on data reported in Adam et al. (2004), the source used by Merck Serono and us to parameterise survival in resected patients. We made this assumption for two reasons: to account for the fact that, on average, mCRC patients undergo more than one liver resection surgery as reported in this source and other studies, and for the sake of consistency with the survival data used in our model.

Section	ACD text	Comment from consultee	Response from assessment group
Page 29 Paragraph 4.36	The Committee discussed the Assessment Group's estimates of the proportion of people who have resection of liver metastases after first-line treatment. It heard from clinical experts that, for patients whose tumours are initially unresectable, chemotherapy with or without cetuximab or panitumumab could shrink the metastases enough to be resected in about 15% of people.	The LLD population is a preselected subset of patients with metastatic disease confined only to the liver. Data for this preselected population supports a resection rate of between 9% (Ye et al) and 12.5% (Adam) for chemotherapy alone, compared to a resection rate of between 28% and 31% for cetuximab plus chemotherapy (Folprecht et al13, Ye et al.17, RESECT18). Merck would like to draw the panel's attention to the following paragraph from TA176 TA176 in 2008. Section 4.5 in NICE TA176 states: "It [the Appraisal Committee] heard from the clinical specialists that the number of patients receiving potentially curative liver resection in the CRYSTAL and OPUS trials was lower than that seen in UK clinical practice, which is based on management by multidisciplinary teams involving highly specialised liver surgical services. The clinical specialists stated that a more realistic rate for potentially curative resection with chemotherapy in general was approximately 12–15%, which could rise to approximately 30–35% with the addition of cetuximab."	Please see our previous response to this comment
Page 31 Paragraph 4.38	Resection rates were higher in the original appraisal, ranging from 30–43% compared with about 7–31% in the current appraisal. These were based on clinical expert opinion and the results of an open-label phase II	In this submission, the studies that support the clinical evidence are CRYSTAL and OPUS. These are studies that included patient with broad metastatic disease. As the patient population in these trials wasn't selected for those with LLD, resection rates are lower than they would be if they	Please see our previous response to this comment

Section	ACD text	Comment from consultee	Response from assessment group
	trial comparing cetuximab plus FOLFOX with cetuximab plus FOLFIRI (the CELIM trial). The Committee heard that the CELIM trial studied a specific subgroup of people with KRAS wild-type metastatic colorectal cancer who had metastases confined to the liver, good performance status and who were fit for surgery. It considered that the population in the CELIM trial was narrower than the population relevant to the current appraisal.	were LLD studies: CRYSTAL RAS wt resection rates - cetuximab/FOLFIRI 7.3% vs FOLFIRI alone 2.1%; OPUS KRAS wt - cetuximab/FOLFOX 9.8% vs FOLFOX alone.	
Page 12 Paragraph 4.9	In Merck Serono's deterministic base case of all patients, using the list price for cetuximab, the incremental cost-effectiveness ratios (ICERs) were £61,894 per quality-adjusted life year (QALY) gained for cetuximab plus FOLFOX and £74,212 per QALY gained for cetuximab plus FOLFIRI, compared with chemotherapy alone. Cetuximab plus chemotherapy produced approximately 0.3 extra QALYs compared with chemotherapy alone. Merck Serono did not provide estimates of cost effectiveness for the subgroup of people with metastases confined to the liver who have cetuximab weekly.	Under the current NICE guidance issued in TA176, cetuximab in combination with FOLFOX or FOLFIRI, within its licensed indication, has demonstrated cost-effectiveness and is recommended by NICE for use in patients with unresectable metastases confined to the liver. As a result Merck did not provide an initial cost-effectiveness assessment in this appraisal, as the understanding was that the cost-effectiveness had already been established and would be improved beyond the current guidance in TA176 based on 2 key facts: a) This assessment is based on a better defined patient population who are more likely to benefit from cetuximab, due to improved molecular targeting (all RAS wild-type patients instead of KRAS exon 2 wild-type patients); b) A patient access scheme that is significantly increased in patient coverage in comparison to the	We disagree, as in this HTA, the cost-effectiveness of all relevant patient populations, including the liver-limited subpopulation, is re-appraised.

Section	ACD text	Comment from consultee	Response from assessment group
		original offering (all first line RAS wild type mCRC patients compared to mCRC patients with liver only metastasis as in TA176). A pragmatic stance taking these factors alone into consideration, and applying the same disease management assumptions in TA176, should vastly improve the value of cetuximab to patients meeting these criteria, compared to the previous assessment and represent increased value to the NHS.	
Page 18/19 Paragraph 4.20	In the Assessment Group's base-case analysis of the subgroup of people with metastases confined to the liver, cetuximab and panitumumab produced more incremental QALYs than chemotherapy alone (0.40–0.57) and the ICERs were lower than for the full population. The ICERs for cetuximab (using the discounted price) plus chemotherapy were about £130,000 per QALY gained compared with chemotherapy alone. The ICER for panitumumab (using the confidential discounted price) plus chemotherapy was substantially above £30,000 per QALY gained compared with chemotherapy alone. NICE cannot report the exact ICERs for panitumumab because the patient	The numbers quoted here are an inaccurate reflection of the true ICERs for the LLD patient population. This can primarily be explained by the fact that in the ERG model patients continue to get treated beyond 16 weeks, whereas in actuality patients in this group get treatment for 8-12 weeks, and up to 16 weeks, as was noted by the clinical experts. In addition, in the Assessment Groups model patients remain on treatment following surgical resection of the liver. Applying a 16 week stopping rule in the Assessment Group's model for the liver-resection patient subgroup with the corrected administration costs and the TA176 assumptions, and resection rates of 12.5% for chemotherapy and 28% for cetuximab/chemo, reduces the ICERs from £130,000/QALY to £27,581/QALY for cetuximab/FOLFIRI and from £186,000/QALY to	Please see our previous response to such comments.

Section	ACD text	Comment from consultee	Response from assessment group
	access scheme is confidential. Page 32 Paragraph 4.39 The ICERs for cetuximab and panitumumab were lower in the subgroup of people with metastases confined to the liver. The ICER for cetuximab was about £127,000 per QALY gained when it was combined with FOLFOX and £129,000 per QALY gained when combined with FOLFIRI, both compared with chemotherapy alone. The ICER for panitumumab plus FOLFOX remained substantially above £30,000 per QALY gained compared with FOLFOX. NICE cannot report the exact ICERs for panitumumab because the patient access scheme is confidential.	£30,268/QALY for cetuximab/FOLFOX. This demonstrates the importance of applying this stopping rule in the model.	
Page 9 Paragraph 4.3	The Assessment Group stated that the clinical evidence was limited because it reflected subgroup analyses. The trials were analysed post-hoc after re-evaluating tumour samples from people with KRAS wild-type exon 2 tumours, and reclassifying them by RAS wild-type status as currently defined. The Assessment Group noted that there were few samples available for re-analysis and missing data further reduced the power of some studies. The Assessment Group stated that	The paragraph makes reference to the fact that the RAS wild-type data under consideration to represent the clinical evidence for both cetuximab and panitumumab are post-hoc sub-group analyses. While Merck do not contest this, it should be noted that modern science moves faster than clinical trials. Much research has been undertaken to understanding the molecular and genetic pathways that play a role in identifying those patients that are likely to benefit from anti-EGFR therapies such as cetuximab and panitumumab and to exclude those patients that do not benefit. These data were considered robust enough to have warranted amends to the	No further comment

Section	ACD text	Comment from consultee	Response from assessment group
	the trial populations were generally balanced with respect to baseline characteristics, which lessened confounding bias.	marketing authorisations of both drugs in 2013 and increasing the personalisation of medicines such as cetuximab means that patients who gain no clinical benefit are not exposed to unnecessary side-effects for no treatment gain.	
Page 25 Paragraph 4.29 Page 28 Paragraph 4.33	The Committee discussed the clinical trial evidence for cetuximab and panitumumab in people with RAS wild-type metastatic colorectal cancer. It heard that the Assessment Group considered that survival data were not sufficiently mature, and that the size of the effect was confounded by the use of different second and subsequent lines of treatment across the trial arms. The Committee would have preferred to see a model based on survival data from trials, but understood that the trial data for cetuximab and panitumumab may have been confounded by second-line drugs that are not commonly used in the NHS.	With regards to data maturity, PFS and OS data from CRYSTAL and OPUS are mature and no further data is expected from these studies. In addition, as science has progressed since these studies were conducted and the benefit seen when combining cetuximab with chemotherapy in this patient population is well accepted, it is unlikely that any further clinical trials would be undertaken comparing cetuximab/chemotherapy to chemotherapy alone in patients fit for triplet therapy. Therefore, funding decisions should be made on the available data. In the CRYSTAL trial [redacted] of patients in the cetuximab/FOLFIRI group and [redacted] of patients in the FOLFIRI alone group received subsequent chemotherapy treatment in the ITT population. Of this only [redacted] in the cetuximab/FOLFIRI group and [redacted] in the FOLFIRI alone group received a subsequent anti-EGFR therapy. As can be seen there was a low level of personalised medicine use in later lines of treatment. In the case of bevacizumab use, it is balanced between the two arms and so wouldn't be expected to cause an imbalance in the outcomes. Regarding subsequent anti-EGFR use,	Please see our earlier comments to Amgen.

Section	ACD text	Comment from consultee	Response from assessment group
		there was approximately three times the use in the FOLFIRI alone arm compared to the cetuximab/FOLFIRI arm which may have improved outcomes for those patients in the FOLFIRI alone group. Even with this, the benefits seen when adding cetuximab to FOLFIRI were still significantly better than the FOLFIRI alone group. There were similar findings in the OPUS trial with [redacted] of patients receiving a subsequent anti-cancer therapy in either arm. EGFR-targeted subsequent therapies were received by [redacted] of patients in the cetuximab/FOLFOX arm and [redacted] in the FOLFOX alone arm.	
Page 27 Paragraph 4.32	The Committee concluded that the clinical evidence surrounding the degree to which cetuximab and panitumumab are effective in RAS wild-type metastatic colorectal cancer was subject to considerable uncertainty.	In the context of the head to head clinical trial data under consideration here (CRYSTAL, OPUS), There is an evidence base beyond that under consideration in this appraisal that suggests that cetuximab can extend median overall survival to in excess of 30 months, which is a step change to that observed across many studies that have investigated the efficacy of multiple lines of chemotherapy, where median survival durations are in the region of 20 months.	The direct head to head trial data gave the following results: OPUS CET+FOLFOX vs. FOLFOX OSHR 0.94 (95% CI 0.56, 1.57). Median OS 19.8 months CET+FOLFOX vs. 17.8 months FOLFOX CRYSTAL CET+FOLFIRI vs FOLFIRI OSHR 0.69 (95% CI 0.54,0.88) Median OS 28.4 months CET+FOLFIRI vs 20.2 months FOLFIRI We cannot comment on the other sources of data that Merck Serono mention here as they have not provided sources
Page 35 Paragraph 4.41	The Committee recalled hearing from the clinical experts that patients in the clinical trials of cetuximab and panitumumab were younger and fitter	The committee expressed reservations regarding the applicability to the UK population of the clinical trial data used to support these submissions. Clinical experts discussed that in practice	No comment required.

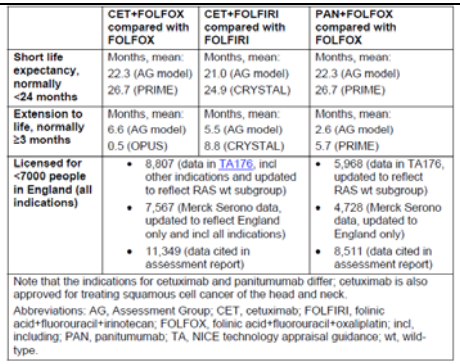
Section	ACD text	Comment from consultee	Response from assessment group
	than patients in clinical practice in England, so patients in clinical practice may not achieve the level of survival benefit estimated. The Committee considered that these estimates were not sufficiently robust.	cetuximab is reserved for a subgroup of mCRC patients who are fit enough to tolerate triple therapy treatment and that the patients in the supportive studies were younger, had better performance status and fewer co-morbidities than the broad metastatic CRC population. Merck agrees that the patient population represented in clinical studies indeed represents a subset of the entire mCRC patient population, and that subset corresponds with those selected for cetuximab treatment in clinical practice, namely those of better performance status, who can tolerate and benefit from triple therapy. Therefore the clinical data findings should be considered relevant to UK practice.	
Page 15 Paragraph 4.17	Duration of first-line treatment. The Assessment Group considered that Merck Serono underestimated the mean duration of treatments. This resulted in lower drug acquisition costs and lower ICERs than the Assessment Group's estimates. The Assessment Group noted that treatment duration was the most important issue explaining the difference between the results of the Merck Serono model and the Assessment Group's model.	Duration of first line treatment. Merck provided the mean values for treatment duration from the OPUS & CRYSTAL trials, in the response to the Assessment Group report, sent to NICE on 21st September 2015, having initially used median values, which were inconsistent with a mean calculated value from the Assessment Group. Merck notes that the Assessment Group model used a mean value extrapolated from the median using an unconventional method as opposed to using the actual uncensored mean values of treatment duration reported in the clinical trial reports provided by Merck. The panel noted uncertainty around length of treatment with cetuximab/chemo, and that the real world treatment duration estimated by experts was	Please see earlier response. In particular, as discussed earlier, we assume a mean treatment duration for CET+FOLFOX of 8.7 months, not 14.4 months as Merck Serono suggest here.

Section	ACD text	Comment from consultee	Response from assessment group
		far shorter, around 6 months, than that modelled by the ERG, which was 10.7 months for cetuximab/FOLFIRI and 14.4 months for cetuximab/FOLFOX. Merck has analysed real world data from [redacted] that have completed 1st line treatment with cetuximab plus either FOLFIRI or FOLFOX between 2012 & 2015, and the mean treatment duration in the real world was [redacted] (Appendix 5), which supports clinical expert estimate. This data is based on chart reviews conducted through market research for the period between March 2013 to October 2015 corresponds to approximately [redacted] of the CDF applications in this period and therefore can be considered to be a more accurate reflection of cetuximab treatment duration in the UK. As outlined, real world cetuximab/chemotherapy treatment durations are around [redacted], whereas treatment duration with chemotherapy alone is estimated to be approximately [redacted] for FOLFIRI and slightly shorter for FOLFOX due to neuropathy at [redacted] based on expert clinical opinion.	
Page 24 Paragraph 4.28	The Committee understood that, in clinical trials, first-line cetuximab or panitumumab is given until disease progression. But, it heard from clinical experts that clinical practice in the UK includes treatment holidays and so patients are not treated continuously until disease progression. The Committee	Merck would like to reinforce the comments made by the clinical experts. The understanding should be that the intention in clinical trials is that treatment with either cetuximab in combination with chemotherapy would be continued until disease progression. In reality, the CRYSTAL, OPUS & FIRE-3 trials that used cetuximab in combination with either FOLFIRI or FOLFOX, the mean treatment duration was significantly shorter	No further comments required.

Section	ACD text	Comment from consultee	Response from assessment group
	concluded that treatment duration with cetuximab or panitumumab in clinical trials may not reflect clinical practice in England.	than the progression free survival that was observed. This is can occur due to many reasons, including of the side of effects of combination treatment and the desire of patients to have breaks from treatment. Patients in clinical trials are also more likely to have longer treatment due to wider support available while in the study.	
Page 24 Paragraph 4.28 Page 29 Paragraph 4.35 Page 29	The Committee understood that, in clinical trials, first-line cetuximab or panitumumab is given until disease progression. But, it heard from clinical experts that clinical practice in the UK includes treatment holidays and so patients are not treated continuously until disease progression. The Committee concluded that treatment duration with cetuximab or panitumumab in clinical trials may not reflect clinical practice in England. The Committee noted that the estimates of the duration of first-line treatment differed in the models from Merck Serono and the Assessment Group. It understood from clinical experts that, in England, first-line treatment does not continue uninterrupted until disease progression. The Committee concluded that the	In developing its model the Assessment Group utilised modelled estimates of mean treatment durations for cetuximab in combination with FOLFOX or FOLFIRI using exponential extrapolation of the median treatment durations report in the clinical trials rather than using actual mean treatment durations from studies or real world data. The panel noted uncertainty around length of treatment with cetuximab/chemo, and that the real world treatment duration estimated by experts was far shorter, around 6 months, than that modelled by the ERG, which was 10.7 months for cetuximab/FOLFIRI and 14.4 months for cetuximab/FOLFOX. These figures were based on a flawed and unconventional extrapolation of median treatment periods as reported in the respective clinical trials. As there is no evidence to support these overestimated treatment lengths, and in response to the Appraisal Committee's recommendation for investigating real-world treatment length in England, Merck has analysed real world data from [redacted] that have completed 1st line treatment with cetuximab plus	Please see earlier response. In particular, as discussed earlier, we assume a mean treatment duration for CET+FOLFOX of 8.7 months, not 14.4 months as Merck Serono suggest here.

Section	ACD text	Comment from consultee	Response from assessment group
Paragraph 4.35	Assessment Group's estimates of treatment duration may not reflect clinical practice, and would have preferred to see the model validated with observational data.	either FOLFIRI or FOLFOX between 2012 & 2015, and the mean treatment duration in the real world was [redacted] (Appendix 5), which supports clinical expert estimate. This data is based on chart reviews conducted through market research for the period between March 2013 to October 2015 corresponds to approximately [redacted] of the CDF applications in this period and therefore can be considered to be a more accurate reflection of cetuximab treatment duration in the UK. As outlined, real world cetuximab/chemotherapy treatment durations are around [redacted], whereas treatment duration with chemotherapy alone is estimated to be approximately [redacted] for FOLFIRI and [redacted] for FOLFOX based on expert clinical opinion. Merck has supplied both the real world data and the actual mean clinical trial treatment durations.	
Page 18 Paragraph 4.19	In the Assessment Group's base-case analysis of all patients, both cetuximab plus chemotherapy and panitumumab plus chemotherapy generated more QALYs than for chemotherapy alone: 0.15–0.35 more QALYs compared with FOLFOX and 0.30 QALYs compared with FOLFIRI. However, the additional costs using list prices were substantial: up to about £69,000 for cetuximab or panitumumab compared with FOLFOX or FOLFIRI. When the Assessment Group used the list	The statements above show the impact of price discounts on ICERs as estimated by the Assessment Group. Given that Merck offered a substantial PAS to the value of 35.6% off cetuximab list price, the ICERs based on the PAS discount highlight the fact that cetuximab would not be cost-effective even at zero price, which shows the flaws in the methodology applied in this assessment, and that the price is not the main driver for cost effectiveness in this case. The main driver, as identified by both Merck and the Assessment group, is the length of treatment in the first line setting and the associated cost of NHS provision of healthcare. Therefore, the current	No further comments required.

Section	ACD text	Comment from consultee	Response from assessment group
	prices for panitumumab and cetuximab, the ICERs compared with chemotherapy alone were £239,007 per QALY gained for panitumumab plus FOLFOX, £165,491 per QALY gained for cetuximab plus FOLFOX, and £227,381 per QALY gained for cetuximab plus FOLFIRI. When the Assessment Group used the discounted price for panitumumab (discount commercial in confidence), the ICER was substantially above £30,000 per QALY gained compared with FOLFOX. When the Assessment Group used the discounted price for cetuximab, the ICERs were about £135,000 per QALY gained for cetuximab plus FOLFOX and £183,000 per QALY gained for cetuximab plus FOLFIRI, both compared with chemotherapy alone.	methodology penalises cetuximab-chemotherapy for extending patients' survival compared to chemotherapy alone.	
Page 32 Paragraph 4.39	In the overall population, the ICER for cetuximab was about £135,000 per QALY gained when it was combined with FOLFOX and £183,000 per QALY gained when combined with FOLFIRI, both compared with chemotherapy alone. The Committee noted that the ICER for panitumumab plus FOLFOX was also substantially above £30,000 per QALY gained vs.FOLFOX.		

Section	ACD text	Comment from consultee	Response from assessment group
Page 20 Table 3		The table above shows that cetuximab has met 2 of the 3 criteria of end of life conditions for the broad mCRC population. The third criteria refers to the number of patients that are eligible for cetuximab in all indications. In relation to the size of the population for all licensed indications in England, we noted that NICE differentiated between cetuximab and panitumumab based on the indications under the license. We believe that to achieve a fair comparison between the two medicines, both should be treated on equal grounds and assessed in accordance with the size of the colorectal cancer population for balanced evaluation. Therefore Merck contends that head and neck cancer patients should not be included in this evaluation, for the reason outlined above. This is an unusual situation as the products in question do not share same licensed indications and therefore we ask the committee to take this into account when considering this criteria, particularly given that both agents have been studied in the H&N setting with cetuximab showing benefit in this setting and panitumumab failing to show benefit. Merck's understanding of the EOL criteria is that they were instated to determine the maximum number of patients that could possibly be treated with a new medicine. Cetuximab received marketing authorisation in 2004 and therefore its estimated usage can be determined with some certainty. In mCRC cetuximab has been subject to 4302	Please see our response to Merck Serono's earlier comments on the EoL criteria.

Section	ACD text	Comment from consultee	Response from assessment group
		CDF applications for mCRC in **all lines** (1st, 2nd and subsequent lines) of therapy, in the 30 month period between March 2013 and Sept 2015. For first line mCRC in combination with either FOLFOX or FOLFIRI, there were approximately 600 patients treated with cetuximab for the period of Sept 2014 to Sept 2015 on the CDF. In SCCHN, NICE TA145 NICE restricted the funded population to only those locally advanced SCCHN patients with a Karnofsky score of above 90 in whom all forms of platinum based chemotherapy were contraindicated or not tolerated. The number of patients with locally advanced (LA) SCCHN eligible for cetuximab treatment was estimated in TA145 to be 8% of the total SCCHN population. The committee were of the opinion that there are 3,000 SCCHN patients in England, therefore this equates to 240 patients (3,000 x 8%). NICE TA 172 did not recommend the use of cetuximab for SCCHN patients with recurrent or metastatic disease (RM). Cetuximab is currently available for RM SCCHN patients via the CDF and for the period of Sept 2014 to Sept 2015, there were around 150 applications in this setting. Therefore, in total it is estimated that approximately 400 patients get treated with cetuximab in England for SCCHN in both the LA and RM settings annually. If this number is added to the 5,968 RAS wild type mCRC patients in England (data in TA176, updated to reflect RAS wild type subgroup), the total remains below the 7,000 limit stipulated by	

Section	ACD text	Comment from consultee	Response from assessment group
		the end-of-life criteria. And as outlined above, only around 4,300 patients were treated with cetuximab over the period of 2.5 years (2013-2015) when cetuximab was available on the CDF in ALL lines, with approximately 600 patients treated in the first line annually, therefore it can be stated with certainty that the number of patients that would be treated with cetuximab for 1st line mCRC even combined with those treated under NICE for SCCHN would never reach 7,000. Based on real world usage, for both mCRC and SCCHN, approximately 1,000 patients would be treated annually. Cetuximab is well established in the UK, it has been available since 2011 and so has been used in clinical practice for a long period of time, and it is unlikely that treatment patterns would now change. Merck would also urge the commitee to consider the recent publication of the newly launched NICE/NHSE CDF consultation that proposes a change to the EOL criteria in the Guide to the Methods of Technology Appraisal 2013 that removes the requirement for the size of the eligible population to be less than 7,000 in England. If this proposal is accepted through the consultation, this change is planned to be effective from 1st April 2016. Therefore, this would then mean that when the Final Guidance for this MTA is published, cetuximab will meet the EOL criteria and qualify for the higher threshold.	

Other comments

Consultee	Comment from consultee	Response from assessment group
Beating Bowel Cancer	The most recent trials reveal median survival for patients with RAS wild type tumours to be in excess of 30 months[i] – a striking improvement in a relatively short period of time. Adding almost 2 years to median survival (with 50% of patients living longer than 30 months) is of enormous clinical impact and of great benefit to patients and their family. i European Journal of Cancer July 2015Volume 51, Issue 10, Pages 1243–1252 FOLFOX4 plus cetuximab treatment and RAS mutations in colorectal cancer C. Bokemeyer C.-H. Köhne F. Ciardiello H.-J. Lenz V. Heinemann U. Klinkhardt F. Beier K. Duecker J.H. van Krieken S. Tejpar	For clarity, the trials quoted in this reference are the CALGB study (as previously stated this is still only reported in abstract and did not randomise to chemotherapy) and FIRE-3 and PEAK both which investigate bevacizumab plus chemotherapy as a comparator.
	We would urge the Committee to reconsider the full patient expert testimony it heard directly from Ben Ashworth, 36, a terminally-ill father of three from Preston. In its consideration of the evidence we feel the committee has not taken fully into account the full extent of the benefits for patients and their families in terms of extension of life. In the document it states that "the key benefit of cetuximab treatment was that the adverse reactions (such as skin reactions) were much more manageable than the adverse reactions they had previously experienced with chemotherapy alone (including debilitating fatigue and neuropathy." The adverse effects of the treatment were the least relevant.	We would like to thank both Ben Ashworth and Barry Murphy for their testimonies. They have both proved very informative. Unfortunately, evidence on the effects of specific adverse events such as neuropathy or fatigue are currently unclear. Trends from the head to head trials CRYSTAL and OPUS reported that CET+chemotherapy had similar levels of serious adverse events compared to chemotherapy alone, with CET+FOLFIRI tending to have higher incidences than FOLFIRI. However with small numbers for each of the individual types of adverse events these results are currently uncertain.

Consultee	Comment from consultee	Response from assessment group
	In the current appraisal, treatment duration ranged from 38–46 weeks in the Assessment Group's model and 25 weeks in the Merck model, which the Committee had concluded were overestimates. Clinical experts who gave evidence to the Committee advised that Merck's estimates of treatment duration better reflected clinical practice in England than the Assessment Group's. Our Medical Advisory Board has advised us that clinical practice is 24-30 weeks at most. This shorter duration will impact greatly on the cost of ongoing treatment.	Please see our comments above.
Saifee Mullamitha	2.1 5 year survival is under 60%. Should read under 5-10%	We agree
	4.14 Assessment Group are reluctant to use overall survival endpoints from clinical trials ostensibly in light of perceived use of second line dugs not commonly used in the NHS. This has been mentioned a few times in the document. I am not entirely sure or clear of the robustness of this assumption. Overall survival has to be considered the gold standard in clinical trials and has to be rated above other end points. The arms actually were quite balanced in my opinion in the well conducted trials that were discussed.	Please see our comments above.
	4.17 I am unclear as to how the mean duration of treatment estimation has affected the economic modelling but suggest the one obtained from clinical trials would be more reliable and be the one that is used.	We do indeed take the estimated mean treatment duration from the clinical trials.

Consultee	Comment from consultee	Response from assessment group
	4.18 Note comment above. Again would suggest using OS directly from randomised controlled trials	Please see our comments above.
	4.25 ''Resection is successful in about 90% patients.'' Just to clarify by this we did not mean 90% of patients receiving these drugs went for resection. In various databases about 13-15% of patients with previously unresectable liver disease became resectable courtesy systemic treatments. **Resection rates** are proportional to **response rates** from treatment regimens which in turn are increased by use of **anti-EGFR agents**. In good MDTs vast majority of patients deemed resectable on basis of post treatment scans are indeed successfully able to have a liver resection (in personal practice 80-90%). Our sentiments above are more clearly & accurately summarised in section 4.36	No comment required.
	4.28 Treatment holidays with cetuximab. In England we have been using the cetuximab within CDF guidelines which do not allow treatment breaks (in excess of 4 weeks) unless there are exceptional circumstances. This clinical practice is therefore in line with what transpires in clinical trials.	No comment required.
	4.29 Note 4.14 above. Also in clinical trials the population was relatively younger; this is not unique solely in the trials in question. This is universally true for almost all colorectal trials and infact non CRC oncological trials and should have no bearing on real life practice. We would take biological age into consideration when using drugs rather than the chronological age; in practice therefore the age factor is not relevant and should not be cited as a source of uncertainty.	No comment required.
	4.41 'from clinical experts that life expectancy is longer when mets confined to the liver.' I don't think this is true at all. We must have been misconstrued here; patients with disease	This response is consistent with our modelling assumptions.

Consultee	Comment from consultee	Response from assessment group
	confined to the liver do not necessarily fare better (unless they have been able to have resectional surgery). Infact in absence of liver surgery (prospects of which are enhanced by anti-EGFR use) they do much worse compared to patients with little or no liver affliction from disease.	
NCRI/RCP/RCR/ACP	We believe that both clinical experts stated that FOLFOX 4 is a more expensive regimen than FOLFOX6, due to the need for attendance for a bolus dose of 5FU on day 2 in FOLFOX4, but this appears to have been transcribed incorrectly in the ACD.	We agree, see comments above.
	Secondly, on page 23, the report states that patients who develop disease progression following liver resection may be offered further surgery followed by chemotherapy. The majority of patients in this situation are likely to progress with inoperable and incurable disease and so proceed straight to palliative chemotherapy.	No comment required.
	Concern over the generalisability of the trial data to the English metastatic colorectal cancer population. In the CRYSTAL and PRIME trials the median age of patients was 60 and 62 and over 90% were of performance status 0-1. In routine clinical practice within the NHS our patients with metastatic colorectal cancer are older and often of poorer performance status. However, due to the potential toxicity of the combination of a biological agent in addition to chemotherapy the vast majority of patients offered this treatment option will be of a performance status of 0-1, so	No comment required.

Consultee	Comment from consultee	Response from assessment group
	will more closely reflect the population recruited within the clinical trials. These decisions are based on the patient's performance status and symptoms, the extent of disease and the patient's wishes including their potential tolerance of specific toxicities and the importance to them of prolonged progression-free and overall survival. Published SACT data from January 2014 to December 2014 show that only 278 first cycles of FOLFIRI plus cetuximab were given, with a total number of 2224 cycles given. Although the data is not complete, the majority of NHS Trusts were submitting data at this point.	

Consultee	Comment from consultee	Response from assessment group
	Robustness of trial data The management of colorectal cancer has remained the same for many years, with little improvement in outcomes for patients with widespread metastatic disease. The introduction of the biological agents, in particular the anti-EGFR antibodies, has transformed the management of some of these patients with rapid improvement of symptoms and both statistically and clinically significant improvements in survival. The colorectal oncology community believe the robustness of the trial data and in particular the overall survival data from CRYSTAL and PRIME in the relevant biomarker-selected subgroups. In 2004 Tournigand et al published a trial in which patients were randomised to receive FOLFIRI followed by FOLFOX on disease progression, or FOLFOX followed by FOLFIRI. The overall survival in this study was 21.5 months compared to 20.6 months. These survival figures are almost identical (in the RAS wild type population) to the chemotherapy only arm in the CRYSTAL study (20.2 months) and the PRIME trial (19.7 months). We feel that the concerns raised over the effect of subsequent treatments (that are not funded by the NHS after NICE approval or through the Cancer Drugs Fund) on overall survival should be considered as minimal. Over a 10 year period the addition of cetuximab and panitumumab has been the only major advance in the first line treatment of colorectal cancer.	No further comments required.

Consultee	Comment from consultee	Response from assessment group
	End of life criteria We believe that panitumumab and cetuximab should fall within the end of life criteria. The committee agreed that for both drugs the only field that fell outside the set criteria was the number of patients who would be eligible for treatment. The PenTag model suggest that 95% of the population of England, Wales and Scotland live within England, Merck suggests this figure is 84% and our calculations based on mid 2014 population data suggests this is 87%, so altering the calculations on the model. The end of life criteria states the treatment is licensed or otherwise indicated for small patient populations and will take into account the cumulative population for each licensed indication. It seems extraordinary that the patient population with head and neck cancers are included within this current calculation, as the indication for the use of cetuximab in this population is either with radiotherapy in locally advanced disease or in combination with platinum based chemotherapy in metastatic disease and therefore should be considered distinct from the indication in the metastatic colorectal cancer population.	No further comments required.
	Methodological issues The conflation (described in the section above) of the use of the targeted agents under review in entirely separate cancers, in this case in a much more co-morbid population, and with different combination of systemic therapies and/or radiotherapy is incomprehensible to our patients and to the	No further comments required.

Consultee	Comment from consultee	Response from assessment group
	clinical community. The use of survival statistics (eg mean overall survival) which are never used by clinicians and the use of modelled data (eg mean overall survival modelled from mean progression-free survival abstracted from trial data) rather than actual data is also inappropriate in our view. We believe that these methodological flaws significantly undermine the validity of the NICE process as regards the use of these drugs in the view of both patients and clinicians. Our experts believe that the addition of the anti-EGFR antibodies to chemotherapy has made a significant advance in the treatment of metastatic colorectal cancer, for a relatively small group of patients selected based on their performance status and extent of disease. The SACT data demonstrates that use of cetuximab with FOLFIRI has been modest. Our experts have concerns over many of the assumptions made by PenTAG in their modelling and feel that both cetuximab and panitumumab should meet end of life criteria if the head and neck indication is excluded and the correct population of England used. Overall, our experts believe that if the ACD is upheld, patients with metastatic colorectal cancer will return to limited options of treatment. This will not only have an impact on outcomes but will also severely affect the ability of patients in England to have access to international studies	

Consultee	Comment from consultee	Response from assessment group
	of new treatments; which will expect the use of anti-EGFR antibodies in previous lines of treatment. This would clearly have a detrimental effect on patients, clinicians and the national targets set for trial recruitment. Our experts note that these agents are deeply embedded into the guidelines for the management of metastatic colorectal cancer written by the American Society of Clinical Oncology and the European Society of Medical Oncology, after due consideration of the published data. The UK will therefore be alone amongst the developed world, if this ACD is upheld.	

[i] European Journal of Cancer July 2015Volume 51, Issue 10, Pages 1243–1252 FOLFOX4 plus cetuximab treatment and RAS mutations in colorectal cancer C. Bokemeyer C.-H. Köhne F. Ciardiello H.-J. Lenz V. Heinemann U. Klinkhardt F. Beier K. Duecker J.H. van Krieken S. Tejpar

Response to Request for Additional Data

Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer [ID794]

Amgen Limited

February 2016

File name	Version	Contains confidential information	Date
		Yes AIC: Highlighted in yellow and underlined	July 2016

Table of Contents

Description of data sets and analyses presented

For all analyses requested, we have focused on data from the PRIME RCT and used the most recent data snapshot (Overall survival [OS] update analysis: data cut-off date 24 Jan 2013).

All analyses presented are based on the predefined retrospective wild-type (WT) RAS (no *KRAS* or *NRAS* mutations in exons 2, 3 or 4) subset analysis (512 randomised patients). Data from this population is presented in our manufacturer submission, the key WT RAS manuscript (Douillard et al, 2013) and the Vectibix SmPC (Vectibix SmPC).

Gene alterations that were not pre-specified (KRAS and NRAS exon 3 [codon 59] mutations) were analysed as exploratory endpoints. Tumour samples with wild-type *KRAS* exon 2 (codons 12/13) status were tested for additional *RAS* mutations; seven patients were subsequently found to have mutations at codon 59 of exon 3 of KRAS or NRAS. Similar (slightly improved for refined subset) efficacy results were seen in this refined (505 randomised patients) WT RAS population (Vectibix SmPC; Douillard et al, 2013).

In the interests of simplicity and consistency, all analyses presented are based on the **predefined WT RAS population (n=512)** in PRIME, which is referred to as 'excluding codon 59'. This is also the most conservative approach, since refinement of the WT RAS population slightly improved efficacy for panitumumab. The same approach was taken for analyses in the subgroup with metastases confined to the liver.

Data requested for all patients with RAS wild-type mCRC

Treatment duration

Committee Request: 'If not already provided, an estimate of the mean and restricted mean of treatment duration from the trials for each treatment'.

Committee Request: 'A clear explanation of the methods used to estimate the mean treatment duration (including reference documents)'

Treatment duration was known for all patients except one in the panitumumab plus FOLFOX arm, who was still receiving panitumumab at the time of the OS update snapshot (see Appendix Table 8). The trial data therefore provide near-to-complete information on panitumumab dosing. This significantly reduces any uncertainty regarding treatment duration and justifies the use of the mean treatment duration, i.e. restricted mean, as observed in the trial.

The mean treatment duration was calculated as the area under the Kaplan-Meier curve of time to discontinuation of treatment (Royston et al, 2011). Patients for whom the treatment has not been discontinued are censored at their last follow-up date in the study, i.e. the area under the curve up to the last known data point is used. This is equivalent to a simple mean of all treatment duration times, had all patients discontinued treatment. Only the restricted mean (and not the unrestricted mean) is presented, because the difference of one patient is not expected to substantially alter the estimate.

Mean treatment duration is presented for the PRIME OS update analysis in Table 1. The trial mean treatment durations (8.19 months for panitumumab plus FOLFOX; 7.23 months for FOLFOX alone) are lower than those estimated by the Assessment Group (9.3 months for panitumumab plus FOLFOX; 9.0 months for FOLFOX alone). The Assessment Group

estimated mean treatment duration from the median (and quartiles) which has a tendency to lead to an overestimate. The mean treatment duration based on the actual trial data should be used in the base case.

Table 1. Mean treatment duration in PRIME (WT RAS safety analysis set)

Treatment duration (months)	Panitumumab + FOLFOX (N=256)	FOLFOX (N=250)
Panitumumab + FOLFOX	8.19	-
Any treatment	9.61	7.23

Based on OS update analysis (data cut-off 24 January 2013).
Analysis based on 'excluding codon 59'.
The safety analysis set is defined as patients who received at least one dose of panitumumab or chemotherapy (506 patients out of 512 randomised).
Source: Amgen data on file.

Kaplan-Meier curves for time to discontinuation of treatment are presented for panitumumab plus FOLFOX and FOLFOX alone in the Appendix (Figures 1 and 2).

For consistency, and to align with the other analyses presented, treatment duration data presented here are based on the WT RAS population, excluding codon 59. Data on median treatment duration previously provided to the Assessment Group, were based on the WT RAS population including codon 59. However mean treatment duration in this population was almost identical to that seen in the population excluding codon 59; with restricted mean duration of 8.17 for panitumumab + FOLFOX in the combination arm (vs 8.19 in Table 1) and 7.24 months for FOLFOX in the FOLFOX alone arm (vs 7.23 in Table 1) (Amgen data on file).

Mean dose intensity is also relevant for the economic model and the Assessment Group estimated this for panitumumab plus FOLFOX by assuming that it was equal to the median dose intensity from PRIME (80%). The mean (SD) dose intensity estimated directly from the PRIME study was 79% (16%) (Amgen data on file).

OS adjustment for subsequent treatments

Committee Request: 'An estimate of the hazard ratio for the association between treatment and overall survival adjusted for life-extending treatments not routinely available in the NHS (for example using IPCW) (if not already provided) including the treatments for which the analyses control and the proportion treated in each group.'

As reported in our manufacturer submission (Appendix IV, Table 10), subsequent treatment in PRIME was more common and used earlier in the FOLFOX arm than the panitumumab plus FOLFOX arm, in particular anti-EGFR therapy. Anti-EGFR therapy was used by 19% of patients in the FOLFOX arm vs 7% in the panitumumab plus FOLFOX arm in the primary OS analysis; this increased to 27% vs 17% in the OS update analysis (Table 2).

Table 2. Use of subsequent anti-EGFR therapy and bevacizumab in PRIME (WT RAS efficacy analysis set)

Subsequent treatment	Panitumumab + FOLFOX (N=259)	FOLFOX (N=253)
Anti-EGFR therapy		
Incidence, n (%)	43 (16.6)	69 (27.3)
Median (Q1,Q3) time to use, months	27.2 (19.2, 41.2)	17.4 (9.8, 25.4)
Bevacizumab		
Incidence, n (%)	50 (19.3)	35 (13.8)
Median (Q1,Q3) time to use, months	16.8 (10.6, 24.6)	13.9 (9.3, 18.7)

Q, quartile.
Based on OS update analysis (data cut-off 24 January 2013).
Analysis based on 'excluding codon 59'.
Source: Amgen data on file.

Analysis exploring the impact of subsequent anti-EGFR therapy on OS using the inverse probability of censoring weighting (IPCW) method, based on the most recent snapshot (OS update analysis), was provided in our response to the ACD and is summarised in Table 3. The OS hazard ratio (HR) for panitumumab plus FOLFOX versus FOLFOX was 0.69 (95% CI 0.50 to 0.95) in the IPCW analysis compared with the ITT analysis HR of 0.77 (95% CI 0.64 to 0.94). This suggests that the true OS benefit for panitumumab plus FOLFOX versus FOLFOX may be larger than that observed in the PRIME intent to treat (ITT) analysis where selective crossover is not taken into account.

We have now conducted additional analysis exploring the impact of subsequent bevacizumab use. As reported in our manufacturer submission, use of bevacizumab was reasonably similar between arms: 13% of FOLFOX patients vs 16% of panitumumab plus FOLFOX patients (primary OS analysis); this increased to 14% of FOLFOX patients and 19% of panitumumab plus FOLFOX patients in the OS update analysis (Table 2). Analysis using IPCW to explore the impact of subsequent bevacizumab use is summarised in Table 3: The OS HR for panitumumab plus FOLFOX versus FOLFOX was 0.76 (95% CI 0.61, 0.94) in the IPCW analysis, which was very similar to that seen in the ITT analysis. This suggests that subsequent bevacizumab use has not distorted the OS treatment benefit for panitumumab plus FOLFOX versus FOLFOX observed in the PRIME trial ITT analysis.

Table 3. Impact of subsequent anti-EGFR therapy and bevacizumab on OS in PRIME using IPCW analysis (WT RAS efficacy analysis set)

	OS HR (95% CI) Panitumumab + FOLFOX vs FOLFOX (N=512)
Intent to treat analysis[a]	0.77 (0.64, 0.94)
IPCW analysis looking at influence of subsequent anti-EGFR therapy[a]	0.69 (0.50, 0.95)
IPCW analysis looking at influence of subsequent bevacizumab therapy[b]	0.76 (0.61, 0.94)

CI, confidence interval; HR, hazard ratio; IPCW, inverse probability of censoring weighted; OS, overall survival; WT, wild-type.
Based on OS update analysis (data cut-off 24 January 2013).
Analysis based on 'excluding codon 59'.
[a] Source: (Peeters et al, 2013).
[b] Source: Amgen data on file.

In summary, the impact of subsequent anti-EGFR therapy is likely to have underestimated the true OS benefit associated with panitumumab plus FOLFOX versus FOLFOX observed in the PRIME trial. Subsequent bevacizumab use does not appear to have distorted the OS benefit observed. Therefore, on balance we would conclude that the OS HR from the PRIME ITT analysis should be considered conservative.

Committee Request: 'Please provide justification for selecting the method used to adjust for life extending treatments not routinely available in the NHS, including information on potential confounders.'

The IPCW method was selected to adjust for the impact of life extending treatments not routinely available in the NHS, specifically anti-EGFR therapies and bevacizumab.

The IPCW method uses a weighted Cox model to overcome estimation bias associated with non-adherence to the original randomised treatment assignment (i.e. crossover). Patients are censored at the start of the new therapy and IPCW corrects for the potential bias due to the selective censoring of patients at change of treatment by using weighting. The weights allow follow-up of patients who remain on the randomised treatment until death to account not only for themselves but also for comparable patients with similar baseline and time-dependent characteristics who switched treatment prior to death. For our analysis, we used weighting based on potential confounders, which included treatment, age, gender, race, region, primary diagnosis, site of metastases (not used for the liver metastases only subgroup analysis), number of baseline metastases and included time-dependent covariates for ECOG status and disease progression status.

The ITT approach ignores selective crossover to subsequent therapy after treatment progression. As patients who received FOLFOX alone crossed over earlier and more frequently to anti-EGFR therapy compared with those receiving panitumumab plus FOLFOX this potentially leads to bias for the ITT analysis. Under the assumption that no confounding variables are missing from the weight estimation, the IPCW analysis is expected to eliminate

or reduce this source of bias and provide better estimates of the magnitude of the true treatment effect had there been no selective crossover (Robins et al, 2000).

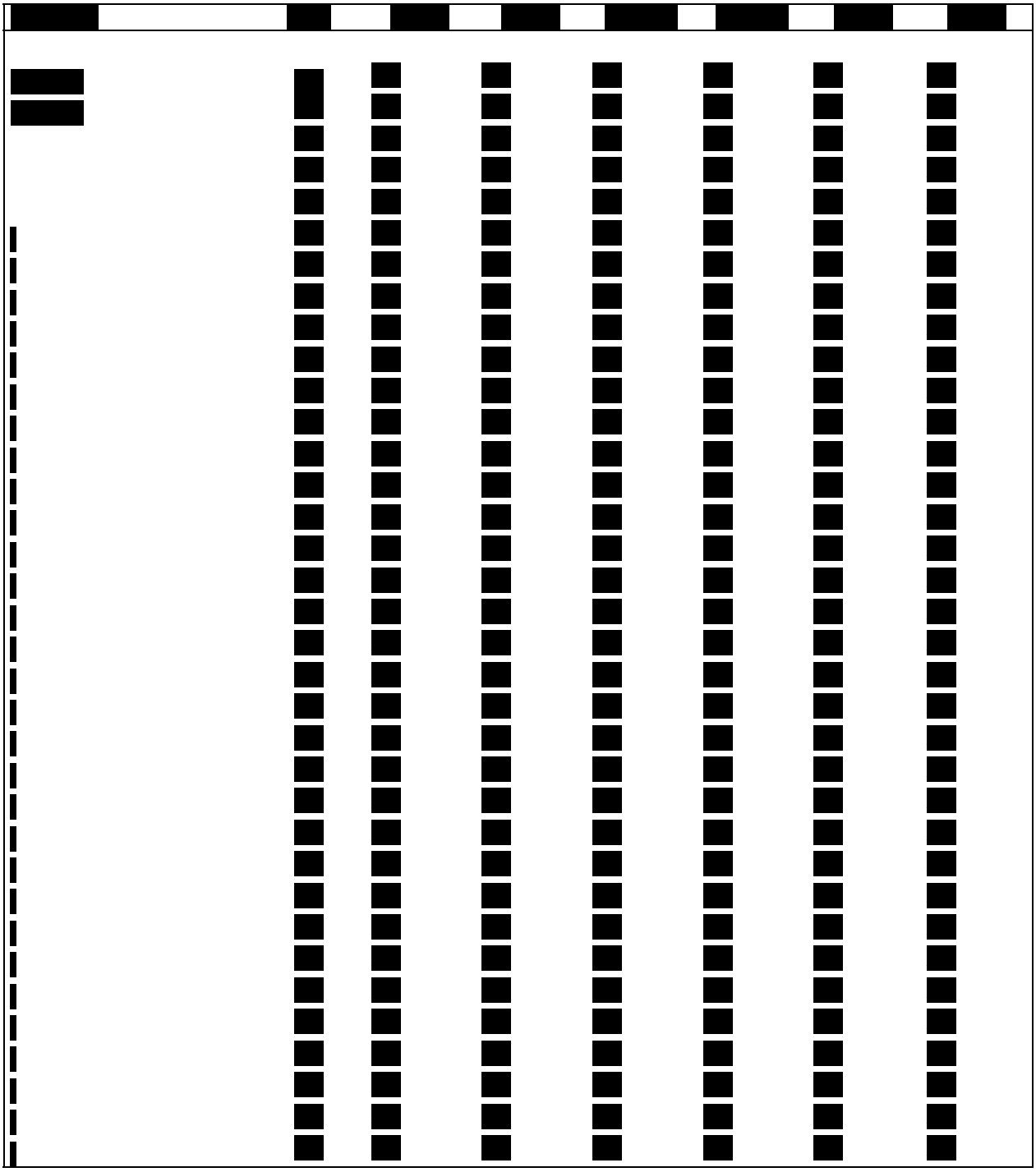
Data requested for patients with RAS wild-type mCRC with metastases confined to the liver

Overall survival Kaplan-Meier data

Committee Request: 'The overall survival Kaplan-Meier data including numbers at risk at each time point, numbers censored, and how censored by each treatment arm'

These data are presented for the PRIME OS update analysis in Table 4.

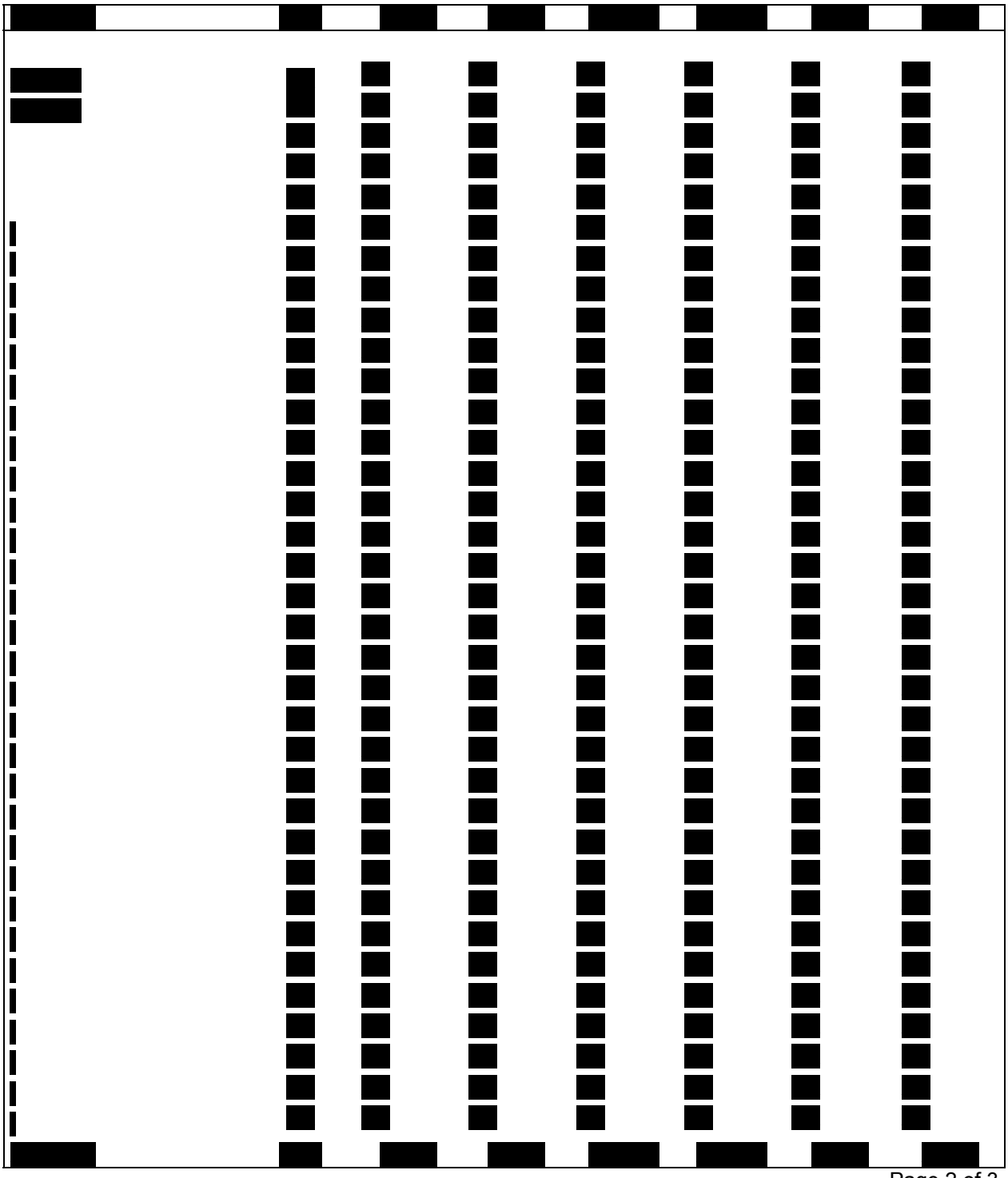
Table 4. Kaplan-Meier estimates of Overall Survival in PRIME
(WT RAS efficacy analysis set: subgroup with metastases confined to the liver)



Page 1 of 3

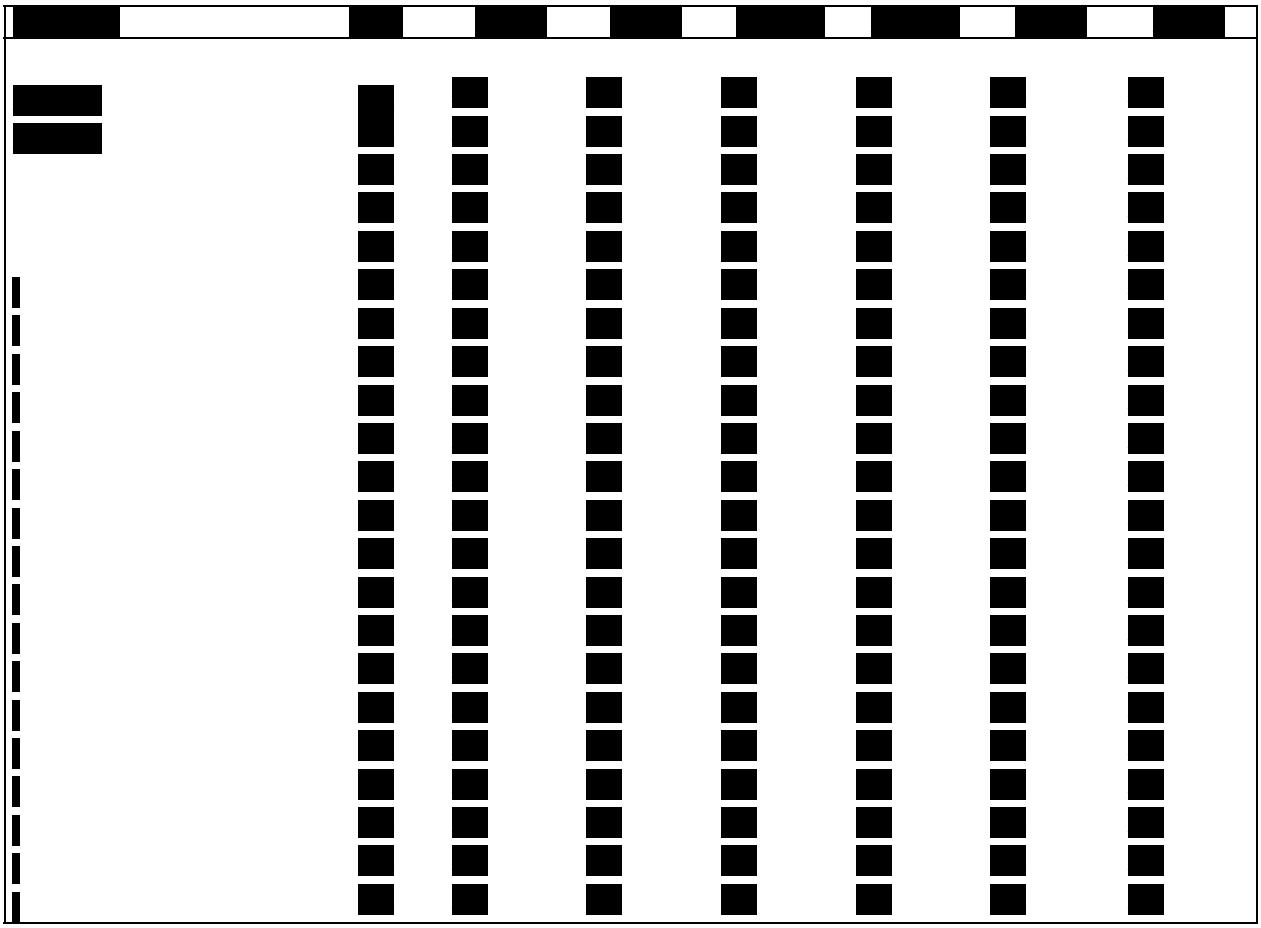
SE, standard error.
Based on OS update analysis (data cut-off 24 January 2013) 'excluding codon 59'
Survival time is defined as time from first subsequent therapy to date of death; subjects who have not died by the analysis data cut-off date will be censored at their last contact date.
Censored data is indicated with *.
Source: Amgen data on file.

Table 4. Kaplan-Meier estimates of Overall Survival in PRIME (WT RAS efficacy analysis set: subgroup with metastases confined to the liver)



SE, standard error.
Based on OS update analysis (data cut-off 24 January 2013) 'excluding codon 59'
Survival time is defined as time from first subsequent therapy to date of death; subjects who have not died by the analysis data cut-off date will be censored at their last contact date.
Censored data is indicated with *.
Source: Amgen data on file.

Table 4. Kaplan-Meier estimates of Overall Survival in PRIME (WT RAS efficacy analysis set: subgroup with metastases confined to the liver)



Page 3 of 3

SE, standard error.
Based on OS update analysis (data cut-off 24 January 2013) 'excluding codon 59'
Survival time is defined as time from first subsequent therapy to date of death; subjects who have not died by the analysis data cut-off date will be censored at their last contact date.
Censored data is indicated with *.
Source: Amgen data on file.

Treatment duration

Committee Request: 'If not already provided, an estimate of the mean and restricted mean of treatment duration from the trials for each treatment'

Committee Request: 'A clear explanation of the methods used to estimate the mean treatment duration (including reference documents)'

Mean treatment duration from the PRIME study is presented for the subgroup with metastases confined to the liver in Table 5 (OS update analysis). Treatment duration was known for all patients in this subgroup.

The restricted mean treatment duration was calculated as described in section 0. Since all patients had discontinued treatment, this is equivalent to a simple mean of all treatment duration times.

Table 5. Mean treatment duration in PRIME (WT RAS safety analysis set: subgroup with metastases confined to the liver)

Treatment duration (months)	Panitumumab + FOLFOX (N=49)	FOLFOX (N=41)
Restricted mean		
Panitumumab + FOLFOX	9.27	-
Any treatment	10.49	8.56

Based on OS update analysis (data cut-off 24 January 2013).
Analysis based on 'excluding codon 59'.
The safety analysis set is defined as patients who received at least one dose of panitumumab or chemotherapy (90 patients out of 90 randomised in this subgroup).
Source: Amgen data on file.

Kaplan-Meier curves for time to discontinuation of treatment are presented for panitumumab plus FOLFOX and FOLFOX alone for the subgroup with metastases confined to the liver in the Appendix (Figures 3 and 4).

The mean (SD) dose intensity estimated directly from the PRIME study for the subgroup with metastases confined to the liver was 76% (17%) (Amgen data on file).

OS adjustment for subsequent treatments

Committee Request: 'An estimate of the hazard ratio for the association between treatment and overall survival adjusted for life-extending treatments not routinely available in the NHS (for example using IPCW) (if not already provided) including the treatments for which the analyses control and the proportion treated in each group.'

New analysis has been conducted to explore the impact of subsequent anti-EGFR and bevacizumab treatment in the subgroup of patients with RAS WT mCRC with metastases confined to the liver in PRIME, based on the OS update analysis. As in the overall WT RAS population, the % of patients receiving subsequent anti-EGFR therapy was higher in the FOLFOX arm than the panitumumab plus FOLFOX arm (29% vs 18%). Bevacizumab was received slightly more frequently in the combination arm than the FOLFOX arm (29% vs 22%) (Table 6).

The impact of subsequent anti-EGFR and bevacizumab use on OS was explored using IPCW and results are presented in Table 7. Given the small size of the subgroup with liver metastases, confidence intervals around the hazard ratios are wide and therefore point estimates should be interpreted with caution.

Table 6. Use of subsequent anti-EGFR therapy and bevacizumab in PRIME (WT RAS efficacy analysis set, subgroup with metastases confined to the liver)

Subsequent treatment	Panitumumab + FOLFOX (N=49)	FOLFOX (N=41)
Anti-EGFR therapy Incidence, n (%) Median (Q1,Q3) time to use, months	 9 (18.4) 38.3 (20.0, 44.7)	 12 (29.3) 26.3 (15.2, 30.7)
Bevacizumab Incidence, n (%) Median (Q1,Q3) time to use, months	 14 (28.6) 23.4 (13.8, 26.7)	 9 (22.0) 17.4 (13.9, 20.3)

Q, quartile.
Based on OS update analysis (data cut-off 24 January 2013).
Analysis based on 'excluding codon 59'.
Source: Amgen data on file.

Table 7. Impact of subsequent anti-EGFR therapy and bevacizumab on OS in PRIME using IPCW analysis (WT RAS efficacy analysis set, subgroup with metastases confined to the liver)

	OS HR (95% CI) Panitumumab + FOLFOX vs FOLFOX N=90
Intent to treat analysis	0.71 (0.43, 1.17)
IPCW analysis looking at influence of subsequent anti-EGFR therapy	0.75 (0.44, 1.31)
IPCW analysis looking at influence of subsequent bevacizumab therapy	0.86 (0.49, 1.51)

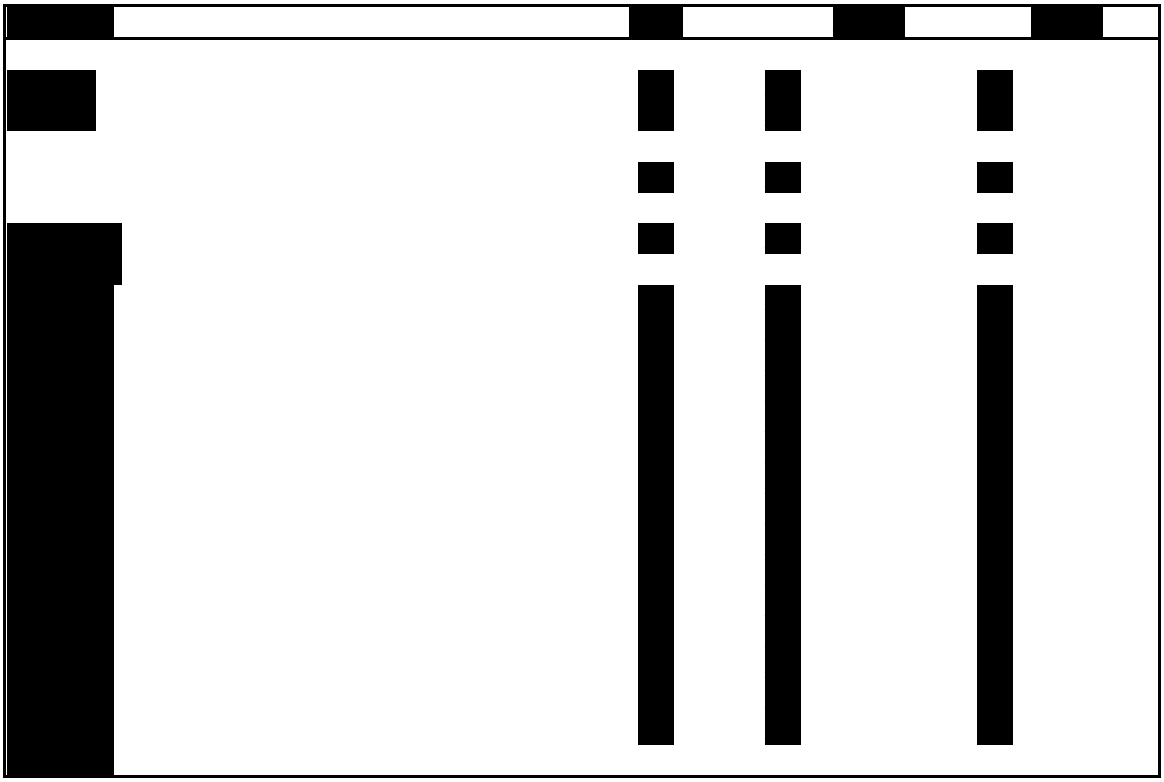
CI, confidence interval; HR, hazard ratio; IPCW, inverse probability of censoring weighted; OS, overall survival; WT, wild-type.
Based on OS update analysis (data cut-off 24 January 2013).
Analysis based on 'excluding codon 59'.
[a] Source: Amgen data on file.

Committee Request: 'Please provide justification for selecting the method used to adjust for life extending treatments not routinely available in the NHS, including information on potential confounders.'

This is described in section 2.2.

Appendix

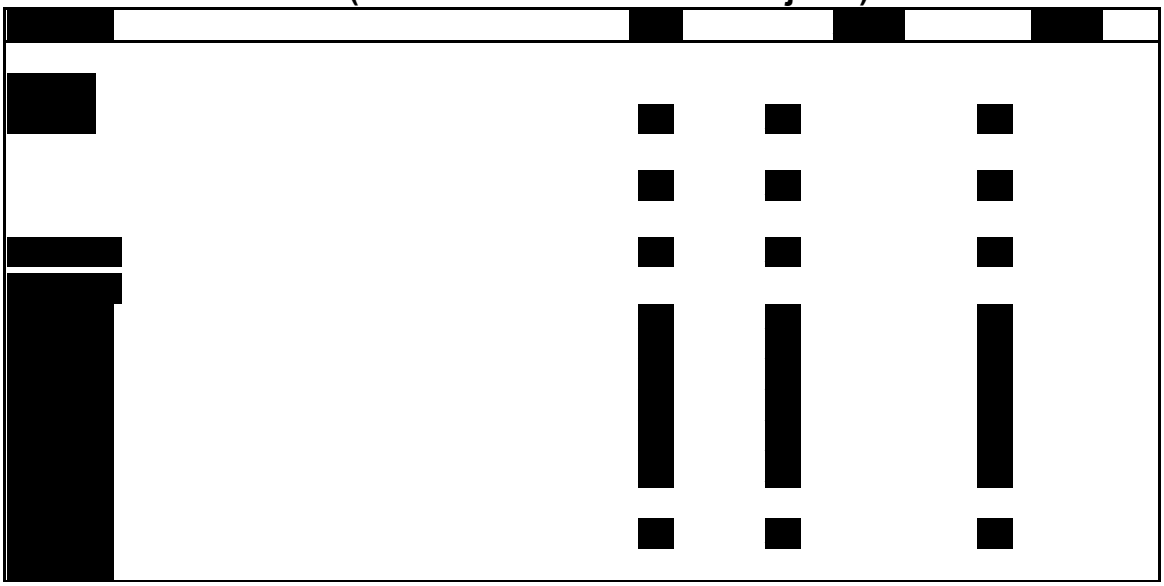
Table 8. Subject disposition in PRIME: OS update analysis
(WT RAS - all randomised subjects)



Page 1 of 2

[a]Subjects randomized to FOLFOX alone arm who inadvertently receive panitumumab will be analyzed in the Panitumumab Plus FOLFOX group for the safety analysis.
[b]Reasons are mutually exclusive.
[c]Ineligibility is judged by the investigator and not by the Independent Eligibility Review Committee.
[d]Intervention Toxicities.
Percents are based on the number of subjects randomized.
The data snapshot date for this analysis is 24JAN2013 (OS update analysis)
Source: Amgen data on file.

Table 8. Subject disposition in PRIME OS update analysis (WT RAS all randomised subjects)



Page 2 of 2

[a]Subjects randomized to FOLFOX alone arm who inadvertently receive panitumumab will be analyzed in the Panitumumab Plus FOLFOX group for the safety analysis.
[b]Reasons are mutually exclusive.
[c]Ineligibility is judged by the investigator and not by the Independent Eligibility Review Committee.
[d]Intervention Toxicities.
Percents are based on the number of subjects randomized.
The data snapshot date for this analysis is 24JAN2013 (OS update analysis)
Source: Amgen data on file.

Figure 1. Kaplan-Meier plot of time to discontinuation of Panitumumab+FOLFOX combination (WT RAS safety analysis set: Panitumumab+FOLFOX arm)

Based on OS update analysis (data cut-off 24 January 2013). Analysis based on 'excluding codon 59'. The safety analysis set is defined as patients who received at least one dose of panitumumab or chemotherapy. Source: Amgen data on file.

Figure 2. Kaplan-Meier plot of time to discontinuation of FOLFOX (WT RAS safety analysis set: FOLFOX alone arm)

Based on OS update analysis (data cut-off 24 January 2013). Analysis based on 'excluding codon 59'. The safety analysis set is defined as patients who received at least one dose of chemotherapy. Source: Amgen data on file.

Figure 3. Kaplan-Meier plot of time to discontinuation of Panitumumab+FOLFOX combination (WT RAS safety analysis set: Panitumumab+FOLFOX arm; subgroup with metastases confined to the liver)

Based on OS update analysis (data cut-off 24 January 2013). Analysis based on 'excluding codon 59'. The safety analysis set is defined as patients who received at least one dose of panitumumab or chemotherapy. Source: Amgen data on file.

Figure 4. Kaplan-Meier plot of time to discontinuation of FOLFOX
(WT RAS safety analysis set: FOLFOX alone arm; subgroup with metastases confined to the liver)

Based on OS update analysis (data cut-off 24 January 2013). Analysis based on 'excluding codon 59'. The safety analysis set is defined as patients who received at least one dose of chemotherapy. Source: Amgen data on file.

References

Douillard JY, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. *N Engl J Med*. 2013;369:1023–1034.

Peeters M, Douillard JY, Siena S ea, et al. Impact of post-protocol anti-epidermal growth factor receptor therapy on survival in wild-type KRAS/NRAS metastatic colorectal cancer: Data from the PRIME study. Poster presented at Markers in Cancer - a joint meeting by ASCO, EORTC and NCI, Brussels, 7-9 November 2013. 2013.

Robins JM, Finkelstein DM. Correcting for noncompliance and dependent censoring in an AIDS Clinical Trial with inverse probability of censoring weighted (IPCW) log-rank tests. *Biometrics*. 2000;56:779-788.

Royston P, Parmar MK. The use of restricted mean survival time to estimate the treatment effect in randomized clinical trials when the proportional hazards assumption is in doubt. *Stat Med*. 2011;30:2409-2421.

Vectibix SmPC. Summary of product characteristics. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000741/WC500047710.pdf (accessed 10 February 2015).

Multiple Technology Appraisal (MTA): Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer [ID794]

Merck's response to additional requests for data analyses by the Appraisal Committee-Summary of analyses, remodelling and findings

Executive Summary

Colorectal cancer remains the UK's second most common cause of cancer death and patients with this disease have a high unmet need. This is particularly true in the metastatic setting where treatment options are limited. Targeted therapies have been available in the UK to mCRC patients since 2011, and without access to them, the chemotherapies in use a decade ago would be the only alternatives. During the course of this technology appraisal, the Appraisal Committee and the manufacturers have heard the voices of patients, their advocates, physicians and other key experts, and there appears to be a strong commitment from all parties to work together constructively to reach a positive decision in this appraisal; one which ensures continued access for patients to life-extending targeted medications.

Following the second Appraisal Committee Meeting on 6th January 2016, NICE issued a request to the manufacturers (Amgen and Merck) for additional analyses to enable the Committee to make recommendations in the MTA of cetuximab and panitumumab as targeted treatments for first line RAS wild-type metastatic colorectal cancer. This document presents Merck's response to these requests.

Merck have proposed a revised patient access scheme and presented analyses founded on a reasonable, evidence-based set of assumptions which demonstrate that cetuximab is a cost-effective life-extending treatment alternative to chemotherapy alone. We ask the Committee to consider the overall value that cetuximab brings to patients with mCRC, the second most common cause of cancer death in the UK and a cancer with a high unmet need.

During the course of this extended appraisal process, the NICE Appraisal Committee have shared their concerns and undertaken additional explorations of the remaining uncertainties in the economic case for cetuximab. We agree that not all of the outstanding questions can be answered by the trial data and that an exploration of additional modelling scenarios will facilitate more informed decision making. The Committee's preferred set of base case assumptions are reasonable ones to make in these circumstances with the exception that it would seem more appropriate to use actual drug doses received by patients rather than an estimate. This aligns to the Committee's apparent preference to base their assumptions on the actual data where possible.

In order to underwrite remaining uncertainty in the cost-effectiveness arguments, Merck have revised the current simple patient access scheme (PAS) for cetuximab. Cetuximab will now be available to the NHS with a simple discount of [redacted] off the list price at the point of invoicing (commercial in confidence). When this new PAS is implemented into PenTAG's most current economic model alongside a set of reasonable assumptions including those preferred by the Committee, we believe that cetuximab in

combination with chemotherapy is a cost-effective treatment option at an ICER threshold of £50,000 per QALY gained for patients with RAS wild-type (wt) metastatic colorectal cancer.

The additional analyses requested by NICE which adjust for the effects of post-study anti-cancer therapies not routinely available on the NHS (cetuximab, panitumumab and bevacizumab in second or subsequent lines), suggest that the ITT analysis of the CRYSTAL trial underestimated the overall survival gain associated with cetuximab treatment. When the overall survival (OS) in the total CRYSTAL population is adjusted for the effects of these post-study anti-cancer therapies, the HR improves from 0.69 to [redacted] using the RPSFTM method which is Merck's preferred approach due to limitations with the IPCW method in this case. Merck submits that this HR should be applied to the model. Merck also provide an adjustment of the overall survival data in the LLD patient population in CRYSTAL. In this analysis the OS HR improves from 0.65 in the ITT analysis to [redacted] with RPSFTM. This revised estimate cannot be implemented as the functionality to model OS in this patient subgroup is not available in the Merck's version of PenTAG's model.

Merck also suggests that actual treatment doses from the clinical trial (CRYSTAL) be applied to the model, rather than an estimate of doses, and that the model undergo a minor adaptation to enable it to better reflect the clinical implications of the Committee's preferred assumptions around resections.

Applying these assumptions, alongside the Committee's preferred assumptions on resection rates and length of treatment produces an ICER of [redacted] for cetuximab/FOLFIRI versus FOLFIRI alone in the overall population assuming weekly dosing. Merck submits that the amendments proposed are aligned with the Committee's requests and are fully supported by clinical trial data. Merck further notes that this analysis underestimates the value of cetuximab due to its assumptions around a weekly dosing schedule. The NHSE's CDF listing for cetuximab recommends a fortnightly dosing schedule and this is current clinical practice in the UK. Merck advocates that the economic model should reflect the way the medicine is used in the NHS and has been funded through the CDF up to now. To do otherwise inserts a "phantom" cost which the NHS does not incur into the economic analysis and inappropriately overestimates the actual administration costs of cetuximab. Applying fortnightly dosing (alongside the assumptions above), the ICER for cetuximab/FOLFIRI versus FOLFIRI alone is [redacted].

The analyses in question are based on the combination of cetuximab plus FOLFIRI with analyses from the CRYSTAL trial. It is not possible to produce similar analyses for the OPUS trial, due to limitations of the data. However, the efficacy of cetuximab in combination with FOLFOX has been established in a number of RCTs, and is similar to that shown with FOLFIRI. Merck are offering the proposed PAS for cetuximab combined with either FOLFIRI or FOLFOX backbones, and we urge the Committee to take a pragmatic approach in this area.

With regard to application of the End-of-Life threshold, Merck notes that in the indication under consideration cetuximab meets the amended criteria laid out in the new CDF process, which will take effect prior to the conclusion of this MTA and therefore the £50,000/QALY threshold should apply.

Key assumptions and areas of discussion

In requesting additional data analyses, the committee also outlined a series of preferred assumptions which are listed in the table below.

Table 1: Committee's preferred assumptions for base case

The Assessment Group's resection rates associated with cetuximab and panitumumab:

- Total population, resection rate of 20.7%
- Subgroup of people with metastases confined to the liver, resection rate of 31.3%
- The Assessment Group's estimates for duration of progression-free survival for patients with liver metastases were most plausible
- The Assessment Group's updated estimate of drug administration
- Assessment Group's Average body surface area 1.85 m2
- Including FOLFOX6 rather than FOLFOX4
- Mean duration of treatment from the trials

Merck applied these assumptions where possible to calculate a revised ICER, and addressed a number of areas of uncertainty. A summary of these areas and Merck's proposed approach are presented below. Detailed methodological discussion and analyses are reserved for the appendix which follows.

1. Adjustment for post study treatments.

The Appraisal Committee requested new analyses of data from both the CRYSTAL and OPUS trials, the bulk of which relates to adjustment of overall survival data for the confounding effects of life-extending treatments received post-study which are not routinely available in the NHS. Merck undertook RPSFT and IPCW analyses of the CRYSTAL trial to address this request. Both methods are recognized as valid approaches to address the issue of confounding of overall survival by post-study treatments. Merck submits that the RPSFT model is best suited to the data under analysis due to limitations with the IPCW method in this case (see Appendix 1).

From the perspective of the NHS, the ITT analysis of overall survival in the CRYSTAL trial (currently implemented into the model) may not be representative of the likely benefit associated with cetuximab. This is driven by the impact of the imbalance between the two study arms in the proportion of patients who received an EGFR inhibitor (EGFRi), mostly cetuximab, in the later line setting. [redacted] of patients in the FOLFIRI arm received EGFRi in later line treatment, compared to [redacted] of cetuximab plus FOLFIRI patients. The rates of treatment with VEGF inhibitors were similar across the groups. When the imbalance is accounted for through statistical adjustment, the HR shifts from 0.69 to [redacted]. Merck submits that this revised HR reflects the impact of cetuximab in first-line mCRC in the NHS setting and should be applied in the model.

2. Total monthly doses of cetuximab

Mean durations of treatment were established as [redacted] for cetuximab plus FOLFIRI, and [redacted] for FOLFIRI alone (as presented in Merck's comments on the ACD). PenTAG had used this and other assumptions to model the approximate total monthly doses of cetuximab to apply in the model. The actual CRYSTAL trial data (taking account of wastage) shows a total dose of 2,101 mg used in the first month and 1,971 mg in later months (see Appendix 2). Merck suggests that the Committee apply these study data within the model rather than estimated amounts which are approximately 15% higher, an approach aligned with their desire to replace assumptions with clinical data where feasible.

3. Estimating resection rates for the chemotherapy population

The Committee identified preferred resection rate assumptions for the EGFRi treated patient population, in both the unresected (20.7%) and LLD (31.3%) populations. In order to calculate an appropriate estimate for patients treated with chemotherapy only, Merck has applied the relative effect from CRYSTAL in each setting (see Appendix 3). Relative to the Committee's preferences, this leads to assumptions of a 6% R0 resection rate for FOLFIRI patients in the overall mCRC population, and 12% in the LLD population. These estimates align with the literature for patients treated with chemotherapy only and seem appropriate (Adam R, 2004).

A small adaptation to the model is required in order to apply these assumptions in a clinically rational way. The current PenTAG model holds the survival times of resected and unresected patients in a strict relationship around the total population survival modelled from the CRYSTAL trial, with the mean OS for patients that receive R0 resection being derived from Adam et al. (55 months) and the mean OS for remaining patients being calculated by subtracting this from the total population to reach a number that represents the mean OS for patients that don't receive an R0 resection (32.1 with cetuximab/FOLFIRI versus 24.3 months with FOLFIRI alone). Currently in the model, increasing the proportion of patients who are resected causes a reduction in the modelled mean survival of unresected patients, which we know should not be the case. The overall survival for a particular patient group should remain the same regardless of the size of the group. In revised modelling Merck has delinked this relationship, fixing the mean overall survival of unresected patients at the 32.1 with cetuximab/FOLFIRI versus 24.3 months with FOLFIRI alone and the PFS of unresected patients at the 12.3 months versus 9.2 months as approximated with the PenTAG method and the original trial resection rates.

4. End of Life Criteria

Merck's base case argues that treatment with cetuximab in both the overall metastatic colorectal cancer populations and for those whose disease is limited to the liver meet NICE's criteria for End of Life. In the overall patient group, the Committee have previously concluded that cetuximab plus FOLFIRI/FOLFOX met two of the three historical EOL criteria; namely it was licensed for patients with a short life expectancy and there was evidence that it offered an extension to life.

Importantly, the EOL criteria are in the process of change as a result of the impending changes to NICE methodology in relation to the new CDF, and the requirement for the size of the eligible population to be less than 7,000 in England is to be removed. We assume this change has occurred as of April 1st, 2016. Merck would urge the Committee to consider this detail given that this MTA is likely to conclude at a time when cetuximab will indeed meet the revised EOL criteria.

End of Life Criteria for LLD populations. In the subgroup of patients with disease limited to the liver, the Committee considered that the criterion of short life expectancy (normally < 24 months) was not met and the criterion of an extension to life normally of ≥3 months average was probably met.

With regards to the short life expectancy of the liver limited disease subgroup, Merck believe that the non-resected patient is the appropriate comparator group in this context, because cetuximab is a bridge to an effective treatment (i.e. resection). The LLD patient population who are treated with cetuximab/chemo are those who are *not considered to be eligible for liver surgery* and require down staging to become eligible. LLD patients who do not undergo resection have a median overall survival of approximately 12* to 22† months. Regarding the criterion relating to extension of life, the additional survival benefit conferred by cetuximab/chemotherapy is significantly greater than three months due to the fact that successful treatment down-stages patients sufficiently to allow them to undergo liver surgery as a result of cetuximab's efficacy at tumour shrinkage, significantly lengthening life-expectancy.

5. Fortnightly Dosing

As discussed at the previous Appraisal Committee Meetings, cetuximab is typically administered intravenously every two weeks in combination with chemotherapy in first line mCRC in England. This pattern of usage has emerged during the many years that cetuximab has been available and makes pragmatic sense for patients and physicians and financial sense for the NHS given the dosing schedule of the chemotherapy backbone. With this schedule, clinic visits are reduced by half and quality of life is likely to be improved for the patient.

Indeed, NHS England currently commissions Erbitux® (cetuximab) for use in first-line RAS wild-type metastatic colorectal cancer (mCRC), under the Cancer Drugs Fund (CDF)‡ with administration of cetuximab as a 2-weekly regimen (at a dose of 500mg/m^2). This regimen is also reflected in the NCCN colorectal cancer guidelines§. Using either regimen, a patient receives the same amount of cetuximab over a two week period. In essence current usage is double the weekly dose, given fortnightly. Studies which have assessed this revised dosing schedule confirm comparable activity and safety with the once weekly schedule (see Appendix 4). When queried (see Appendix 5), a number of UK oncologists reference Tabernero 2008 (Tabernero, 2008), which evaluated the pharmacokinetics and pharmacodynamics of 2-weekly cetuximab compared to weekly cetuximab and concluded they were

* Morris et al. real world UK data (Morris EJ, 2010)

† CELIM study (Folprecht, 2014)

‡ National Cancer Drugs Fund List, Ver6.0. https://www.england.nhs.uk/wp-content/uploads/2015/11/ncdf-list-nov-15.pdf

§ National Comprehensive Cancer Network Guidelines: Colon Cancer. Available at: http://www.nccn.org/patients/guidelines/colon/

equivalent, as their evidence for switching to the 2-weekly dosing regimen. In addition, the UK mCRC oncologists cited patient convenience and nurse and unit capacity as reasons for using cetuximab on a fortnightly basis as opposed to weekly.

Applying the alternative assumption of a weekly administration of cetuximab would introduce 'phantom' costs into the assessment as the treatment is not delivered in this way in current practice in the NHS. The impact of such an assumption is significant (an additional [redacted] of administration cost per patient is inappropriately attributed to treatment with cetuximab plus FOLFIRI versus FOLFIRI alone when weekly dosing is assumed).

6. Revised Patient Access scheme for cetuximab

Merck has proposed a new patient access scheme for cetuximab, through a simple PAS which increases the level of discount off the cetuximab list price from [redacted] to [redacted] (commercial in confidence). This reflects Merck's commitment to secure access for mCRC patients through this appraisal. The proposed discount applies to both the FOLFIRI and FOLFOX backbones, see Appendix 6.

7. BRAF status

In addition to RAS mutations, approximately 8-10% of mCRC patients have mutations in the BRAF gene. Having a BRAF mutation is widely accepted to be a negative prognostic marker for patients with colorectal cancer, meaning that patients with BRAF mutant tumours have a worse prognosis regardless of the treatment they receive (Tran, 2011). Data from the CRYSTAL and OPUS trials combined show that the addition of cetuximab to 1st line FOLFIRI/FOLFOX led to increased ORR, PFS and OS in both the BRAF mutant (non-significant) and wild-type (significant) subgroups of the pooled analysis of CRYSTAL and OPUS (KRAS [exon 2] wt population) (Bokemeyer, 2012). Although not significant – likely due to sample size (n=38 with chemotherapy only, n=32 with cetuximab/chemotherapy) – the poorer prognostic subgroup (BRAF mt) still derived benefit from cetuximab (median OS with chemotherapy: 9.9 months versus 14.1 months with cetuximab/chemo). Therefore we do not consider it necessary to account for BRAF mutation status in our analyses.

8. Efficacy with both FOLFOX and FOLFIRI

Merck contends that the clinical data supports the efficacy of cetuximab in combination with either FOLFOX or FOLFIRI chemotherapy backbones. Examination of first line studies beyond that under consideration in this appraisal suggests that cetuximab in combination with FOLFOX or FOLFIRI can extend median overall survival to in excess of 30 months (FIRE3 – 33.1 months (Stintzing, 2014), CALGB-80405 - 32 months (Lenz, 2014), CECOG/CORE2 – 28.5 months (Brodowicz, 2014).

Cetuximab in combination with FOLFOX

Cetuximab in combination with FOLFOX has demonstrated clinical benefit compared to FOLFOX alone. In addition to the OPUS study, the use of cetuximab with FOLFOX is supported by clinical trial data

including the FOLFOX group from the CALGB-80405 study (Lenz, 2014), the FOLFOX arm from the APEC study and the CORE2 study (Brodowicz, 2014) which show strong efficacy data of 28-32 months median OS for cetuximab in combination with FOLFOX.

These data are consistent with the outcomes seen for cetuximab in combination with FOLFIRI reflecting similar outcomes for cetuximab/FOLFOX as cetuximab/FOLFIRI.

- In the CALGB-80405 study, patients were treated with cetuximab/chemotherapy vs bevacizumab/chemotherapy. The choice of chemotherapy backbone was left up to the investigators discretion. In the RAS wild-type analysis, PFS for patients for cetuximab/FOLFOX was 11.3 months and 12.7 months for cetuximab/FOLFIRI and OS was 32.5 months and 32 months respectively for cetuximab/FOLFOX vs cetuximab/FOLFIRI.
- In the APEC study in RAS wild-type patients, outcomes for cetuximab/FOLFOX vs cetuximab/FOLFIRI on a 2-weekly schedule were comparable; PFS 13.3 vs 12.8 months and OS 27.8 vs 28.7 months respectively.

These studies reinforce that there are similar outcomes whether cetuximab is used in combination with either FOLFOX or FOLFIRI.

The phase II OPUS study, as a relatively small data set, is most affected by sample size reductions as a result of post hoc analysis based on licence restriction. In general, when the patient population is refined from Intention-To-Treat population to the KRAS wild-type population to the RAS wild-type population, due to the exclusion of patients that do not benefit from cetuximab, there is an improvement in outcomes (Figure 1). This has been observed in multiple studies and is the rationale behind the restriction of the cetuximab indication to RAS wild-type patients.

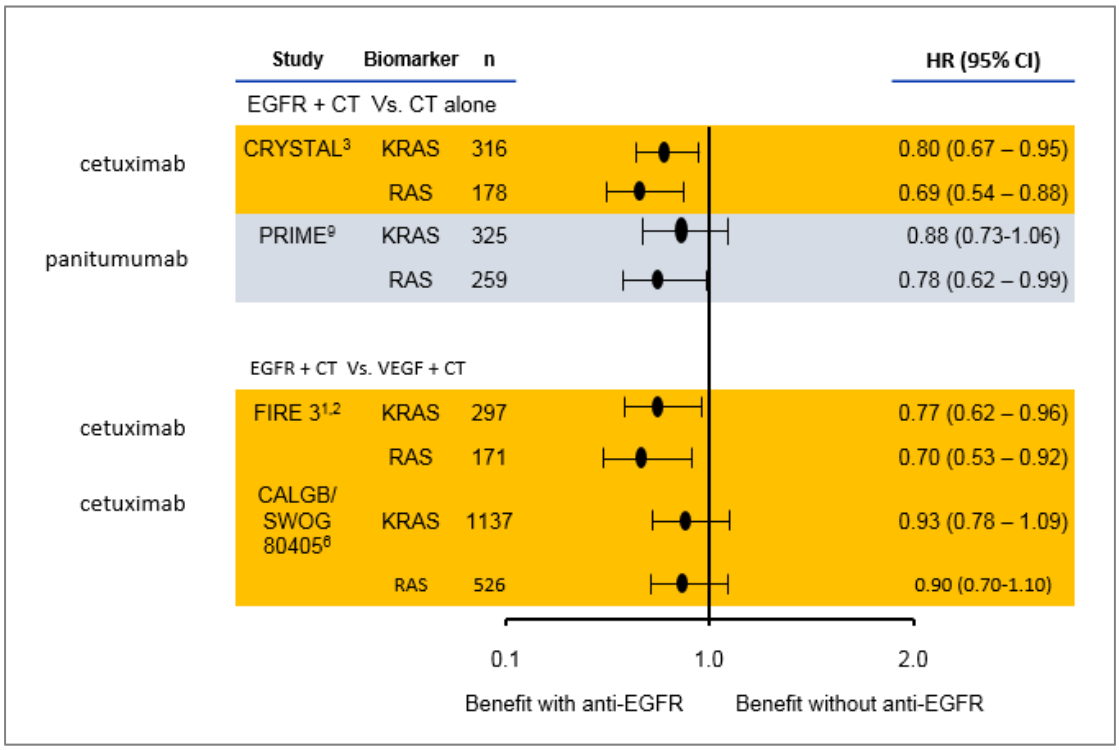


Figure 1: Improved hazard ratios in studies when population refined from KRAS to RAS wild-type

Therefore, although OPUS is the study used to represent the clinical data section for cetuximab/FOLFOX in this submission due to it being the only head to head trial against FOLFOX alone, other studies support comparable outcomes are seen when cetuximab is administered with either FOLFOX or FOLFIRI.

Appendices

Appendix 1: Additional analyses requested by the Appraisal Committee

6.1. CRYSTAL STUDY (overall population)

6.1.1. Arithmetic mean treatment duration

Merck provided summary mean duration of treatment information to NICE in response to the Appraisal Consultation Document (dated 8th December 2015). The duration of therapy was defined as [last dosing date – first dosing date + 7]/7 and the arithmetic mean estimated from the resulting dataset of patients' treatment durations.

[redacted] presents the mean duration of cetuximab treatment (in weeks) in the cetuximab/FOLFIRI arm of the CRYSTAL study, this was [redacted].

[redacted]

Error! Reference source not found. presents the mean duration of irinotecan treatment in the chemotherapy arm. This was [redacted].

[redacted]

6.1.2. Restricted mean treatment duration

NICE also requested the 'restricted mean' which is a measure of average duration from time 0 to a pre-specified time point. This may be useful when data are censored and when addressing hazard ratios. Here, there are no censored data and therefore, the restricted mean to the longest duration is equal to the arithmetic mean presented above.

6.1.3. PSACT adjusted OS data

The Committee's specific request was for an adjustment of OS data for the effects of life-extending treatments not routinely available in the NHS, specifically requesting the hazard ratios. In PenTAG's overall survival model, the Assessment Group have adjusted for the costs of subsequent treatments, but not for their benefits. The intent of this request for additional analyses is to ensure that the economic model is internally consistent and that survival estimates approximate those that are most likely in real practice in the NHS.

EGFR targeted therapies are not routinely funded beyond first line and bevacizumab is not routinely funded by the NHS for mCRC. As such, Merck assessed whether there were any imbalances in the receipt of these two therapy types in the two arms in the CRYSTAL trial. **Error! Reference source not found.** below presents the probability of anti-EGFR and anti-VEGF use post study discharge.

[redacted]

Therapy	Cetuximab/FOLFIRI arm (n=178)	FOLFIRI alone arm (n=189)
EGFR *Cetuximab*	[redacted]	[redacted]
Bevacizumab (VEGF)	[redacted]	[redacted]

The probability of receiving an anti-EGFR targeted therapy (mainly cetuximab) is clearly different across the treatment arms, with significantly more patients in the FOLFIRI alone arm receiving anti-EGFR therapy in subsequent lines compared to the cetuximab/FOLFIRI combination arm. This is not the case for the anti-VEGF bevacizumab where there is a balanced proportion of treatment in both arms. It is therefore likely that any bias in overall survival estimates which may exist must be driven

by the difference in the use of cetuximab after the experimental phase of the study. For this reason, the RPSFTM and IPCW adjustments are done only for the use of cetuximab after the experimental period *in both arms*.

The ITT analysis of overall survival in the overall patient population of the CRYSTAL trial have previously been presented to NICE, see Figure 2. The Cox Proportional Hazard Ratio is estimated at 0.69.

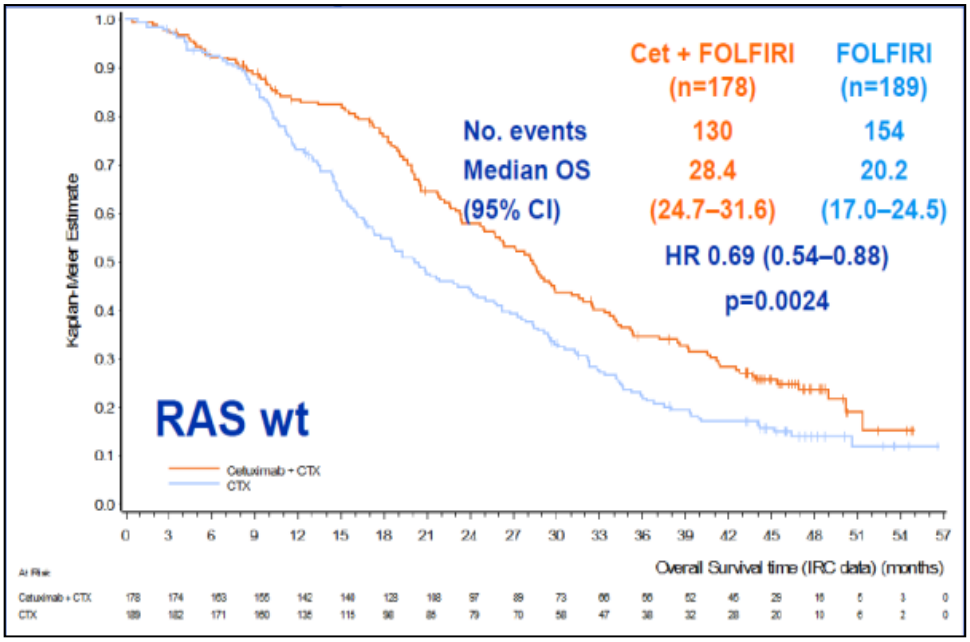


Figure 2: Overall survival in RAS-wt population in CRYSTAL

Several statistical methods are available to adjust estimates of overall survival for the potential confounding effect of post-study anti-cancer treatments.[**]

We disregard the simple methods such as excluding or censoring switchers due to associated selection bias. Instead we have undertaken an assessment of the feasibility of running two complex methods, the Inverse Probability of Censoring Weights (IPCW) and the Rank Preserving Structural Failure Time Models (RPSFTM). The IPCW censors switchers and weights remaining observations to "remove censoring-related selection bias", whilst the RPSFTM estimates the counterfactual survival times.

a. Methods and results of IPCW

In brief, with the IPCW method, patients are artificially censored at the time of switch to another treatment. The remaining observations are then weighted based upon covariate values and a model of the probability of being censored. Key to IPCW is the ability to model as accurately as possible the variables contributing to treatment switching so that patients remaining in the analysis (those who do not switch treatments) are re-analysed in a way that effectively removes the selection bias due to

[**] Latimer, N. & Abrams, K.R. Technical Support Document 16: Adjusting Survival Time Estimates in the Presence of Treatment Switching. NICE DSU. http://www.nicedsu.org.uk/TSD16_Treatment_Switching.pdf

censoring. Confidence in the IPCW method largely rests on how well the dataset lends itself to the accurate development of this predictive model.

In IPCW, the steps followed are:

1. Model the censoring mechanism
2. Estimate the product limit estimator and Cox Proportional Hazards estimator for time to censoring for each subject *j* at each time point
3. Calculate the IPCW weights for each subject
4. Estimate the survival and or Cox model for time to event in the absence of censoring using the IPCW weights.

A regression was run to determine whether there were any statistically significant associations between baseline variables or time-dependent variables and the probability of receiving a non-NHS relevant treatment post study discharge. There were no significant associations with baseline or time-dependent variables in the CRYSTAL trial dataset. The decision on what variables to include in the model therefore had to be made in a more pragmatic way. Merck sought expert clinical opinion and understood that as well as patient fitness/quality of life, in practice the availability of the medicine is a key driver of treatment switching decisions in the NHS. Pharmerit therefore undertook an assessment of whether centre number (as a proxy for 'availability of treatment') would be an important explanatory variable to include in the model. Out of 29 treating centres in the CRYSTAL trial, 7 of them treat more than 25% of their patients with cetuximab after FOLFIRI. These were labelled as 'good availability centres' and this was used as an explanatory variable for the probability of censoring. We also included response to therapy and quality of life as further explanatory variables. The result of the regression analysis including these variables is presented below in Table 2.

Table 2: Regression analysis of QoL, centre and response variables

	Coefficients Cetuximab				
	Estimate	Std.Error	z-value	Pr(>|z|)	
(Intercept)	-4.6747	1.5583	-3	0.0027	**
Centre (proxy for availability)	0.5924	0.5368	1.104	0.2698	
QoL	-0.4672	0.5488	-0.851	0.3946	
Response	1.2942	0.7843	1.65	0.0989	
	Coefficients FOLFIRI				
	Estimate	Std.Error	z-value	Pr(>|z|)	
(Intercept)	-1.8178	0.545	-3.335	0.000852	***
Centre (proxy for availability)	1.2362	0.3368	3.67	0.000243	***
QoL	-0.5181	0.3178	-1.63	0.103088	
Response	0.6431	0.3312	1.942	0.05216	

Error! Reference source not found. below IPCW results from a model which includes treatment response, centre of treatment and last observed quality of life score.

In spite of its significant methodological limitations in the context of our dataset, IPCW analysis suggests that the CRYSTAL ITT analysis slightly underestimated overall survival (from the perspective of the NHS where the impact of second line treatments is important and should be stripped out). This is an expected trend given the imbalance in use of cetuximab post-study across the two treatment arms. The overall survival hazard ratio improves from 0.69 to [redacted] with this analysis. However, our experts have advised extreme caution in interpreting this analysis due to the limitations.

Pharmerit also applied a simplified two-stage method, related in its assumptions to the IPCW. This method is usually considered when switching is permitted only after disease progression or after another specific disease-related time point. It uses this disease-related time point as a secondary 'baseline' beyond which an accelerated failure time model is fitted to estimate the treatment effect received by patients who switch (compared to those who don't). The acceleration factor is then used to shrink survival times of the switching patients in order to generate a counterfactual dataset post-progression. As highlighted, and as with other two-stage methods, this approach is appropriate when switching can occur after a specific disease-related time-point (such as progression). This is because the underlying assumption of setting a second baseline is that patients are at a similar stage of disease at this time point. Whilst our adjustments are not pinned to a progression event; instead we adjust for post-study therapies, i.e. following study discharge, it is likely that the discharge date represents conceptually such a time point. Indeed, the data suggest that discharge is triggered by the need for additional non-protocol treatments and as one would expect such need is later in the cetuximab arm than in the FOLFIRI arm.

The two-stage analysis benefits from utilising a further explanatory variable in the model than the IPCW analysis does, namely the time till discharge, however, we do not consider the analysis to be useful in the context of this response. The output is not a single adjusted hazard ratio for the entire trial follow up (which NICE have requested), but rather an adjusted HR in the 'post-discharge date' population. The results of this two stage method are presented alongside the IPCW analysis results for completeness in **Error! Reference source not found.** below.

[redacted]

	Adjusted hazard ratios				
	Central	Mean	2.50%	50%	97.50%

Simply censoring at switching time	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IPCW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Two-stage method: adjusted OS HR in post-study discharge population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

As can be seen above, the adjusted hazard ratio in the post-discharge population is identical to that in the overall IPCW analysis (i.e. over the whole trial time frame). Consequently, the two stage analysis is more favourable for cetuximab than the IPCW because there is treatment effect to add in the time before study discharge. Importantly though, two stage methods must be interpreted with caution because in common with IPCW, they assume no unmeasured confounders. An assumption that Merck and Pharmerit believe is likely violated.

b. Methods and results of RPSFTM

In brief, to correct for the effects of switching and late treatments, RPSFTM assumes that the effect of treatment is linearly related to the time that one has been treated. Under this assumption, these steps are followed:

1. Assume that the treatment reduces time to death with a factor exp(μ) while patient is on treatment
2. Consider the expected survival without treatment in both arms by multiplying the period on treatment with exp(-μ)
3. Find the factor such that both arms are equal
4. Use the factor to calculate expected survival (the counterfactual) and observation times without repeat treatment
5. Re-analyse expected survival and observation times
6. Re-censor counterfactual survival times at the earliest possible censoring time (Latimer, 2013).

Our RPSFTM analysis was conducted as outlined above and re-censoring of the counterfactual survival times was applied to correct for informative bias linked to censoring in the 16 patients whose counterfactual survival was censored. We have applied the recensoring using three different time points:

- The earliest censored time (02/09/2006)
- The second earliest censored time (02/08/2007)
- The third earliest censored time (19/01/2009)

Latimer et al advise that selection bias which is a feature of the RPSFTM analysis can be avoided by recensoring counterfactual survival times at the *earliest* possible censoring time. In our analyses, this represents the most favourable adjusted OS HR ([redacted]). Following expert advice from Pharmerit, we have elected instead to represent the more conservative estimate, the HR derived from recensoring at the second earliest censoring time ([redacted]), as the most reasonable result from this analysis. We do this to strike a balance between the fear of bias and loss of information.

Error! Reference source not found. below provides the results of the RPSFTM adjustment of overall survival for the use of cetuximab post-study discharge (in both arms) incorporating no recensoring (a biased estimate) and recensoring at the three described time points. All curves are shifted downwards from those in the ITT analysis of the trial (i.e. OS worsens due to removal of benefit of post-study anti-EGFR).

[redacted]

In summary, following adjustment of overall survival data for the confounding effects of the imbalance across the treatment arms in the use of post-study cetuximab therapy, the OS hazard ratio in the overall population in the CRYSTAL trial improves from 0.69 (the ITT analysis) to [redacted].

Discussion

The OS adjustments of overall survival in the overall RAS-wt population in CRYSTAL suggests that the ITT analysis of trial data may have underestimated the OS increment associated with cetuximab treatment. Adjustment for the confounding effects of post-study anti-cancer therapies not routinely available on the NHS has reduced the ICERs (in both the IPCW, two-stage and the RPSFTM methods). The adjusted analyses are dependent on key assumptions and trial characteristics and outputs of the model should be considered carefully when identifying which of the adjustment methods is most plausible.

The 'no unmeasured confounders' assumption is a key limitation of the IPCW (and hence the two-stage) method. For these methods to be robust, data on all time-dependent prognostic factors for mortality that also independently predict informative censoring must be available. None of the expected variables were significantly associated with censoring (switching). Merck have attempted to incorporate treatment availability through the proxy of centre identifier, however in truth it is an unmeasured confounder. There are likely to be other drivers of the retreatment decision that have not been captured. As a consequence one may consider that the fundamental assumption of the IPCW analysis is violated. Pharmerit have advised us to interpret the results of the IPCW analysis of this dataset with extreme care.

In light of the limitations of the IPCW methodology as it applies to the CRYSTAL overall population dataset, Merck consider that the RPSFTM method is more reliable. For reasons described above (striking a balance between fear of bias and loss of information), we apply the adjusted overall hazard ratio of [redacted] in the economic model. Utilising the version which re-censors at the earliest censoring time would have improved outcomes in the model (i.e. our assumption is conservative).

6.2. CRYSTAL STUDY (LLD population)

6.2.1. KM data (including numbers at risk and censored at each time point)

Overall survival of patients with LLD in the CRYSTAL study is represented in Figure 3.

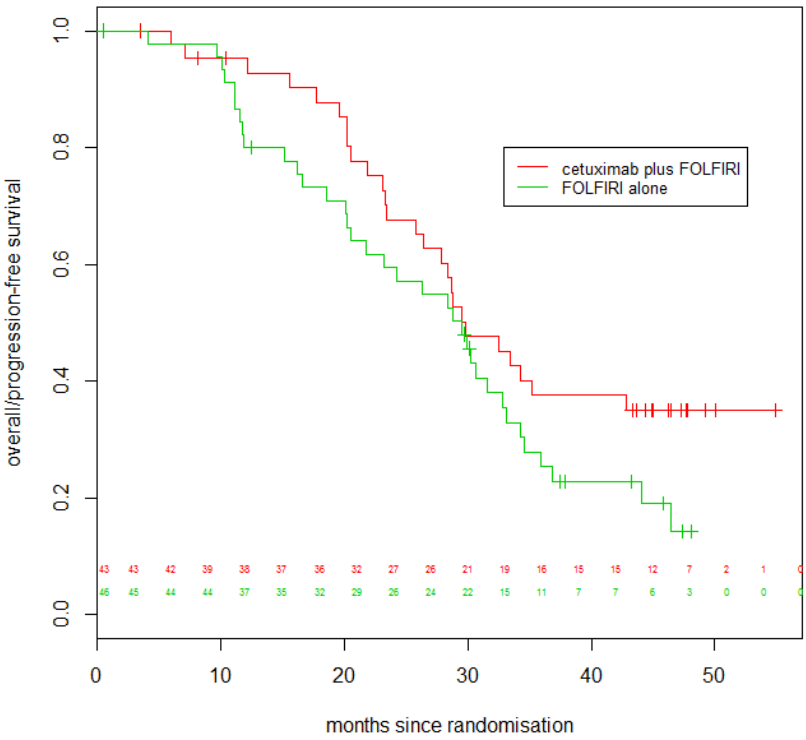


Figure 3: Kaplan-Meier analysis overall population OPUS trial

6.2.2. Arithmetic mean treatment duration

The figure below presents the mean treatment duration for patients with liver-limited disease, estimated in the same way as has been described in Section 6.1.1.

As is seen in **Error! Reference source not found.**, mean treatment duration in the LLD subgroup of patients was .

6.2.3. Restricted mean treatment duration

In the absence of censoring, the restricted mean treatment duration is as estimated above.

6.2.4. PSACT adjusted OS data

The IPCW and RPSFTM methods described above were applied to the subgroup of patients in the CRYSTAL trial who had disease limited to the liver (n=43 in the cetuximab/FOLFIRI arm versus n=46 in the FOLFIRI only arm).

The results of each of these analyses are presented below. Consistent with the recensoring applied in the overall population analyses, we present the RPSFTM results following recensoring at two time points, the earliest time of censoring in the counterfactual survival arm (29/06/2007) and the second earliest (1/2/2009).

Results of the analyses are presented in **Error! Reference source not found.** below.

As expected, the OS hazard ratio improves with adjustment from that in the ITT analysis. Confidence intervals are wide reflecting the uncertainty due to small sample size. Following the same principle as applied in the overall population analysis, we can assume that the recensoring analysis which is done at the second earliest time of counterfactual survival censoring provides a pragmatic balance between risk of bias and loss of information. On this basis, the RPSFTM adjustment of the overall survival data in the RAS-wt LLD subgroup of CRYSTAL trial results in a hazard ratio of [redacted]

6.3. OPUS STUDY (overall population)

6.3.1. KM data (including numbers at risk and censored at each time point)

There were a total of 38 RAS-wt patients randomised to cetuximab/FOLFOX in the OPUS trial and 49 randomised to FOLFOX alone. Their overall survival is represented in Figure 4 below.

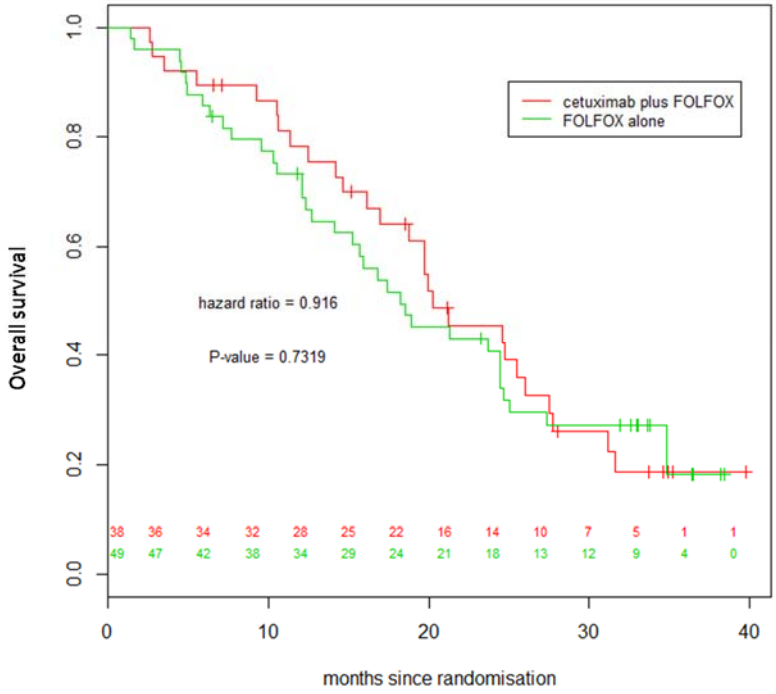


Figure 4: Overall survival of total RAS wt population in OPUS

6.3.2. Arithmetic mean treatment duration

Merck have previously provided the arithmetic mean treatment durations for OPUS (overall RAS wt population). The results are reflected in the tables below (academic in confidence).

The mean duration of cetuximab treatment in the treated arm in this study is [redacted]. The mean duration of oxaliplatin treatment in the combination arm is [redacted].

6.3.3. Restricted mean treatment duration

In the absence of any censoring and as no specific timeframe for the restriction was requested by NICE, this value is the same as the arithmetic means provided above.

6.3.4. PSACT adjusted OS data

Pharmerit deemed the sample size in OPUS unlikely to be large enough to provide RPSFTM and IPCW adjusted OS figures that we could have any confidence in. For this reason we do not undertake adjustments of the overall survival data in this trial.

6.4. OPUS STUDY (LLD population)

6.4.1. KM data (including numbers at risk and censored at each time point)

There were a total of 12 RAS-wt patients randomised to cetuximab/FOLFOX in the OPUS trial and 15 randomised to FOLFOX alone. Their overall survival is represented in **Error! Reference source not found.** below.

6.4.2. Arithmetic mean treatment duration

Pharmerit have estimated arithmetic mean treatment durations for OPUS (overall RAS wt population). The results are reflected in the table below.

		Min.	1st Q	Median	Mean	Std	3rd Q	Max	N
Cetuximab _FOLFOX arm	Cetuximab								
FOLFOX arm	Oxaliplatin								

The mean duration of cetuximab treatment in the treated arm in this study is . The mean duration of oxaliplatin treatment in the combination arm is .

6.4.3. Restricted mean treatment duration

In the absence of any censoring and as no specific timeframe for the restriction was requested by NICE, this value is the same as the arithmetic means provided above.

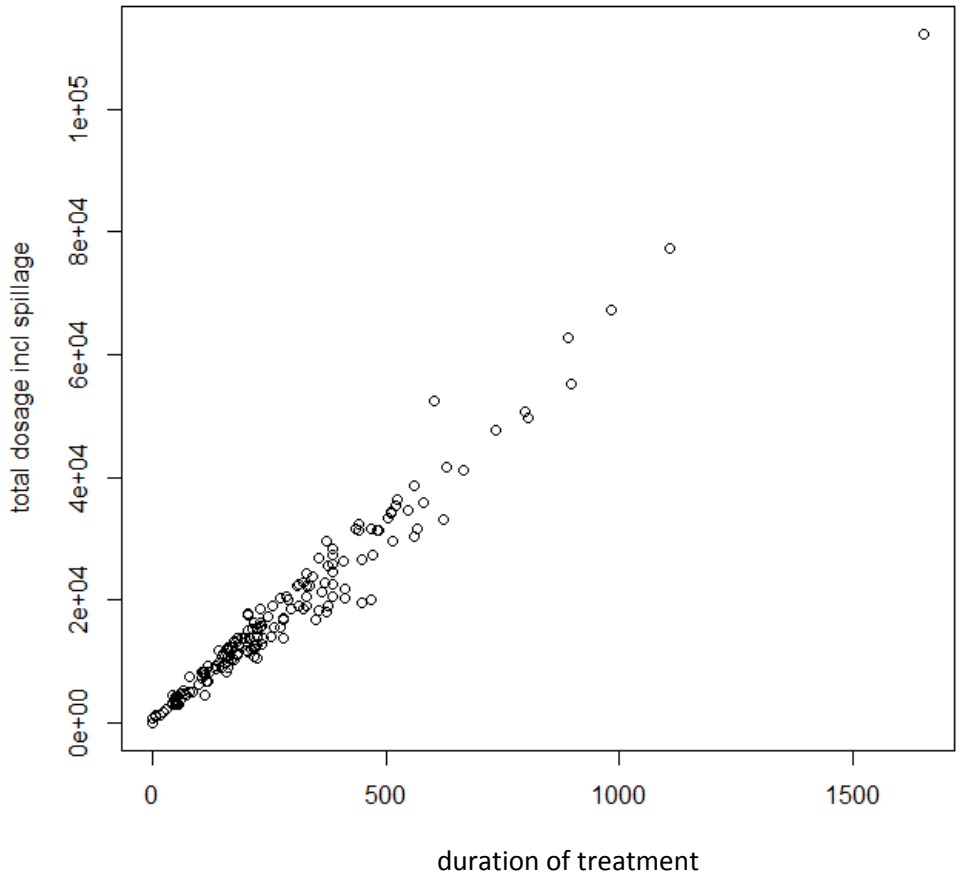
6.4.4. PSACT adjusted OS data

As above, Pharmerit deemed the sample size in OPUS unlikely to be large enough to provide RPSFTM and IPCW adjusted OS figures. In the LLD patient subgroup of this trial there are even fewer patients (n=12 in the combination arm, n=15 in the chemotherapy alone arm). We do not attempt any adjustments of the OS given this sample size.

Appendix 2: Total monthly doses of cetuximab

In order to estimate the actual doses of cetuximab delivered to patients in the CRYSTAL trial, the following method was employed.

A linear regression analysis with duration of treatment as the dependent variable and total dose as the independent variable was run to assess the relationship between these variables. Figure below presents the results.



In this regression, the constant term of this relationship is interpreted as an estimate of the average dose for the first month and the time-coefficient is interpreted as the average dose per subsequent month. Individual patient's total doses were rounded up to the nearest 100mg, thereby incorporating wastage in the total dose estimate.

Results show that in the CRYSTAL trial patients received 2,101mg of cetuximab on average in their first month of treatment and on average 1,971mg in the subsequent months.

Appendix 3: Estimation of resection rates in the comparator arms

The Committee have expressed their preferred assumption relating to resection rates in patients receiving EGFR inhibitors (20.7% for all patients and 31.3% for patients with liver-limited disease). To model resection rates appropriately, an estimate of resection rates in the comparator arm is also required. There are limited data in the literature about resection rates with FOLFIRI or FOLFOX alone. Studies suggest ranges from 2.1% for FOLFIRI from CRYSTAL (Van Cutsem E, 2015) and 4.1% to 7.6% for FOLFOX from the OPUS (Bokemeyer C, 2015) and PRIME studies (Douillard, 2013).

For the purposes of the economic modelling in this case, Merck have made the reasonable assumption that the relative effect of cetuximab/chemotherapy on resection rates versus chemotherapy alone seen in the CRYSTAL trial can be applied to the Committee's preferred assumption for the combination arm to approximate real life resection rates with chemotherapy alone. This calculates to be 6% for chemotherapy alone and is in line with the range outlined above. The same logic is applied to derive the assumed resection rates in the comparator arm of the liver-limited subgroup in whom the Committee assume a resection rate of 31.3% in the combination treatment arm. Table 3 and Table 4 below present the estimates of the resection rates to be applied in the model for the overall RAS wt population and the LLD subgroup.

Table 3: Estimates of resection rates in RAS wt population (using CRYSTAL study as the basis)

	Cetuximab + CTX	CTX only
Total (n), overall population	178 (100%)	189 (100%)
Number of subjects with no residual tumour after resection (R0)	13 (7.3%)	4 (2.1%)
RR = (13/178)/(4/189)	3.451	
Committee's preferred assumption	20.7%	
Estimated rate in comparator arm assuming relative risk is the same as in CRYSTAL		6.0%

Table 4: Estimates of resection rates in LLD subgroup of RAS wt population (using CRYSTAL study as the basis)

	Cetuximab + CTX	CTX only
Total (n), LLD subjects	43 (100%)	46 (100%)
Number of LLD subjects with no residual tumour after resection (R0)	7 (16.3%)	3 (6.5%)
RR = (7/43)/(3/46)	2.49	
Committee's preferred assumption	31.3%	

Estimated rate in comparator arm (LLD subgroup) assuming relative risk is the same as in CRYSTAL		12.5%

The estimated rate for the chemotherapy alone comparator arm in the LLD subgroup above (i.e. 12.5%) corresponds exactly with the observed resection rates in LLD patients receiving chemotherapy alone in the Adam et al study (Adam R, 2004), confirming this as an accurate calculation of resection rates. In the Ye et al. study (Ye, 2013) which was also carried out in the LLD population, a resection rates of 7.4% for chemotherapy (FOLFOX/FOLFIRI) alone was shown.

On the basis of the above, Merck have therefore assumed a resection rate of 6% in the chemotherapy alone arms in the base case for PenTAG's economic model for the overall RAS wt patient group and 12.5% for the comparator arm in the LLD subgroup. Rates of resection of liver metastases are an important component in the economic model, and cost-effectiveness results in both the overall RAS wt population and in the LLD subgroup are sensitive to the rates assumed in both treatment arms and to the magnitude of the difference between them. Merck have proposed a reasonable and evidence-based set of assumptions for this parameter.

Appendix 4: Fortnightly dosing

Cetuximab is typically administered intravenously every two weeks in combination with chemotherapy in first line mCRC in the UK. This dosing schedule is a doubling of the weekly cetuximab dose administered every 2 weeks. This treatment schedule, whilst differing from that in the Summary of Product Characteristics (SPC), does not alter the total dose of cetuximab administered but rather the administration schedule and has become common treatment practice. As the committee heard from one of the clinical experts from The Christie Hospital, they have not administered cetuximab on a weekly schedule for the last 8 years at the Christie. The National Cancer Drugs Fund (CDF) in England recommended this dosing regimen (NCDF, 2016) in February 2014. Fortnightly administration is the standard of care in many territories, including in the UK via the CDF and this dosing regimen is also supported by numerous guidelines including the London Cancer Alliance (LCA, Accessed 2016) and the NCCN guidelines (NCCN, 2016), which oncologists voted to be the most influential oncology guidelinesat a guidelines update session at the most recent European Cancer Conference (ECC 2015) meeting.

There are a number of studies where cetuximab has been used on a fortnightly basis.

- Tabernero et al. evaluated the pharmacokinetics and pharmacodynamics of 2-weekly cetuximab compared to weekly cetuximab and concluded they were equivalent (Tabernero, 2008). This is the study cited by UK oncologists as the evidence they use 2-weekly cetuximab.
- The randomised CECOG-CORE II phase II study evaluated cetuximab/FOLFOX administered weekly or every two weeks in 152 patients (Brodowicz, FOLFOX4 plus cetuximab administered weekly or every two weeks in first-line treatment of patients with KRAS and NRAS wild-type (wt) metastatic colorectal cancer (mCRC)., 2014). The authors concluded that cetuximab administered every two weeks has comparable activity and a comparable safety profile as weekly dosing in combination with FOLFOX.
- In the APEC study in RAS wild-type patients, outcomes for cetuximab/FOLFOX vs cetuximab/FOLFIRI on a 2-weekly schedule were comparable; PFS 13.3 vs 12.8 months and OS 27.8 vs 28.7 months respectively (Cheng, Final analysis of the phase 2 APEC study: Overall survival (OS) data and biomarker subanalyses for first-line FOLFOX or FOLFIRI with cetuximab (cet) once every 2 weeks in patients (pts) with KRAS or RAS (KRAS and NRAS, exons 2-4) wild-type (wt) metastati, 2015).
- Hubbard and colleagues carried out a review of several studies assessing weekly vs. every two weeks cetuximab dosing and found that the results of dosing cetuximab every 2 weeks were comparable to those obtained from weekly dosing (Hubbard, 2013).

These clinical results are similar to those from studies carried out with weekly dosing regimens such as CRYSTAL and OPUS, which underpin this NICE assessment.

Fortnightly administration also means that cetuximab can be given on the same day as chemotherapy once every 2 weeks reducing clinic visits by half, which results in more convenience and better quality

of life for the patient (Brodowicz, FOLFOX4 plus cetuximab administered weekly or every two weeks in first-line treatment of patients with KRAS and NRAS wild-type (wt) metastatic colorectal cancer (mCRC)., 2014) (Hubbard, 2013) and is also therefore more economical to the NHS. These assertions were supported by UK oncologists' opinion, please refer to Appendix 4.

The following statement is taken from the PenTAG report:

> *"In the CRYSTAL and OPUS RCTs, cetuximab was given weekly. However, in our economic analysis, in common with Merck Serono, we assumed that cetuximab is administered fortnightly, to coincide with FOLFOX/FOLFIRI administration. Fortnightly administration is common clinical practice in the NHS. Further, Merck Serono argue on the basis of an open-label RCT and a literature review that 500mg/m² fortnightly administration is as effective as induction 400 mg/m² followed by weekly 250 mg/m² administration. We consider that this is justified by the clinical evidence."*

Merck contends that although the dosing schedule as outlined in the cetuximab SPC is weekly, common clinical practice in England is 2-weekly administration. There is no change in the total dose of cetuximab administered, just the schedule of administration. Therefore, to model actual costs, 2 weekly administration is a more accurate reflection of the cost burden to the NHS, whereas weekly administration would artificially inflate these figures. Merck is not suggesting NICE make a recommendation for cetuximab which is outside of its license, but rather that NICE models its calculations based on the most accurate reflection of the costs in order to determine the true QALY. Applying an alternative assumption that cetuximab is administered weekly would introduce 'phantom' costs into the assessment as the treatment is not delivered in this way in current practice in the NHS. The impact of such an assumption is significant (an additional [redacted] of administration cost per patient is inappropriately attributed to treatment with cetuximab plus FOLFIRI versus FOLFIRI alone when weekly dosing is assumed).

Appendix 5: Data on File (Oncologist feedback regarding dosing schedule of cetuximab)

UK Cetuximab Dosing Schedule Used in mCRC and Reason

This data on file is to provide information on oncologists feedback regarding dosing of cetuximab in 1st line mCRC and the reason why.

Institution	Dose used	Reason
[redacted]	500 mg/m2 D1 every 14 days with FOLFIRI or FOLFOX	Data shows equivalent PK to 400 mg/m2 loading dose then weekly 250 mg/m^2. It is much more convenient for patients as it halves their visits, is significantly less resource intensive (and hence more cost-effective) for the pharmacists who make it up, the nurses who administer it in our SACT delivery suites and the clinician who assesses the patients and authorises treatment at each visit. This answer is for all the GI oncologists working in the 5 HSC Trusts across N. Ireland and reflects our regional guidelines.
[redacted]	400mg/m(2) as first dose and then 500 mg/m(2) every 2 weeks to co-ordinate with fortnightly administration of FOLFIRI	This reduces patient visits and also reduces the need for chemotherapy chairs. It was shown by Tabernero to be effective and have similar PK to the registered schedule/dose.
[redacted]	500mg/m2 2 weekly	Convenience and as effective
[redacted]	500 bi weekly	
[redacted]	500mg/m2 every 2 weeks	We use a 2 weekly regimen as it is more convenient to patients compared with weekly
[redacted]	500mg/m2 every 2 weeks in combination with FOLFIRI	Mandated by the CDF
[redacted]	2 weekly	1. Pharmacologically proven similarity 2. Patient convenience and preference 3. Increased efficiency
[redacted]	5mg/Kg 2-weekly	The reason is that there are patient benefits in reduced attendance as this is administered alongside

		FOLFOX or FOLFIRI. Clearly this also has a benefit in managing day unit capacity. The justification is the Tabernero data on bi-weekly cetuximab.
[redacted]	2 weekly schedule 500mg/m2 either in combination with folfiri or folfox	Based on the CDF regulations, it is also a lot easier for patients
[redacted]	2 weekly 500mg/mq	Patient convenience. PK and PD data demonstrate equivalence to weekly dosing. Ref: Tabernero et.al. 2008. the Oncologist

Appendix 6: A revised patient access scheme for cetuximab

Merck are proposing a revised patient access scheme within the process of this appraisal. This adjusts the unit cost of cetuximab in the economic model.

The present Patient Access Scheme agreed with the Department of Health is:

Cetuximab (Erbitux®) vial size/strength	List Price (BNF Nov 2014)	Simple PAS price	Discount
20ml/100mg	£178.10	[redacted]	[redacted]
100/500mg	£890.50	[redacted]	[redacted]

Merck have proposed the following increase to the level of discount in a letter to Ministers. We have requested that this new discount be considered commercial in confidence.

Cetuximab (Erbitux®) vial size/strength	List Price (BNF Nov 2014)	Simple PAS price	Discount
20ml/100mg	£178.10	[redacted]	[redacted]
100/500mg	£890.50	[redacted]	[redacted]

These revised unit costs are applied in the PenTAG economic model in the Merck base case.

Appendix 7: Merck base case (using the latest PenTAG model available to Merck)

7.1. Economic modelling results

7.1.1. Base case

In the base case we incorporate the following assumptions:

- PSACT adjusted OS HR ([redacted] from the RPSFTM method)
- Actual (trial) total monthly dose of cetuximab (rather than PenTAG's approximated doses)
- A minor amendment to the PenTAG model functionality. Currently, increasing the proportion of patients who are resected drives a reduction in the modelled mean survival of unresected patients because of the way the model implements the separation of the CRYSTAL survival data into the resected patient and the unresected patient's survival. This is artificial and in order to appropriately incorporate the Committee's preferred resection rates, it is necessary to delink the resection rate inputs from the modelled OS in unresected patients.

The following table presents the results of the analysis using PenTAG's economic model, under the assumptions set out above.

Table 5: Results of cost-effectiveness analysis under main assumptions

	Total cost (£)	Incremental cost (£)	Total QALYs	Incremental QALY	ICER (£/QALY)
Overall population / CRYSTAL study					
Cetuximab/FOLFIRI	[redacted]	[redacted]	2.17	0.71	[redacted]
FOLFIRI	[redacted]		1.46		

The results of the base case analysis show that cetuximab/FOLFIRI is a cost-effective treatment for patients with RAS wt metastatic colorectal cancer.

7.1.2. Additionally incorporating fortnightly dosing

As described, Merck advocate that the economic model should incorporate the costs of delivering cetuximab in the way that reflects standard clinical practice, i.e. a fortnightly administration schedule. When the assumption of fortnightly dosing is incorporated into the above model, the results are as follows:

Table 6: Results of cost-effectiveness analysis incorporating fortnightly dosing

	Total cost (£)	Incremental cost (£)	Total QALYs	Incremental QALY	ICER (£/QALY)
Overall population / CRYSTAL study					
Cetuximab/FOLFIRI	[redacted]	[redacted]	2.17	0.71	[redacted]
FOLFIRI	[redacted]		1.46		

7.2. Details of how the key assumptions were incorporated into the model (to assist replication)

7.2.1. Implementation of adjusted OS HR

PenTAG's base case model excludes the costs of treatments not routinely available on the NHS. In order to ensure consistency in the economic model between costs and effectiveness inputs, NICE requested an adjustment of the overall survival results for the effects of these treatments on overall survival. The adjustment analyses, using both RPSFT and IPCW, suggested that the ITT analysis of the CRYSTAL study may have underestimated overall survival for cetuximab/FOLFIRI versus FOLFIRI. Merck have incorporated these results into the economic model in this sensitivity analyses and their effect is to reduce the ICER.

The PenTAG model appears to be driven substantially by mean PFS and OS values approximated using Winbugs MCMC and hardcoded into the model. We do not have full certainty on how PenTAG intend to implement the revised OS HRs into this structure. We have done so in the following way:

- We approximate the adjusted mean overall survival in the comparator arm by applying the adjusted OS hazard ratio to the mean OS for this arm in the model
- Specifically we amend the formula in cell H18 of OS non-resect! Sheet to =[adjusted HR]^(1/OS_non_resect_CETFOLFIRI_gamma)*mean OS in CET/FOLFIRI
- This approximates a new mean OS in the comparator arm for the overall population of [redacted]
- The standard functionality of the model then splits this overall population into the resected and non-resected patient groups

In isolation, these steps do not correct for the potentially problematic functionality in the model relating to the implementation of resection rates (see below).

7.2.2. Adjustment to model functionality to allow accurate implementation of resection rates

PenTAG's model separates the observed PFS and OS from CRYSTAL into two components – survival of patients who are resected and patients who are not resected. PenTAG approximates survival in the resected patient using data from the Adam et al study (Adam R, 2004), whilst survival for non-resected patients is effectively estimated as the difference between that observed in the CRYSTAL study and the estimated survival for resected patients. The rationale for this approach is PenTAG's view that a non-resected patient's survival is overestimated by assuming it is the same as the overall population (resected plus non-resected patients). The Committee appear to accept this premise.

Having implemented this approach, Merck contends that resection rates in the model cannot simply be changed away from the CRYSTAL trial results without first amending the functionality that links the resection rate inputs to survival in the resected and non-resected groups. Unless this link is broken,

survival (both PFS and OS) artificially reduces for the non-resected patient as the resection rates are increased.

To implement this amendment into our base case, Merck have followed the specific steps below (the order is important because of the fact that resection rates are determining overall survival):

Step		Detail	Rationale
1.	Ensure model resection rates are representing the CRYSTAL trial results (i.e. 7.3% with CET/FOLFIRI v 2.1% with FOLFIRI alone)	On "Resection rates!" sheet, ensure that cells C14 and C16 are at CRYSTAL trial levels	In PenTAG's model, the inputted resection rates quantify the number of patients assigned the survival distribution for a 'resected' patient versus a non-resected one.
2.	Remove the link between resection rate inputs and the estimate of survival in the non-resected patients	• On 'PFS non-resect!' sheet retain values not formulae in cells F20 and H20 • On 'OS non-resect!' sheet retain values not formulae in cells F24 and H24	The link between resection rates and survival in the non-resected patient group must be removed in order to amend the resection rate inputs appropriately.
3.	Once the link is broken, the Committee's preferred resection rates are entered	On "Resection rates!" sheet, enter the base case resection rates	As above

8. References

Adam R, D. V. (2004). Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. *Annals of Surgery, 240*(4), 644-57.

Bokemeyer C, K. C. (2015). FOLFOX4 plus cetuximab treatment and RAS mutations. *European Journal of Cancer*, 1243-52.

Bokemeyer, C. (2012). Addition of cetuximab to chemotherapy as first-line treatment for KRAS wild-type metastatic colorectal cancer: pooled analysis of the CRYSTAL and OPUS randomised clinical trials. *Eur J Cancer*, 1466–1475.

Brodowicz, T. (2014). FOLFOX4 plus cetuximab administered weekly or every two weeks in first-line treatment of patients with KRAS and NRAS wild-type (wt) metastatic colorectal cancer (mCRC). *J Clin Onco*, 32, 2014 (suppl 3; abstr LBA391).

Brodowicz, T. (2014). FOLFOX4 plus cetuximab administered weekly or every two weeks in first-line treatment of patients with KRAS and NRAS wild-type (wt) metastatic colorectal cancer (mCRC). *J Clin Oncol*, LBA391.

Cheng, A.-L. (2015). Final analysis of the phase 2 APEC study: Overall survival (OS) data and biomarker subanalyses for first-line FOLFOX or FOLFIRI with cetuximab (cet) once every 2 weeks in patients (pts) with KRAS or RAS (KRAS and NRAS, exons 2-4) wild-type (wt) metastati. *Journal of Clinical Oncology*, 566.

Cheng, A.-L. (2015). Final analysis of the phase 2 APEC study: Overall survival (OS) data and biomarker subanalyses for first-line FOLFOX or FOLFIRI with cetuximab (cet) once every 2 weeks in patients (pts) with KRAS or RAS (KRAS and NRAS, exons 2-4) wild-type (wt) metastatic. *Journal of Clinical Oncology*, Gastrointestinal Cancers Symposium, 33(3): 566.

Douillard, J. (2013). Panitumumab-FOLFOX4 treatmetn and RAS mutations in colorectal cancer. *N Engl J Med*, 1023-34.

Folprecht, G. e. (2014). Survival of patients with initially unresectable colorectal liver metastases treated with FOLFOX/cetuximab or FOLFIRI/cetuximab in a multidisciplinary concept (CELIM study). *Ann Oncol*, 1018-25.

Hubbard. (2013). Alternate dosing of cetuximab for patients with metastatic colorectal cancer. *Gastrointest Cancer Res*, 47-55.

Latimer, N. e. (2013). *Adjusting survival time estimates to account for treatment switching in randomised controlled trials - a simulation study.* Retrieved from www.shef.ac.uk: https://www.shef.ac.uk/polopoly_fs/1.259501!/file/HEDSDP1306.pdf

LCA. (Accessed 2016). *London Cancer Alliance*. Retrieved from Colorecal Cancer Regimens: http://www.londoncanceralliance.nhs.uk/media/82913/colorectal-regimens-approved-v601-nwlcn-11jul14-no-tracked-changes.pdf

Lenz, H.-J. (2014). CALGB/SWOG 80405: PHASE III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with untreated metastatic adenocarcinoma of the colon or rectum (MCRC): RAS. *ESMO*, Abstract 929.

Morris EJ, F. D. (2010). Surgical management and outcomes of colorectal cancer liver metastases. *Br J Surg, 97*(7), 1110-8.

NCCN. (2016). *National Cancer Control Program*. Retrieved from NCCN: http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

NCDF. (2016). *NCDF List*. Retrieved from National Cancer Drugs Fund List, Ver6.0. : https://www.england.nhs.uk/wp-content/uploads/2015/11/ncdf-list-nov-15.pdf

Stintzing, S. (2014). Independent radiological evaluation of objective response, early tumor shrinkage, and depth of response in FIRE-3 (AIO KRK-0306) in the final RAS evaluable population. *ESMO Congress, Oral Presentation and abstract*, LBA11.

Tabernero, J. (2008). Administration of Cetuximab Every 2 Weeks in the Treatment of Metastatic Colorectal Cancer: An Effective, More Convenient Alternative to Weekly Administration? *The Oncologist*, 113-119.

Tran, B. (2011). Impact of BRAF Mutation and Microsatellite Instability on the Pattern of Metastatic Spread and Prognosis in Metastatic Colorectal Cancer. *Cancer*, 117(20): 4623–4632.

Van Cutsem E, L. H. (2015). Fluorouracil, leucovorin, and irinotecan plus cetuximab treatment and RAS mutations in colorectal cancer. . *J Clin Oncol, 33(7)*, 692-700.

Ye, L. (2013). Randomized controlled trial of cetuximab plus chemotherapy for patients with KRAS wild-type unresectable colorectal liver-limited metastases. *J Clin Oncol*, ;31(16), 1931-8.

The clinical effectiveness and cost-effectiveness of cetuximab (review of TA176) and panitumumab (partial review of TA240) for previously untreated metastatic colorectal cancer: a systematic review and economic evaluation

Addendum:

Between 2nd and 3rd NICE Appraisal Committee meetings

Confidential information that is commercial-in-confidence is [redacted].

Confidential information that is academic-in-confidence is [redacted].

Contents

1 Further analyses requested by NICE

1.1 Background to this MTA

We submitted our final report for this MTA to NICE on 7th August 2015. In it cost effectiveness results were presented for two networks: the 'FOLFOX network' comparing cetuximab plus FOLFOX (CET+FOLFOX) and panitumumab plus FOLFOX (PAN+FOLFOX) to a FOLFOX only arm; and the 'FOLFIRI network' comparing cetuximab plus FOLFIRI (CET+FOLFIRI) to FOLFIRI alone. No evidence for panitumumab plus FOLFIRI was available so this was not included in the networks. In our original report neither CET nor PAN plus chemotherapy appeared cost-effective compared to chemotherapy alone at a willingness to pay threshold of £20,000 per QALY under any scenario. Subgroup analyses, looking at the group pf patient for whom metastases were confined to the liver (henceforth referred to as the 'liver mets subgroup'), also gave incremental cost-effectiveness ratios (ICERs) above £20,000 per QALY gained for CET/PAN+chemotherapy versus chemotherapy alone.

On 26th October 2015, we submitted an Addendum to our report in which we presented cost-effectiveness results assuming:

- Weekly administration of cetuximab. In our original report, we assumed fortnightly administration. Weekly administration increased ICERs for CET+chemotherapy versus chemotherapy.
- Our overall survival (OS) method, where we did not cost for subsequent treatments, and considered the resulting ICERs for PAN+FOLFOX versus FOLFOX and CET+FOLFOX versus FOLFOX as upper bounds, to reflect our belief that that the OS benefit of PAN+FOLFOX versus FOLFOX and CET+FOLFOX versus FOLFOX would probably have been slightly greater than that achieved in the PRIME and OPUS RCTs if no patients had received either CET, PAN or bevacizumab (BEV) as subsequent treatments.

On 4th January 2016, we submitted an Addendum to our report in which we:

- Incorporated the revised patient access scheme (PAS) for panitumumab, a [redacted] discount on the list price. This reduced the ICERs for PAN+FOLFOX versus FOLFOX.
- Substantially reduced our estimated unit costs of drug administration for cetuximab which decreased the ICERs for CET+chemotherapy versus chemotherapy.

The 2nd NICE appraisal meeting was held on 6th January 2016. The Committee felt that it did not have all the evidence and analyses necessary to make clinically meaningful recommendations. Neither a new ACD nor a FAD was released.

After the 2nd committee meeting, NICE asked us, the Assessment Group, for the additional analyses based on the requested parameter values, described in Section 1.2.

1.2 Parameters requested by NICE

1.2.1 Additional information requested by NICE from Amgen and Merck Serono

NICE requested the following information from Amgen and Merck Serono:

OS Kaplan-Meier data

The OS Kaplan-Meier data for the liver mets subgroup, including numbers at risk at each time point, numbers censored, and how censored by each treatment arm. Data was already available for the overall population (henceforth referred to as 'all patients')

Treatment durations

If not already provided, estimated mean and restricted mean treatment duration from the trials for each treatment, plus a clear explanation of the methods used to estimate the mean treatment duration (including reference documents). This was requested separately for both all patients and the liver mets subgroup.

Adjustment for subsequent treatments

NICE requested an estimate of the hazard ratio for the association between treatment and OS adjusted for life-extending treatments not routinely available in the NHS (for example using inverse probability of censoring weighting [IPCW]) including the treatments for which the analyses control and the proportion treated in each group. They also requested that justification for selecting the method used to adjust for life extending treatments, including information on potential confounders, be provided. Again, this was requested separately for both all patients and the liver mets subgroup.

1.2.2 Other parameters requested by NICE

NICE have requested that we use the following parameter values in our updated analyses:

- **Resection rates** as we selected in our original analysis and as given in our original report (Section 6.1.4.1 p251).
- **Progression free survival (PFS) for the liver mets subgroup** as we selected in our original analysis and as given in our original report (Section 6.1.4.4, p267).
- **Unit costs of drug administration** are as we updated in our Addendum of 4th January 2016.

- **Body surface area** is used to estimate the doses of some drugs, including cetuximab. NICE have instructed us to assume our original estimate of 1.85m^2.
- Previously, we assumed a **comparator** of FOLFOX4 in our base case for the FOLFOX network. Instead, NICE now instruct us to assume **FOLFOX6**. FOLFOX4 and FOLFOX6 are assumed to have equivalent clinical effectiveness and as such only the cost of treatment is affected by this change. This alters cost-effectiveness only marginally.
- NICE ask us to continue to estimate **treatment duration** from the RCTs.

1.3 Analyses requested by NICE

After the 2nd NICE committee meeting on 6th January 2016, NICE asked us to estimate cost-effectiveness separately on each of the following 20 = 2 x 2 x 5 bases:

- All patients and Liver mets subgroup (2 bases).
- With and without adjustment for OS for subsequent treatments (2 bases).
- Treatment stopping rules (5 bases):
    1. No treatment stopping modelled
    2. 8 week treatment stopping rule with no change in PFS or OS
    3. 8 week treatment stopping rule with adjusted PFS and OS
    4. 16 week treatment stopping rule with no change in PFS or OS
    5. 16 week treatment stopping rule with adjusted PFS and OS.

2 Critique of additional information provided by Amgen

On 12th April 2016, we received additional data from Amgen. As required, all data was for *RAS* wild type (WT) patients from the PRIME RCT.

2.1 All patients data

Amgen state that there was a clear imbalance between treatment arms (16.6% and 27.3% in the PAN+FOLFOX and FOLFOX arms respectively) in the proportion of patients that received subsequent anti-EGFR treatments. There was less difference for subsequent bevacizumab: 19.3% and 13.8% respectively.

Amgen state that the intention-to-treat (ITT) OS hazard ratio (HR) of 0.77 reduced to 0.69 given IPCW adjustment for subsequent anti-EGFR treatment, and was virtually unchanged given adjustment for subsequent bevacizumab (Table 1). Amgen provided these adjusted OS HRs in 2015.

In our response of 9th October 2015 to comments on our original Assessment Report provided by companies, we explained:

"*We have the following concerns about the statistical techniques to adjust for subsequent treatments.*

1. The interpretation of the hazard ratios is not clear. Amgen say they represent the scenario "when subsequent anti EGFR therapy is taken in to account". Does this mean the counterfactual state in which no patients subsequently receive CET or PAN ?

2. Amgen do not attempt to adjust for the imbalance in the proportions receiving subsequent BEV, although this is less important than for CET or PAN, as a similar proportion of patients received BEV in the two arms (16% and 13%).

3. Amgen consider the KRAS, not the RAS wild type population. This is also probably not important, as the two populations are similar.

4. As Amgen admit, the underlying data was not based on the latest data cut.

5. We are not convinced that it is appropriate to perform some of the statistical techniques on the data from PRIME. For example, the RPSFT method estimates the treatment effect (in terms of an acceleration factor) of subsequent treatments based on its effect first line. However, the subsequent treatment CET was not taken 1st line in PRIME. Also, the impact of subsequent treatments may be largely unknown because only a proportion of patients received each subsequent treatment in both arms, and these may be a biased sample of all patients."

1. Amgen has still not address our first point above. We assume that the adjusted HRs do indeed reflect the counterfactual state in which no patients subsequently receive CET, PAN or BEV.
2. Amgen have now addressed this point.
3. Amgen now identify this as for *RAS* wild-type patients, which is appropriate.
4. Amgen have still not addressed our concern that the underlying data was not based on the latest data cut.

5. Amgen have not addressed this concern.

As discussed in the DSU Technical Support Document 16 (http://www.nicedsu.org.uk/Treatment-switching-TSD(2973293).htm), it is important to discuss and justify the method of adjustment, e.g. IPCW, rank preserving structural failure time models (RPSFTM) or Two-Stage method. However, Amgen have not done this. Instead, they have used the IPCW method without justification. This is important, as cost-effectiveness can be very sensitive to the method.

As requested, Amgen now provide the mean treatment durations for all patients (Table 1) and liver mets subgroup (Table 2). Amgen have stated these values, but have not cited the Clinical Study Report for PRIME. We can therefore only take their values on trust.

On a different matter, Amgen now report the mean dose intensity for PAN+FOLFOX from the PRIME RCT to be 79%. In our original analysis, we estimated a mean dose intensity of 80%, based on the median dose intensity of 80% reported by Amgen. We now include this minor change in all analyses.

Table 1. Data provided by Amgen for All patients in PRIME

	Requested by NICE following AC2	Provided by Amgen before NICE AC2	Provided by Amgen after NICE AC2	PenTAG comments
OS Kaplan-Meier		Provided by Amgen	n/a	n/a
Treatment duration	If not already provided, estimated mean and restricted mean treatment duration from the trials for each treatment	Amgen provided median and interquartile range. Mean estimated by PenTAG as 9.3 months for PAN+FOLFOX and 9.0 months for FOLFOX.	Mean calculated by Amgen as 8.2 months for PAN+FOLFOX and 7.2 months for FOLFOX.	We accept Amgen's revised estimates of the means. These are consistent with Figures 1- 4 in Amgen's report (April 2016). As noted by Amgen, the revised mean treatment durations are slightly lower than those estimated by us previously.
	A clear explanation of the methods used to estimate the mean treatment duration (including reference documents).	n/a as mean not given	Mean treatment duration calculated as area under the Kaplan-Meier curve of time to discontinuation of treatment	We are satisfied with this method
Adjustment for subsequent treatments	Hazard ratio for the association between treatment and OS adjusted for life-extending treatments not routinely available in the NHS (for example using IPCW) (if not already provided) including the treatments for which the analyses control and the proportion treated in each group.	ITT OS HR of 0.77 reduced to 0.69 given IPCW adjustment for subsequent anti-EGFR treatment, and virtually unchanged given adjustment for subsequent bevacizumab.	No change	We used the values provided by Amgen, noting our concerns
	Justification, including information on potential confounders.	Several concerns remain, see text above.		See comment above

2.2 Liver mets subgroup data

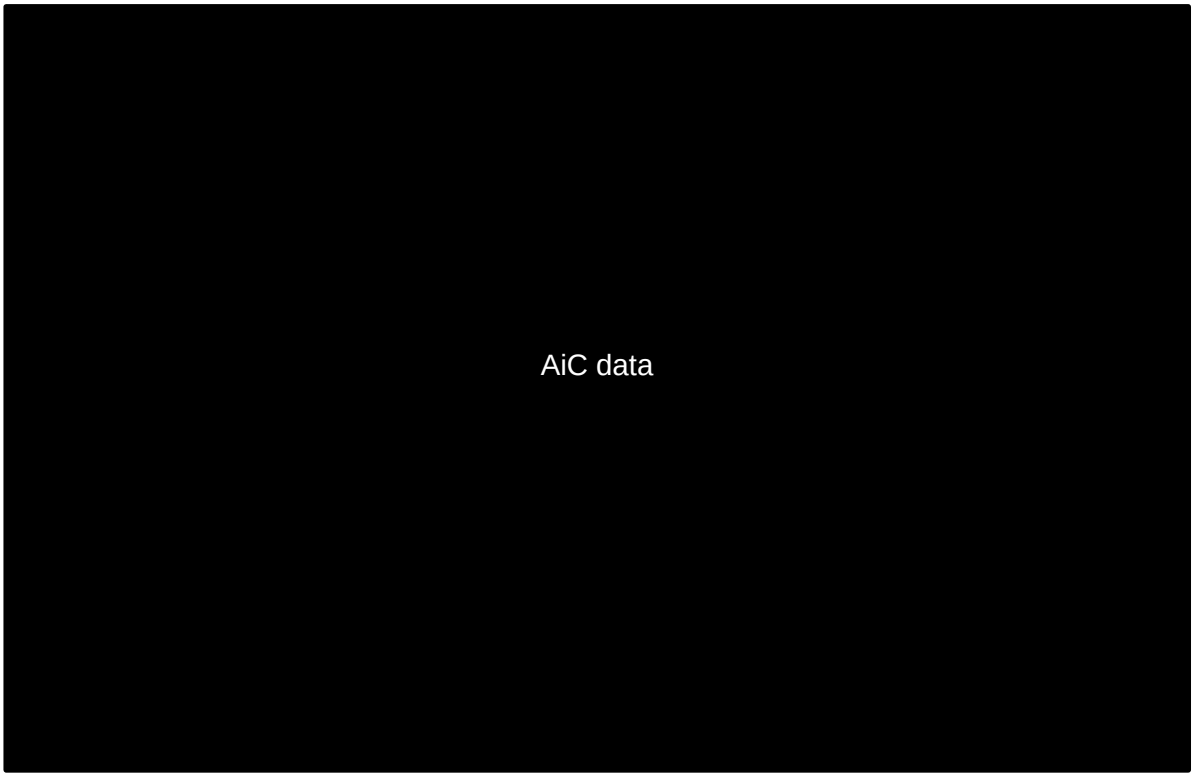
A summary of data for the liver mets subgroup of patients provided by Amgen is given in Table 2 below.

As requested, Amgen have now provided OS Kaplan-Meier data for the liver mets subgroup.

We fit Weibull curves independently to each treatment arm using the same method as in our original analysis (see our original report p267), see Figure 1 below.

We estimated mean OS for the PAN+FOLFOX and FOLFOX arms as [redacted] and [redacted] months respectively. This information was used in our model in exactly the same way as for all patients combined. In particular, the mean OS for unresected patients was estimated from the OS for all patients as described on p273 of our original report for the case of PFS.

Figure 1 . Overall survival for liver mets subgroup PAN+FOLFOX vs. FOLFOX



Notes: The dark blue and red lines represent the Kaplan-Meier data provided by Amgen for FOLFOX4 and PAN+FOLFOX4. The orange and light blue curves represent Weibull curves fit to this data.

In our original analysis, we estimated a mean dose intensity for PAN+FOLFOX of 80% from PRIME. This was taken from the median dose intensity of 80% for all patients reported by Amgen. Amgen now provide the mean dose intensity for liver mets patients at 76%. We now include this minor change in all analyses.

Table 2. Data provided by Amgen for liver mets patients in PRIME

	Requested by NICE following AC2	Provided by Amgen before NICE AC2	Provided by Amgen after NICE AC2	PenTAG comments
OS Kaplan-Meier		Not provided	Provided by Amgen	We estimate mean OS for the PAN+FOLFOX and FOLFOX arms as [redacted] and [redacted] months respectively.
Treatment duration	If not already provided, estimated mean and restricted mean treatment duration from the trials for each treatment	No data. Mean estimated by PenTAG as 9.2 months for PAN + FOLFOX and 9.1 months for FOLFOX.	Mean calculated by Amgen as 9.3 months for PAN + FOLFOX and 8.6 months for FOLFOX.	We accept Amgen's revised estimates of the means. These are consistent with Figures 1- 4 in Amgen's report, and are very similar to those estimated by us previously.
	A clear explanation of the methods used to estimate the mean treatment duration (including reference documents).	n/a	Mean treatment duration calculated as area under the Kaplan-Meier curve of time to discontinuation of treatment	We are satisfied with this method
Adjustment for subsequent treatments	Hazard ratio for the association between treatment and OS adjusted for life-extending treatments not routinely available in the NHS (for example using IPCW) (if not already provided) including the treatments for which the analyses control and the proportion treated in each group.	No adjustment made.	ITT OS HR of 0.71 increased to 0.75 given IPCW adjustment for subsequent anti-EGFR treatment, and independently increased to 0.86 given IPCW adjustment for subsequent bevacizumab.	We used the values provided by Amgen, noting our concerns.
	Justification, including information on potential confounders.	n/a	See comments for all patients above.	See comment above

3 Critique of additional information provided by Merck Serono

On 12th April 2016, we received additional data from Merck Serono. As requested, they have provided data for *RAS* WT patients from the CRYSTAL and OPUS RCTs.

3.1 Revised Patient Access Scheme for cetuximab

At the time of the 2nd NICE committee meeting on 6th January 2016, the PAS for cetuximab was a reduction of [redacted] from the list price.

Now, Merck Serono have revised the PAS to a [redacted] reduction. NICE told us on 12th May 2016 that this PAS has been approved.

3.2 Kaplan-Meier OS data, liver mets subgroup

Merck Serono previously provided OS Kaplan-Meier data for all patients. As NICE, they have now also provided this data for the liver mets subgroup for CRYSTAL (Table 5, Figure 2) and OPUS (Table 6,

Figure 3).

The estimated mean OS for CET+FOLFIRI and FOLFIRI were used directly in the model, as CRYSTAL is the baseline RCT in the FOLFIRI network.

The estimated mean OS for CET+FOLFOX was adjusted by an indirect comparison, as the baseline RCT is PRIME, not OPUS. The choice of baseline RCT is given in our original report (Section 6.1.3.2, p247).

Figure 2 . Overall survival for liver mets subgroup CET+FOLFIRI vs. FOLFIRI

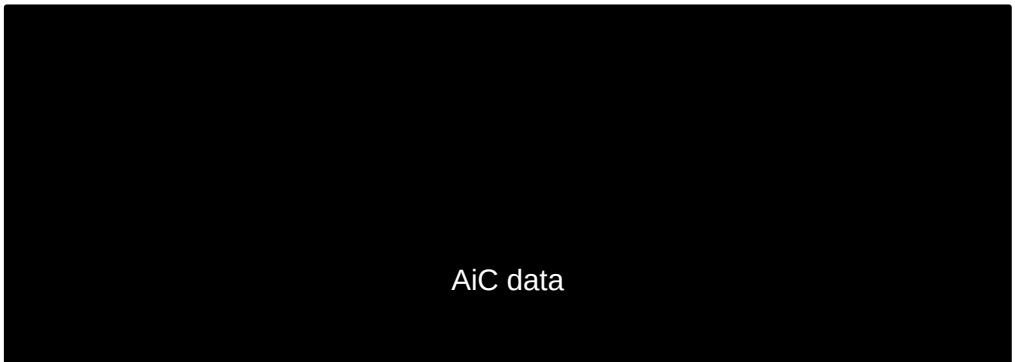
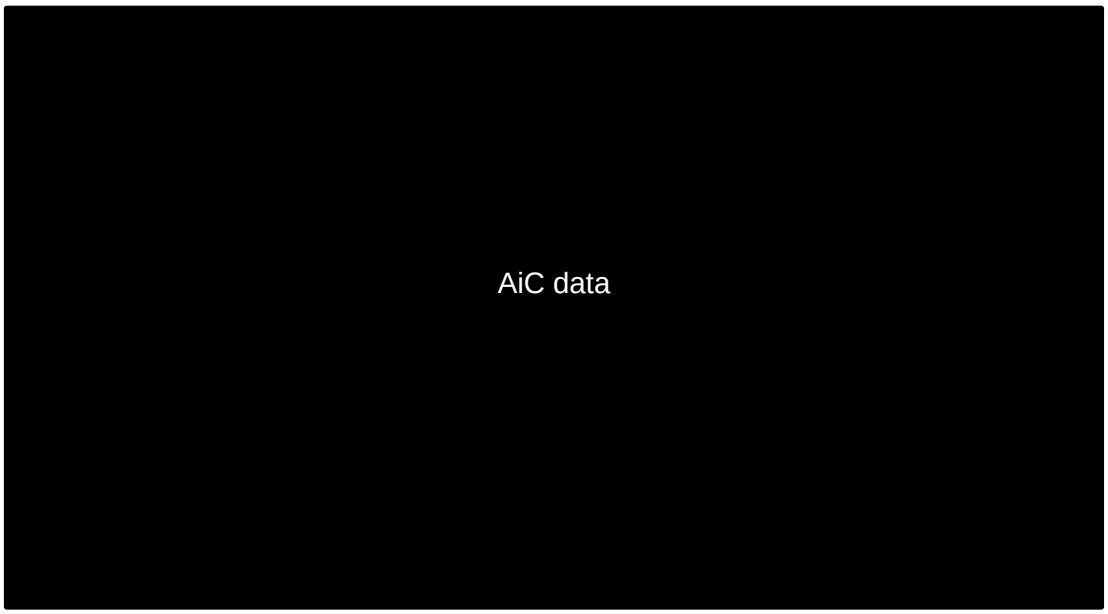


Figure 3 . Overall survival for liver mets subgroup CET+FOLFOX vs. FOLFOX



3.3 Treatment duration

Merck Serono previously provided mean treatment durations for all patients for CRYSTAL (Table 3) and OPUS (Table 4). They now repeat these values. In addition they now provide treatment durations for the liver mets subgroup for both trials (Table 5 and Table 6).

We still have concerns about the accuracy of these figures. In our Addendum of 4th January 2016, we stated:

"*As explained in detail in our response document, Merck Serono now give figures which they claim are the mean treatment durations from CRYSTAL and OPUS. They cite the source of these as the Addenda to the Clinical Trial Reports for CRYSTAL and OPUS. In summary, we believe that the means from the CRYSTAL Study Report are plausible. But given that (a) we do not find these figures in the Study Report and (b) we are concerned that censoring*

may not have been considered, we retain our mean treatment durations in our base case. However, we use Merck Serono's means in scenario analyses, see below. Next, as explained in detail in our response document, we do not find the estimated duration of cetuximab+FOLFOX that Merck Serono claim to have taken from OPUS to be credible. Once again, we retain our estimated mean durations in our base case, and use Merck Serono's means in scenario analyses."

We continued to express our concerns at the NICE committee meeting on 6th January 2016. Merck Serono have not addressed our concerns and have only repeated the mean durations.

For the purposes of this addendum, we take the figures on trust and assume all the mean treatment durations given by Merck Serono, (both the values for all patients given previously and the new data for liver mets patients).

On a separate matter, Merck Serono correctly state that we used the treatment durations from the trials in our model. They now say they it could be preferable to cost for the total study drug using the total dosages from the trials, and that this would predict a total drug cost approximately 15% lower (p4 Merck Serono April 2016 report). However, we believe our method is sound, noting that Merck Serono have ignored our reduction to the total drug acquisition costs by the mean dose intensities from the RCTs. This is likely to explain much of the discrepancy in total drug acquisition costs.

3.4 Frequency of dosing of cetuximab

In our original analyses, both Merck Serono and we, PenTAG, assumed cetuximab to be given fortnightly. Merck Serono justified this decision stating that the CDF listing for cetuximab recommended a fortnightly dosing schedule and that this was current clinical practice in the UK. At the 1st NICE committee meeting on 15th October 2015, NICE advised that all modelling should assume weekly dosing of cetuximab, as this is recommended in the marketing authorisation (Section 4.8 NICE ACD). NICE stated that they can issue guidance only within the marketing authorisation (Section 4.8 NICE ACD).

In their current report, Merck Serono again argue that fortnightly dosing of cetuximab should be modelled and that this substantially decreases the total costs of CET treatment (p5 Merck Serono April 2016 report).

Without a cetuximab stopping rule, the cost-effectiveness of CET is sensitive to dosing frequency. Fortnightly dosing substantially reduces the ICERs. But with a stopping rule, cost-effectiveness becomes less sensitive, as fewer administrations are given.

We do understand Merck Serono's argument that it is more appropriate to assume fortnightly dosing, as this is standard practice in England. However, we also note that CET was administered weekly in CRYSTAL and OPUS, and therefore arguably, we should model weekly CET administration for consistency with the clinical outcomes. Contrary to this, Merck Serono claim there is clinical data that supports the belief that outcomes are equal for weekly or fortnightly administration.

Given that NICE have previously judged that we should assume weekly administration, we continue to make this assumption in all analyses in this report. We believe that it is NICE's decision as to whether modelling a process outside of licence constitutes a recommendation outside of the marketing authorisation.

3.5 End of Life criteria

At the first NICE committee meeting, on 15th October 2015, the committee concluded that neither cetuximab nor panitumumab satisfy the End of Life criteria (Section 4.41 NICE ACD).

Merck Serono now claim that cetuximab meets the amended criteria in the new CDF process, and that these criteria will take effect prior to the conclusion of this MTA. They therefore conclude that the £50,000 per QALY cost-effectiveness threshold for end of life treatments should apply to both the all patients and liver mets subgroup.

Merck correctly state that the NICE committee judged that the life expectancy criterion for the liver mets subgroup was not met. Merck Serono now disagree with this, saying: "*Merck believe that the non-resected patient is the appropriate comparator group in this context, because cetuximab is a bridge to an effective treatment (i.e. resection). The LLD patient population who are treated with cetuximab/chemo are those who are not considered to be eligible for liver surgery and require down staging to become eligible. LLD patients who do not undergo resection have a median overall survival of approximately 12 to 22 months*" (Merck Serono April 2016 report p5). We do not accept this argument. The EoL criterion applies to the life expectancy of the comparator treatment, which is FOLFOX / FOLFIRI alone for some patients, and FOLFOX / FOLFIRI followed by resection for other patients.

We consider the End of Life criteria in Section 4.7.4.3, p40 below.

3.6 Adjustment for imbalance in subsequent treatments

"All patients" group

Merck Serono state that there was a clear imbalance between treatment arms in the CRYSTAL RCT: [redacted] and [redacted] received subsequent EGFR drugs in the CET+FOLFIRI and FOLFIRI arms respectively. There was little difference for subsequent bevacizumab: [redacted] and [redacted] respectively.

Merck Serono considered the IPCW and the RPSFT methods to adjust for this imbalance.

Under the IPCW method, the ITT OS HR of 0.69 from CRYSTAL reduced very slightly to [redacted]. From p13 of Merck Serono's April 2016 report, it appears that this revised hazard ratio represents the counterfactual state in which no patients receive subsequent cetuximab treatment.

However, Merck Serono judged the IPCW method inappropriate, as they report that they found that none of the expected variables were significantly associated with censoring (switching) (p11 Merck Serono's April 2016 report), and the IPCW assumption of no unmeasured confounders is likely to be violated (p14 Merck Serono's April 2016 report). We consulted Dr Ian White (MRC Biostatistics Unit, Cambridge), an expert on statistical adjustment for treatment switching. We agree with his assessment that this argument is illogical. If no observed variables predict switching, this does not tell us whether any unobserved variables predict switching. Therefore, we do not accept Merck Serono's reasoning for rejecting the IPCW method as inappropriate. They provide no further critique of the suitability of the IPCW method.

Merck Serono use the RPSFTM adjustment method in their revised analysis. As explained above, DSU is clear that the suitability of adjustments methods should be considered carefully. However, Merck Serono do not justify the use of this method. For example, they

do not consider the key assumption of the method of the constancy of treatment effect for switcher and non-switchers.

The ITT OS HR of 0.69 reduced to [redacted] given RPSFTM adjustment for subsequent anti-EGFR treatment, and virtually was unchanged given adjustment for subsequent bevacizumab (Table 3). Merck Serono state that selection bias, which is a feature of the RPSFTM analysis, can be avoided by recensoring counterfactual survival times at the earliest possible censoring time. In their analyses, Merck Serono state that this gives the most favourable adjusted OS HR of [redacted]. They instead chose to recensor at the second earliest censoring time, which gives a HR of [redacted], saying that this strikes a balance between the possibility of bias and loss of information. Recensoring at the third earliest censored time gives the least impressive HR of [redacted]. Again, we consulted Dr Ian White on this technical issue of recensoring. He suggests that recensoring may have been implemented incorrectly, saying "*Let C_i be the censoring time for person i, on the observed time scale. Is the first option to recensor at min_i C_i? If so it is inappropriate as the recensoring time for one person should not depend on censoring times for other people. The correct recensoring time is person-specific and is usually min(C_i, C_i*exp(psi))*."

Liver mets subgroup

Merck Serono applied the same methodology for the liver mets subgroup.

The ITT OS HR of 0.647 [redacted] to [redacted] given RPSFTM adjustment for subsequent anti-EGFR treatment (Table 5). As for all patients, recensoring was assumed at the second earliest time of counterfactual survival.

Our criticisms for the all patients analysis apply equal to the liver mets subgroup.

On a different point, Merck Serono claim that we cost for subsequent CET/PAN/BEV treatments (p10 Merck Serono report April 2016), but this is not true. At the time of the 2nd NICE committee meeting, under the OS method, we did not cost for subsequent treatments. We stated that the resulting ICERs were upper bounds given that the OS benefit of treatment is likely to be greater than experienced in the trials, given imbalances in subsequent treatments between treatment arms.

3.7 Resection rates

Merck Serono say (p3 Merck Serono report April 2016) that the committee preferred resection rates "*associated with cetuximab and panitumumab*" are:

- "Total population, resection rate of 20.7%"
- "Subgroup of people with metastases confined to the liver, resection rate of 31.3%"

Merck Serono then say that they then estimated resection rates for chemotherapy only, by applying "*the relative effect from CRYSTAL in each setting*" (p4 Merck Serono report April 2016). They find that this gives a 6% resection rate for FOLFIRI all patients, and 12% for the liver mets subgroup. These compare with 2.1% and 6.5% respectively, taken directly from CRYSTAL, requested by NICE, and used in our analysis.

In fact, NICE instructed us to continue to assume all the resection rates that we have previously used. These include a rate of 20.7% for CET+FOLFOX for all patients and 31.3% for PAN+FOLFOX for liver mets subgroup. But it also includes other rates, such as [redacted] for PAN + FOLFOX for all patients and [redacted] for CET+FOLFOX for liver mets subgroup.

Merck Serono suggest an amendment to our model to allow for modelled resection rates for CET and CET+FOLFIRI that are different from those observed in CRYSTAL (p34 Merck Serono report April 2016). However, we do not see the need for such a change, given that we already take the resection rates for these treatments directly from CRYSTAL.

3.8 All patients data

A summary of data for all patients given by Merck Serono is given below in Table 3 for CRYSTAL and Table 4 for OPUS.

Table 3. Data provided by Merck Serono for all patients in CRYSTAL RCT

	Requested by NICE, following AC2	Provided by Merck Serono before NICE AC2	Provided by Merck Serono after NICE AC2	PenTAG comments
OS Kaplan-Meier		Provided by Merck Serono	n/a	n/a
Treatment duration	If not already provided, estimated mean and restricted mean treatment duration from the trials for each treatment	Mean given as [redacted] weeks for CET+FOLFIRI and [redacted] weeks for FOLFIRI.	Unchanged	Merck Serono have still not addressed our concerns about these figures. However, we use these values in all analyses.
	A clear explanation of the methods used to estimate the mean treatment duration (including reference documents).		Simple mean as no censoring	See comments above
Adjustment for subsequent treatments	Hazard ratio for the association between treatment and OS adjusted for life-extending treatments not routinely available in the NHS (for example using IPCW) (if not already provided) including the treatments for which the analyses control and the proportion treated in each group.	Not provided	Merck Serono judged IPCW method inappropriate. ITT OS HR of 0.69 reduced to [redacted] given RPSFTM adjustment for subsequent anti-EGFR treatment, and virtually unchanged given adjustment for subsequent bevacizumab.	We used the RPSFTM adjusted OS HR in our analyses.
	Justification, including information on potential confounders.	n/a	Merck Serono do not justify appropriateness of RPSFTM.	We have concerns about the technical implementation of recensoring.

Table 4. Data provided by Merck Serono for all patients in OPUS RCT

	Requested by NICE following AC2	Provided by Merck Serono before NICE AC2	Provided by Merck Serono after NICE AC2	PenTAG comments
OS Kaplan-Meier		Provided by Merck Serono	n/a	n/a

Treatment duration	If not already provided, estimated mean and restricted mean treatment duration from the trials for each treatment	Mean given as [redacted] weeks for CET + FOLFOX and [redacted] weeks for FOLFOX.	Unchanged	Merck Serono have still not addressed our concerns about these figures. However, we use these values in all analyses.
	A clear explanation of the methods used to estimate the mean treatment duration (including reference documents).		Simple mean as no censoring	See comments above
Adjustment for subsequent treatments	Hazard ratio for the association between treatment and OS adjusted for life-extending treatments not routinely available in the NHS (for example using IPCW) (if not already provided) including the treatments for which the analyses control and the proportion treated in each group.	Not provided	Not provided.	We do not adjust OS for imbalances in subsequent treatments as no data available.
	Justification, including information on potential confounders.	Not provided	Merck Serono deem patient population too small	

3.9 Liver mets subgroup data

A summary of data for liver mets patients from Merck Serono is given below in Table 5 for CRYSTAL and Table 6 for OPUS.

As requested, Merck Serono have now provided Kaplan-Meier data for the liver mets subgroup, see Figure 2 (CRYSTAL) and

Figure 3 (OPUS). This data was used exactly as described for all patients above.

We estimate mean OS for the CET+FOLFIRI and FOLFIRI arms as [redacted] and [redacted] months respectively (Table 5), and for the CET+FOLFOX and FOLFOX arms as [redacted] and [redacted] months respectively (Table 6).

Table 5. Data provided by Merck Serono for liver mets patients in CRYSTAL RCT

	Requested by NICE, following AC2	Provided by Merck Serono before NICE AC2	Provided by Merck Serono after NICE AC2	PenTAG comments
OS Kaplan-Meier		Not provided	Provided by Merck Serono	We estimate mean OS for the CET+FOLFIRI and FOLFIRI arms as [redacted] and [redacted] months respectively.
Treatment duration	If not already provided, estimated mean and restricted mean treatment duration from the trials for each treatment	Not provided.	Mean calculated by Merck Serono as [redacted] months for CET+FOLFIRI. Mean not provided for FOLFIRI.	Merck Serono have still not addressed our concerns about treatment durations. However, we use these values in all analyses. We estimate mean duration of FOLFIRI as [redacted] months = mean duration of CET+FOLFIRI x ratio of median duration of FOLFIRI all patients / median duration of CET+ FOLFIRI all patients
	A clear explanation of the methods used to estimate the mean treatment duration (including reference documents).	n/a	Simple mean as no censoring	See comments above
Adjustment for subsequent treatments	Hazard ratio for the association between treatment and OS adjusted for life-extending treatments not routinely available in the NHS (for example using IPCW) (if not already provided) including the treatments for which the analyses control and the proportion treated in each group.	No adjustment made.	The ITT OS HR of 0.647 [redacted] to [redacted] given RPSFTM adjustment.	We used the RPSFTM adjusted OS HR in our analyses.
	Justification, including information on potential confounders.	n/a	Merck Serono do not justify appropriateness of RPSFTM.	We have concerns about the technical implementation of recensoring.

Table 6. Data provided by Merck Serono for liver mets patients in OPUS RCT

	Requested by NICE, following AC2	Provided by Merck Serono before NICE AC2	Provided by Merck Serono after NICE AC2	PenTAG comments
OS Kaplan-Meier		Not provided	Provided by Merck Serono	We estimate mean OS for the CET+FOLFOX and FOLFOX arms as [redacted] and [redacted] months respectively.
Treatment duration	If not already provided, estimated mean and restricted mean treatment duration from the trials for each treatment	No data.	Mean calculated by Merck Serono as [redacted] months for CET + FOLFOX and [redacted] months for FOLFOX.	Merck Serono have still not addressed our concerns about treatment durations. However, we use these values in all analyses.
	A clear explanation of the methods used to estimate the mean treatment duration (including reference documents).	n/a	Simple mean as no censoring	See comments above
Adjustment for subsequent treatments	Hazard ratio for the association between treatment and OS adjusted for life-extending treatments not routinely available in the NHS (for example using IPCW) (if not already provided) including the treatments for which the analyses control and the proportion treated in each group.	No adjustment made.	No adjustment made.	We do not adjust OS for imbalances in subsequent treatments as no data available.
	Justification, including information on potential confounders.	n/a	Merck Serono deem patient population too small	

3.10 Merck Serono cost-effectiveness results

Merck Serono adjusted their version of our model as follows (p32 Merck Serono April 2016 report):

- RPSFTM adjusted OS HR of [redacted] for CET+FOLFIRI vs FOLFIRI for all patients.
- Actual (trial) total monthly dose of cetuximab ("*rather than PenTAG's approximated doses*").
- "*Delink the resection rate inputs from the modelled OS in unresected patients.*"

They found an ICERs for CET+FOLFIRI vs. FOLFIRI of approximately:

- [redacted] per QALY, assuming weekly dosing of cetuximab, and
- [redacted] per QALY, assuming fortnightly dosing of cetuximab.

4 PenTAG additional analyses

Here, we discuss our amended model structure and parameters based on the requests from NICE and the data recently provided by the companies.

4.1 PFS or OS method

In the PenTAG model, OS is estimated either by the:

- **"OS method"**, in which OS is estimated directly from that observed in the 1st-line trials of CET and PAN, or
- **"PFS method"**, in which OS is estimated as the cumulative time on 1st-line PFS, 2nd-line PFS and 3rd-line BSC.

NICE have requested additional analyses using the **OS method only**. Therefore, this method is used in all our analyses in this section.

4.2 PAS for CET and PAN

In May 2016, we asked NICE which prices for CET and PAN we should use in our analyses. We have followed their advice, as follows:

- Do not use the list prices for either CET or PAN.
- PAS price for PAN, a reduction of [redacted] on the list price, and
- Revised PAS price for CET, a reduction of [redacted] on the list price (previously [redacted]).

4.3 Treatment duration

We now use the updated treatment durations from Amgen for PAN+FOLFOX vs. FOLFOX.

As stated above, Merck Serono have still not addressed our earlier concerns about mean treatment durations from CRYSTAL and OPUS. However, we take their estimates on trust and use them in all cases.

4.4 OS Kaplan-Meier data for liver mets subgroup

We use the OS Kaplan-Meier data for the liver mets subgroup provided by both companies.

4.5 Adjustment for imbalance in subsequent treatments

As requested by NICE, we use the OS HRs adjusted for imbalances in subsequent treatments in some scenario analyses.

As explained in Section 2.1, p7 above, Amgen chose the IPCW method to adjust the OS HR. We still have many concerns about their adjustment method, including the fact that they did not consider other methods, such as the RPSFT method. Despite these concerns, we use their estimated OS HRs. However, we strongly caution that the adjusted HRs should be treated sceptically.

As explained in Section 3.6, p15, we have serious concerns about the adjustments made by Merck Serono. For example, we are not convinced by their reason for exclusion of the IPCW method, and we have serious concerns about the implementation of recensoring in their chosen method, the RPSFT method. Despite these concerns, we use their estimated OS HRs. Again, we strongly caution that the adjusted HRs should be treated sceptically.

Under the OS method in the PenTAG model, OS is fit independently for each treatment arm by Weibull curves exclusively (Section 6.1.3.2, PenTAG report, August 2015). OS hazard ratios from the RCTs of 1st-line drugs are not used. Instead, the mean OS is the response variable in a simple network meta-analysis. This therefore created a challenge to incorporate the adjusted OS HRs. Specifically, we sought a method to adjust the mean OS values from the network meta-analysis to allow for the changes to the OS hazard ratios, after adjustment for imbalances in subsequent treatments.

Merck Serono suggest this can be achieved by estimating the mean OS adjusted for imbalance in subsequent treatments "*by applying the adjusted OS hazard ratio to the mean OS for this arm in the model*" (p34 Merck Serono report April 2016). They then estimate the adjusted mean OS for FOLFIRI as [redacted] months (down from [redacted] months). Their method uses the adjusted hazard ratio and the mean for CET+FOLFIRI, and appears also to use the formulae for the mean of the Weibull distribution: mean = $\frac{1}{\lambda^{\gamma}}\Gamma\left(1+\frac{1}{\gamma}\right)$. However, we are not convinced by this method, as, for the Weibull distribution, the hazard ratio is not in general constant over time.

Our method can be demonstrated using the example of all patients for PAN+FOLFOX vs. FOLFOX. The ITT OS HR is 0.77, and the ratio of mean OS (FOLFOX / mean PAN + FOLFOX) = [redacted] / [redacted] months = 0.82. The ratio of means after adjustment for imbalances in subsequent treatment was then estimated by simple linear interpolation between the ITT HR / ratio of means and HR = 1, ratio means = 1 as:

= ITT Mean OS (FOLFOX / mean PAN + FOLFOX)

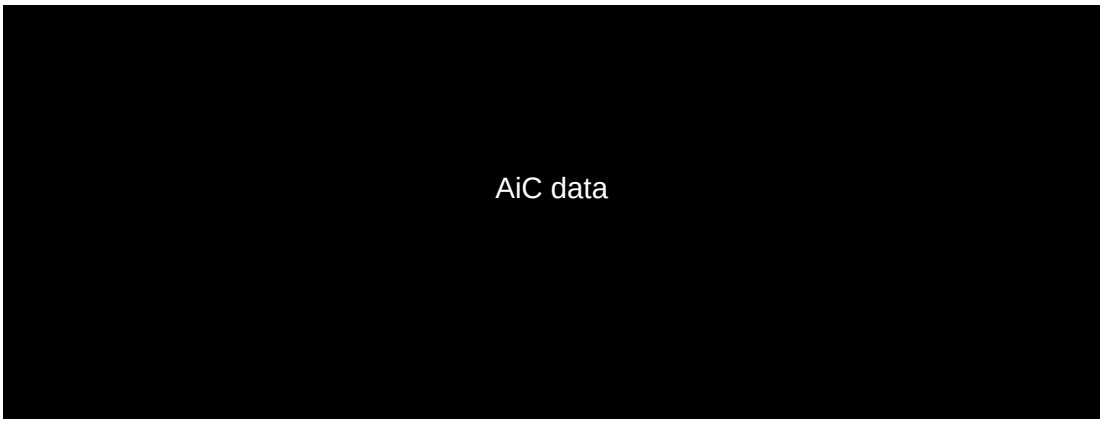
- (ITT HR – adjusted HR) * (1 – ratio of adjusted mean OS) / (1 - ITT H`1R)

= 0.82 – (0.77 – 0.69) * (1 – 0.82) / (1 – 0.77)

= 0.76.

This method is shown graphically in Figure 4 below. This method predicts a greater treatment benefit for CET+FOLFIRI than using Merck Serono's method

Figure 4 . Ratios of mean OS vs. OS HR

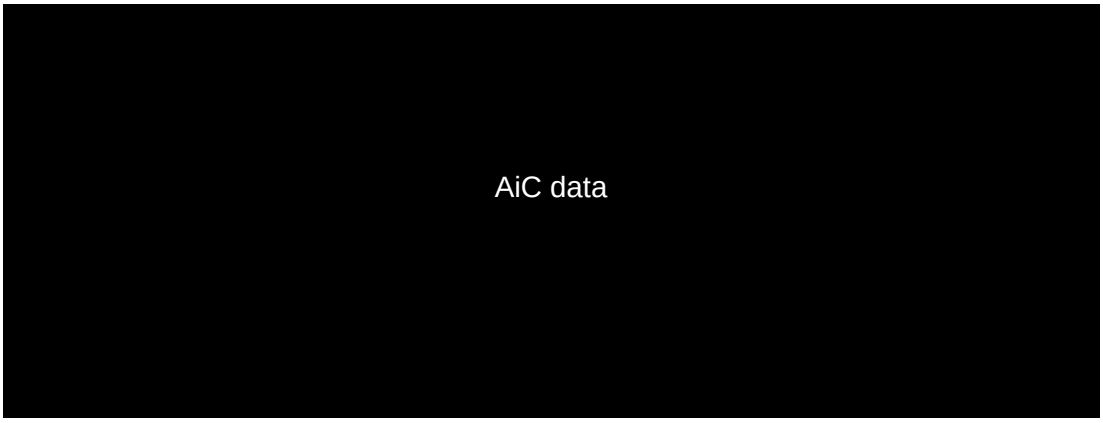


Finally, the mean OS for FOLFOX was estimated as mean OS for PAN+FOLFOX multiplied by the ratio of mean OS after adjustment for subsequent treatments

= [redacted] x [redacted] = [redacted].

In this way, mean OS changes as in Figure 5 below. In most cases, mean OS of FOLFOX and FOLFIRI [redacted] after adjustment, which implies a [redacted] treatment benefit for CET and PAN. Contrary to expectation, OS for FOLFOX for the liver mets subgroup actually [redacted] (see Figure 4). This is because Amgen found that in PRIME, the ITT OS HR of 0.71 increased to 0.75 given IPCW adjustment for subsequent anti-EGFR treatment, and independently increased to 0.86 given IPCW adjustment for subsequent bevacizumab (Table 2, p9).

Figure 5 Change in mean OS after adjustment for imbalance in subsequent treatments



4.6 Treatment stopping rules

NICE asked us to consider the following bases:

- No treatment stopping rule, or,
- 8 week stopping rule, or,
- 16 week stopping rule.

As in TA176, we assume that the stopping rule applies to CET and PAN only, not to FOLFOX or FOLFIRI. NICE have confirmed this.

In early 2016, we told NICE that we believe it is likely that if there had been stopping rules in the RCTs of 1st-line drugs, i.e. if treatment duration had been reduced, then PFS and OS would probably also have reduced. NICE responded by instructing us to work on two separate bases:

- Stopping rule applies, but no change in PFS or OS.
- Stopping rule applies, and PFS and OS adjusted accordingly.

We have done as instructed.

4.6.1 Stopping rule in TA176

In TA176, NICE's recommendation included a stopping rule of 16 weeks for CET when used with FOLFIRI or FOLFOX (NICE TA176 FAD Section 1.3).

In TA176, Merck Serono modelled a scenario which included a stopping rule at 16 weeks for CET when used with FOLFOX. NICE's Decision Support Unit (DSU) noted that Merck Serono had not reduced PFS accordingly. They, and the NICE committee therefore considered Merck Serono's analysis optimistic (NICE TA176 FAD p23). Under the stopping rule, the DSU instead explored modelling patients in the CET + FOLFOX arm by following the CET + FOLFOX PFS curve for 16 weeks, after which they then switched to follow the PFS for FOLFOX arm.

The NICE committee concluded that the most appropriate estimate of clinical effectiveness given the stopping rule lay between no reduction in PFS and the DSU reduction (NICE TA176 FAD p23).

It is difficult to predict the most likely impact on clinical effectiveness given a stopping rule. But we believe that it is likely to be close to that suggested by the DSU. We do not agree with the TA176 NICE committee that the DSU's adjusted clinical effectiveness necessarily represents a lower bound. It is conceivable that once CET or PAN treatment stops then there is a rebound effect whereby progression accelerates.

4.6.2 Impact of stopping rules on durations of CET & PAN treatment

Under the 8 weeks stopping rule, the mean durations on CET and PAN is slightly less than 8 weeks, because some patients stop treatment before 8 weeks.

Working now in months, 8 and 16 weeks, or 1.8 and 3.7 months, are far [redacted] than the mean treatment durations from the trials:

- [redacted] months for CET in CET+FOLFOX.
- 9.3 months for PAN in PAN+FOLFOX.
- [redacted] months for CET in CET+FOLFIRI.

This means that the mean treatment durations of CET and PAN under the stopping rules are significantly [redacted] than the mean durations from the RCTs (Figure 6). Given the high acquisition costs of CET and PAN, this change alone substantially [redacted] the cost-effectiveness of these treatments compared to chemotherapy alone.

We estimate the mean treatment durations for CET and PAN under the stopping rules as:

$$\mu\left(1-\exp(-\frac{T}{\mu})\right)$$

where μ = Mean treatment duration from RCT and T = stopping rule duration = 1.8 and 3.7 months. This expression assume treatment duration follows an exponential distribution. As mentioned above, this expression is only slightly less than T, given that T is substantially shorter than μ. For example, when T = 1.85 months, the adjustment mean duration for PAN+FOLFOX is 1.65 months.

Figure 6 Mean treatment duration by stopping rule

4.6.3 Impact of stopping rules on PFS and OS

Under one basis, we assume that a reduction in treatment duration acts to change (normally reduce) PFS and OS. Specifically, we assume that, when CET or PAN treatment stops, the probability of progression and the probability of death in each model cycle in the CET+FOLFOX and PAN+FOLFOX arms equal the equivalent values in the FOLFOX arm. Similarly for CET+FOLFIRI and FOLFIRI.

This appears to be very similar to the method used by the DSU in TA176 (http://www.nicedsu.org.uk/PDFs%20of%20reports/Cetuximab%20DSU%20final%20report.pdf). The only difference is that we adjust OS as well as PFS, whereas the DSU adjusted only PFS. However, we imagine that in Merck Serono's model for TA176, a change in PFS also changed OS. In this way, our method is similar to that of the DSU.

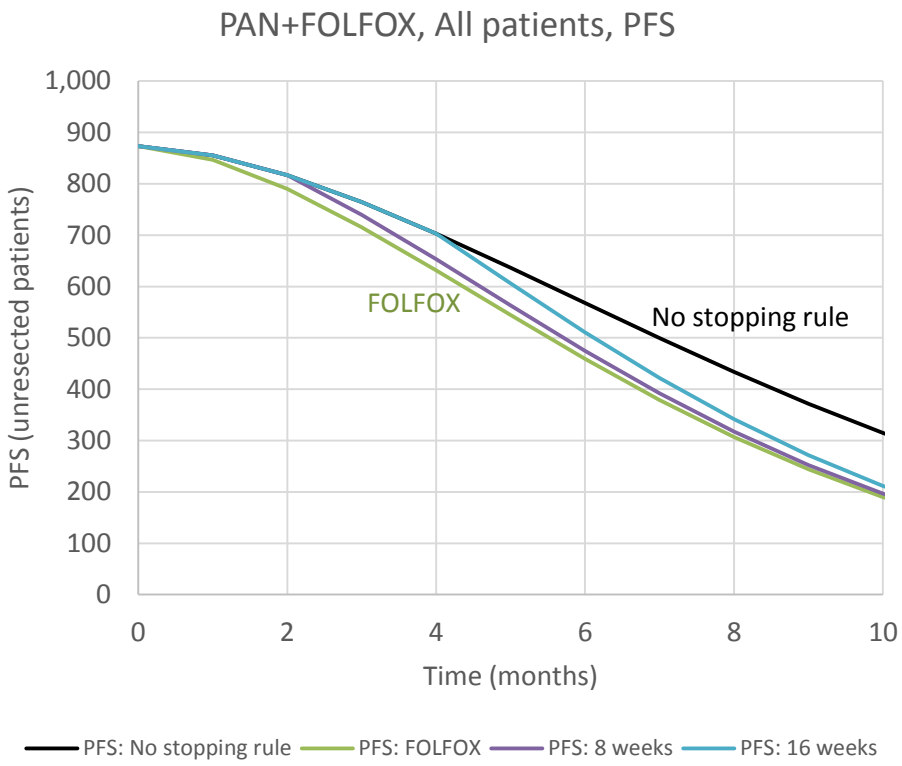
Our method can be seen graphically in Figure 7 for the example of PAN+FOLFOX all patients. This shows that a clear separation between PAN+FOLFOX with no stopping rule and FOLFOX. Also, with a stopping rule, PFS and OS for PAN+FOLFOX become very similar to PFS and OS for FOLFOX.

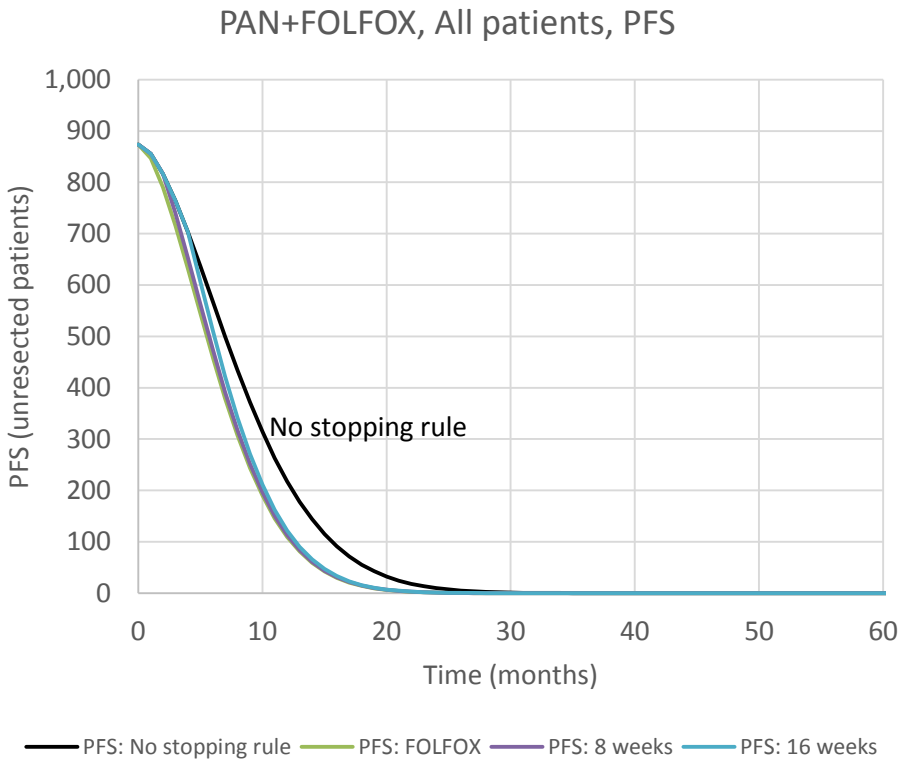
[redacted] patterns are seen for CET+ FOLFIRI.

For CET+FOLFOX (all patients or liver mets subgroup), we find the counterintuitive result that when we adjust OS for treatment stopping, OS actually [redacted]. This is because, in OPUS, we estimate a longer OS for unresected patients in the FOLFOX arm than in the CET+FOLFOX arm, e.g. for all patients, [redacted] vs. [redacted] months. This is plausible given the very similar OS in OPUS for CET+FOLFOX and FOLFOX.

Figure 7 (a) PFS and (b) OS for All patients FOLFOX and PAN+FOLFOX by stopping rule

(a) PFS





(b) OS

4.7 PenTAG revised cost-effectiveness results

In all our results in this section, we stress that we do not have confidence in the OS HRs adjusted for imbalances in subsequent treatments provided by either company.

ICERs corresponding to OS adjusted for subsequent treatments are not given for CET+FOLFOX because Merck Serono did not perform this analysis on the data from OPUS.

We also caution that Merck Serono have not answered our concerns about mean treatment durations from the trials.

4.7.1 All patients results

ICERs for all patients are given in the tables and in figures below.

In all cases, ICERs versus chemotherapy only arms (FOLFOX or FOLFIRI) decrease with the 16 week stopping rule with PFS and OS unadjusted, and decrease further with the 8 week rule. This is due to the substantial reductions in the costs of drug acquisition and administration.

As expected, for PAN+FOLFOX and CET+FOLFIRI, ICERs versus chemotherapy only arms (FOLFOX and FOLFIRI respectively) are far higher when PFS and OS are adjusted given stopping rules compared to no adjustment to PFS and OS. The reverse is found for CET+FOLFOX because, as stated above, life expectancy for unresected patients is actually predicted to be slightly higher for the FOLFOX arm than CET+FOLFOX.

As expected, in all cases, ICERs fall when adjustments are made for imbalances in subsequent treatments between treatment arms.

Table 7. ICERs (£/QALY) for CET+FOLFOX vs. FOLFOX: All patients

Stopping rule	PFS / OS	OS not adjusted for subsequent treatments	OS adjusted for subsequent treatments
None	n/a	[redacted]	n/a
16 weeks	**unchanged**	[redacted]	n/a
8 weeks	**unchanged**	[redacted]	n/a
16 weeks	**changed**	[redacted]	n/a
8 weeks	**changed**	[redacted]	n/a

Figure 8 ICERs (£/QALY) for CET+FOLFOX vs. FOLFOX: All patients

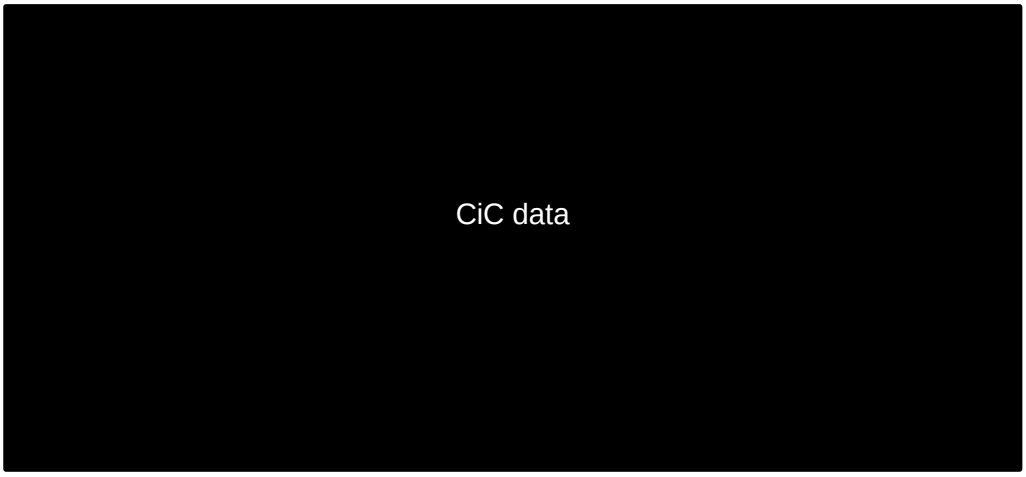


Table 8. ICERs (£/QALY) for PAN+FOLFOX vs. FOLFOX: All patients

Stopping rule	PFS / OS	OS not adjusted for subsequent treatments	OS adjusted for subsequent treatments
None	n/a	[redacted]	[redacted]
16 weeks	**unchanged**	[redacted]	[redacted]
8 weeks	**unchanged**	[redacted]	[redacted]
16 weeks	**changed**	[redacted]	[redacted]
8 weeks	**changed**	[redacted]	[redacted]

Figure 9 ICERs (£/QALY) for PAN+FOLFOX vs. FOLFOX: All patients

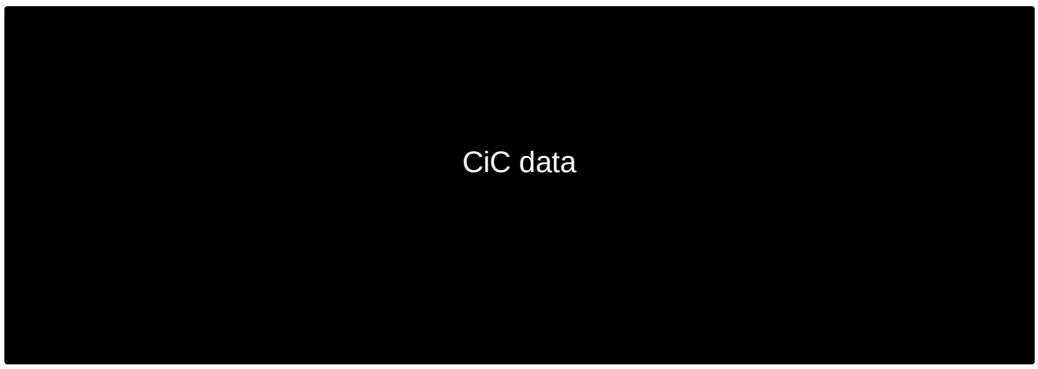
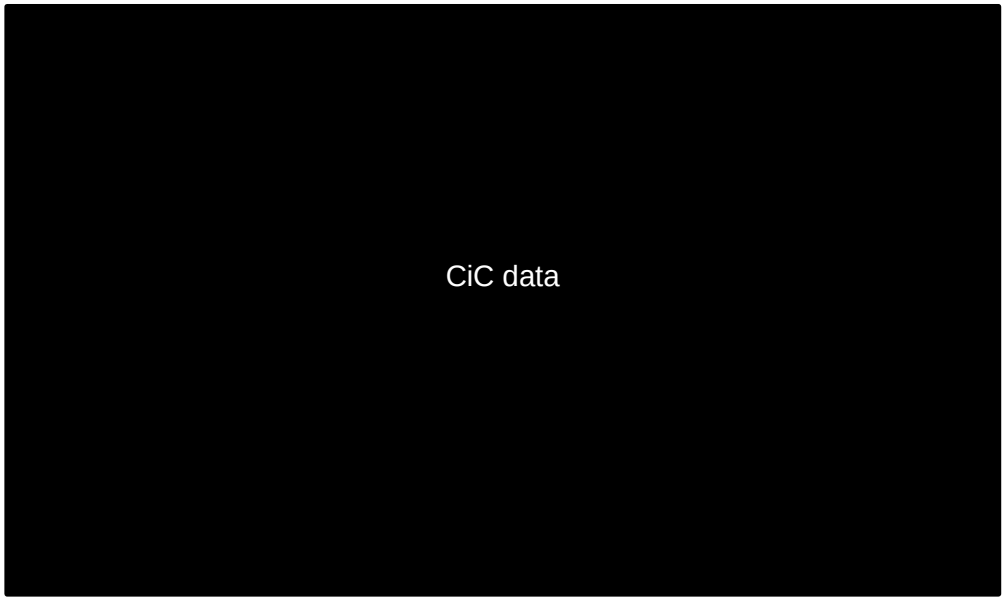


Table 9. ICERs (£/QALY) for CET+FOLFIRI vs. FOLFIRI: All patients

Stopping rule	PFS / OS	OS not adjusted for subsequent treatments	OS adjusted for subsequent treatments
None	n/a	[redacted]	[redacted]
16 weeks	**unchanged**	[redacted]	[redacted]
8 weeks	**unchanged**	[redacted]	[redacted]
16 weeks	**changed**	[redacted]	[redacted]
8 weeks	**changed**	[redacted]	[redacted]

Figure 10 ICERs (£/QALY) for CET+FOLFIRI vs. FOLFIRI: All patients



4.7.2 Liver mets results

ICERs for the liver mets subgroup are given in the tables and in figures below.

The directions of the changes in the ICERs are similar to those for all patients, except concerning adjustments for imbalances in subsequent treatments between treatment arms. When these adjustments are made, the ICERs for PAN+FOLFOX versus FOLFOX with no stopping rule increase, against expectation. This is because, after adjustment for imbalances, we expect a smaller benefit of PAN+FOLFOX. The adjustment has little effect on the ICERs for CET+FOLFIRI versus FOLFIRI because the adjustment is predicted to have little impact on life expectancy.

Table 10. ICERs (£/QALY) for CET+FOLFOX vs. FOLFOX: Liver mets

Stopping rule	PFS / OS	OS not adjusted for subsequent treatments	OS adjusted for subsequent treatments
None	n/a	[redacted]	n/a
16 weeks	**unchanged**	[redacted]	n/a
8 weeks	**unchanged**	[redacted]	n/a
16 weeks	**changed**	[redacted]	n/a
8 weeks	**changed**	[redacted]	n/a

Figure 11 ICERs (£/QALY) for CET+FOLFOX vs. FOLFOX: Liver mets

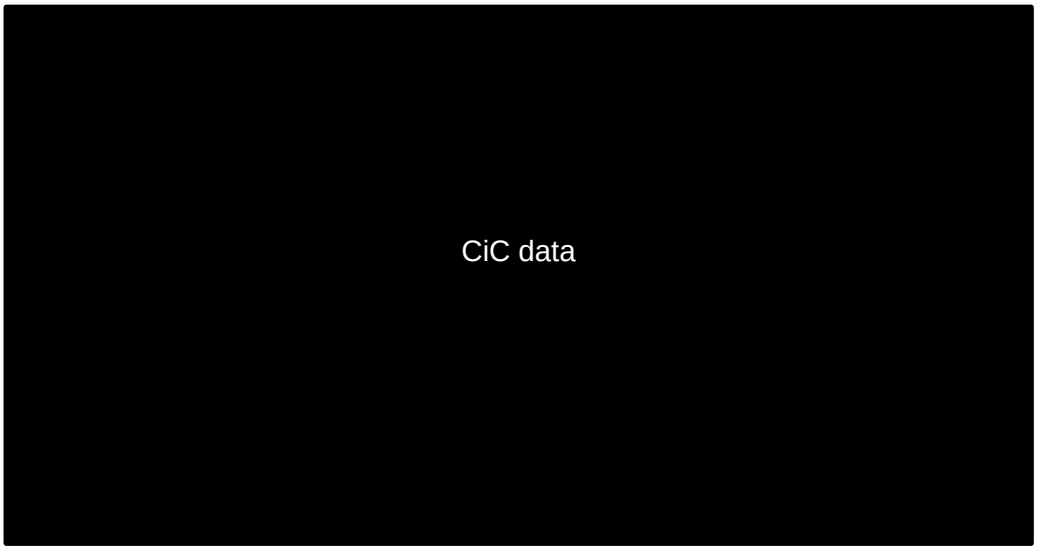


Table 11. ICERs (£/QALY) for PAN+FOLFOX vs. FOLFOX: Liver mets

Stopping rule	PFS / OS	OS not adjusted for subsequent treatments	OS adjusted for subsequent treatments
None	n/a	[redacted]	[redacted]
16 weeks	**unchanged**	[redacted]	[redacted]
8 weeks	**unchanged**	[redacted]	[redacted]
16 weeks	**changed**	[redacted]	[redacted]
8 weeks	**changed**	[redacted]	[redacted]

Figure 12 ICERs (£/QALY) for PAN+FOLFOX vs. FOLFOX: Liver mets

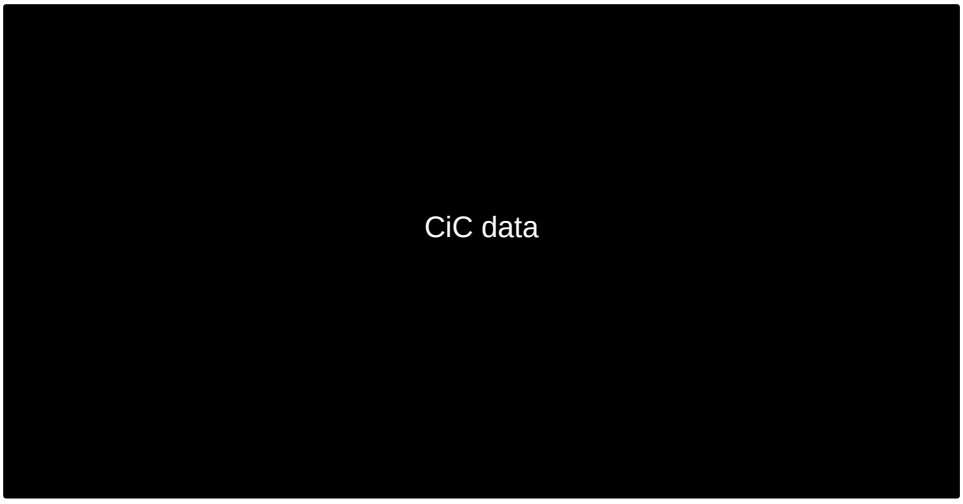
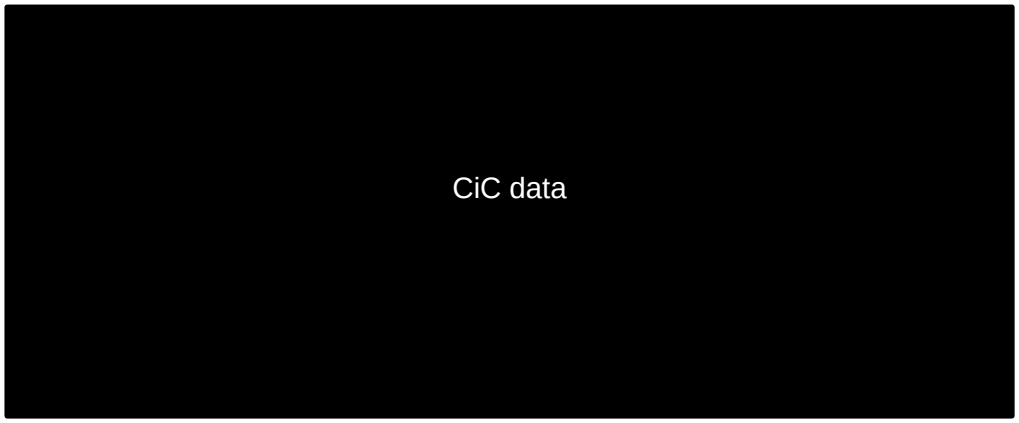


Table 12. ICERs (£/QALY) for CET+FOLFIRI vs. FOLFIRI: Liver mets

Stopping rule	PFS / OS	OS not adjusted for subsequent treatments	OS adjusted for subsequent treatments
None	n/a	[redacted]	[redacted]
16 weeks	**unchanged**	[redacted]	[redacted]
8 weeks	**unchanged**	[redacted]	[redacted]
16 weeks	**changed**	[redacted]	[redacted]
8 weeks	**changed**	[redacted]	[redacted]

Figure 13 ICERs (£/QALY) for CET+FOLFIRI vs. FOLFIRI: Liver mets



4.7.3 Uncertainty in cost-effectiveness

Given that the deterministic cost-effectiveness results vary considerably, there is clearly vast structural uncertainty. We did not perform probabilistic sensitivity analyses because parameter uncertainty represents only a portion of total uncertainty. We consider that PSAs would not help the NICE committee in its decision making processes.

However, we can say qualitatively that parameter uncertainty is greatest for CET+FOLFOX vs. FOLFOX because OPUS was a relatively small trial, and parameter uncertainty is much greater for the liver mets subgroup compared to all patients, as it represents only about 25% of all patients.

4.7.4 End of Life criteria: life expectancy on FOLFOX/FOLFIRI and extension to life

4.7.4.1 EoL criteria: All patients

The EoL criteria for life expectancy of the comparator < 2 years and incremental life expectancy of treatment > 3 months is satisfied only for CET+FOLFIRI vs. FOLFIRI for all

scenarios in which OS adjusted for subsequent treatments (Table 13 to Table 15). But we stress our concerns with these adjustments. Black shading indicates that the criterion is not satisfied, white shading that the criterion is satisfied.

Table 13. Life expectancy (years) for CET+FOLFOX vs. FOLFOX: All patients

Stopping rule	PFS / OS	OS not adjusted for subsequent treatments		OS adjusted for subsequent treatments	
		Life expectancy FOLFOX	Incr. life expectancy with CET+FOLFOX	Life expectancy FOLFOX	Incr. life expectancy
None	n/a	2.35	0.17	n/a	n/a
16 weeks	**unchanged**	2.35	0.17	n/a	n/a
8 weeks	**unchanged**	2.35	0.17	n/a	n/a
16 weeks	**changed**	2.35	0.37	n/a	n/a
8 weeks	**changed**	2.35	0.37	n/a	n/a

Key: black shading indicates that the criterion is not satisfied, white shading that the criterion is satisfied. n/a represents scenarios for which the information is unavailable

Table 14. Life expectancy (years) for PAN+FOLFOX vs. FOLFOX: All patients

Stopping rule	PFS / OS	OS not adjusted for subsequent treatments		OS adjusted for subsequent treatments	
		Life expectancy FOLFOX	Incr. life expectancy	Life expectancy FOLFOX	Incr. life expectancy
None	n/a	2.35	0.50	2.18	0.67
16 weeks	**unchanged**	2.35	0.50	2.18	0.67
8 weeks	**unchanged**	2.35	0.50	2.18	0.67
16 weeks	**changed**	2.35	0.09	2.18	0.11
8 weeks	**changed**	2.35	0.09	2.18	0.11

Key: black shading indicates that the criterion is not satisfied, white shading that the criterion is satisfied. n/a represents scenarios for which the information is unavailable

Table 15. Life expectancy (years) for CET+FOLFIRI vs. FOLFIRI: All patients

Stopping rule	PFS / OS	OS not adjusted for subsequent treatments		OS adjusted for subsequent treatments	
		Life expectancy FOLFIRI	Incr. life expectancy	Life expectancy FOLFIRI	Incr. life expectancy
None	n/a	2.10	0.80	1.82	1.08
16 weeks	**unchanged**	2.10	0.80	1.82	1.08
8 weeks	**unchanged**	2.10	0.80	1.82	1.08
16 weeks	**changed**	2.10	0.22	1.82	0.25
8 weeks	**changed**	2.10	0.22	1.82	0.25

Key: black shading indicates that the criterion is not satisfied, white shading that the criterion is satisfied. n/a represents scenarios for which the information is unavailable

4.7.4.2 EoL criteria: Liver mets subgroup

The EoL criterion for life expectancy of the comparator < 2 years is not satisfied in any scenario (

Table 16 to Table 18). The incremental life expectancy criterion is satisfied in most cases.

Table 16. Life expectancy (years) for CET+FOLFOX vs. FOLFOX: Liver mets

Stopping rule	PFS / OS	OS not adjusted for subsequent treatments		OS adjusted for subsequent treatments	
		Life expectancy FOLFOX	Incr. life expectancy	Life expectancy FOLFOX	Incr. life expectancy
None	n/a	3.41	0.15	n/a	n/a
16 weeks	**unchanged**	3.41	0.15	n/a	n/a
8 weeks	**unchanged**	3.41	0.15	n/a	n/a
16 weeks	**changed**	3.41	0.38	n/a	n/a
8 weeks	**changed**	3.41	0.39	n/a	n/a

Key: black shading indicates that the criterion is not satisfied, white shading that the criterion is satisfied. n/a represents scenarios for which the information is unavailable

Table 17. Life expectancy (years) for PAN+FOLFOX vs. FOLFOX: Liver mets

Stopping rule	PFS / OS	OS not adjusted for subsequent treatments		OS adjusted for subsequent treatments	
		Life expectancy FOLFOX	Incr. life expectancy	Life expectancy FOLFOX	Incr. life expectancy
None	n/a	3.41	0.55	3.63	0.33
16 weeks	**unchanged**	3.41	0.55	3.63	0.33
8 weeks	**unchanged**	3.41	0.55	3.63	0.33
16 weeks	**changed**	3.41	0.41	3.63	0.36
8 weeks	**changed**	3.41	0.41	3.63	0.37

Key: black shading indicates that the criterion is not satisfied, white shading that the criterion is satisfied. n/a represents scenarios for which the information is unavailable

Table 18. Life expectancy (years) for CET+FOLFIRI vs. FOLFIRI: Liver mets

Stopping rule	PFS / OS	OS not adjusted for subsequent treatments		OS adjusted for subsequent treatments	
		Life expectancy FOLFIRI	Incr. life expectancy	Life expectancy FOLFIRI	Incr. life expectancy
None	n/a	2.63	0.90	2.52	1.00
16 weeks	**unchanged**	2.63	0.90	2.52	1.00
8 weeks	**unchanged**	2.63	0.90	2.52	1.00
16 weeks	**changed**	2.63	0.34	2.52	0.35
8 weeks	**changed**	2.63	0.33	2.52	0.34

Key: black shading indicates that the criterion is not satisfied, white shading that the criterion is satisfied. n/a represents scenarios for which the information is unavailable

4.7.4.3 EoL criteria: Summary

A summary of all End of Life criteria is given in the table below. Here, we supplement the earlier conclusions of the Committee with our additional findings in this report. Key differences from the Committee's previous conclusions are shown underlined in bold font. Based on this, we find that NICE's previous judgement that no treatment satisfies the EoL criteria remains.

As stated in Section 3.5, p15, Merck Serono now claim that cetuximab meets the amended criteria in the new CDF process, and that these criteria will take effect prior to the conclusion of this MTA. We are not aware of the amended criteria in the new CDF process. However, even without the population size criterion, we find that all treatments fail on at least one other criterion, with the possible exception of CET+FOLFIRI for all patients, where we repeat that we believe that the OS adjustment for subsequent treatments has probably not been implemented correctly.

Table 19. End of life criteria

	CET+FOLFIRI / FOLFOX		**PAN+FOLFOX**	
	NICE ACD Table 5	**PenTAG analyses in this report**	**NICE ACD Table 5**	**PenTAG analyses in this report**
All patients				
Short life expectancy, normally <24 months average	Criterion met	**Only for CET+FOLFIRI vs. FOLFIRI for all scenarios in which OS adjusted for subsequent treatments**	Criterion met	**Criterion not met**
Extension to life, normally ≥3 months average	Criterion met	**Only for CET+FOLFIRI vs. FOLFIRI for all scenarios in which OS adjusted for subsequent treatments**	Criterion met	**Criterion not met**
Licensed for <7000 people in England (all indications)	Criterion not met	No change	Criterion probably not met	No change
Liver mets subgroup				
Short life expectancy, normally <24 months average	Criterion not met	No change	Criterion not met	No change
Extension to life, normally ≥3 months average	Criterion probably met, estimates not robust	No change	Criterion probably met, estimates not robust	No change
Licensed for <7000 people in England (all indications)	Criterion not met	No change	Criterion probably not met	No change

4.7.5 Comparison with Merck Serono ICERs

As explained in Section 3.10, p23, Merck Serono adjusted their version of our model in the following ways (p32 Merck Serono April 2016 report):

- RPSFTM adjusted OS HR of [redacted] for all patients.
- Actual (trial) total monthly dose of cetuximab (rather than PenTAG's approximated doses).
- Delink the resection rate inputs from the modelled OS in unresected patients.

They found an ICER for CET+FOLFIRI vs. FOLFIRI of approximately:

- [redacted] per QALY, assuming weekly dosing of cetuximab, and
- [redacted] per QALY, assuming fortnightly dosing of cetuximab.

Our corresponding value for weekly dosing of CET (without stopping rule) is approximately [redacted] per QALY, which is similar to Merck Serono's value of [redacted]. It is difficult to be sure of the reason for the discrepancy, but we imagine this is largely due to Merck Serono's adjustment to resection rates.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cetuximab and panitumumab for previously untreated metastatic colorectal cancer

Response to Assessment Group's Addendum

Prepared by:

23rd August 2016

Confidential information that is academic-in-confidence is highlighted and underlined

Confidential information that is commercial-in-confidence is highlighted and underlined

Table of Contents

Summary and Introduction

We have carefully reviewed the Assessment Group's (AG) Addendum for the appraisal of panitumumab combination therapy for the treatment of adults with previously untreated, RAS wild-type (WT) metastatic colorectal cancer (mCRC); which included both consideration of additional information provided by Amgen and also additional analyses undertaken by the AG at the request of the Committee. **However, we are concerned that the additional analyses conducted by the AG do not follow the Committee's preferred assumptions, draw clinically implausible conclusions and will consequently not help the Committee's decision making.**

We believe that the evaluation of panitumumab as an End of Life (EoL) therapy modelled using clinically appropriate assumptions together with the [redacted] patient access scheme (PAS) ([redacted]), would demonstrate panitumumab to be a cost effective treatment.

We have presented our responses to issues identified within the AG Addendum in Sections 1 to 3 under the following headings: 1. Assessment Group additional analyses, 2. Consideration of panitumumab in combination with FOLFIRI, and 3. Assessment Group's concerns regarding Amgen additional analyses.

1. Assessment Group additional analyses

We do not agree with the AG's conclusion that the EoL criteria are not met for any FOLFOX and FOLFIRI combinations with anti-EGFRs, other than cetuximab+FOLFIRI. Both FOLFIRI and FOLFOX combinations with the anti-EGFR agents meet the revised EoL criteria.

The NICE Appraisal Committee deemed both FOLFIRI and FOLFOX combinations to meet two out of the three EoL criteria, failing only to meet the criteria relating to population size, which is no longer a criterion for EoL (Table 5 of ACD). However the AG has now concluded otherwise that only the FOLFIRI combination with cetuximab (but not the FOLFOX combinations with the anti-EGFR agents) would meet EoL (for short life expectancy and extension to life).

The consideration of short life expectancy is based on a narrow assessment of evidence and does not take into account the broader set of evidence identified by a systematic literature review, which consistently supported a short life expectancy of <24 months for both combinations. From all studies which included a FOLFOX arm, the median OS in the FOLFOX arm ranged from 10.7 months to 20.5 months (Appendix 8, Amgen submission). Indeed, one study in which almost 90% of the patients had died at evaluation, yielded a median OS of 15.4 months for FOLFOX (Seymour et al, 2007). There is therefore considerable evidence to show that panitumumab plus FOLFOX therapy is indicated for patients with a short life expectancy of normally less than 24 months. It is noteworthy that the median overall survival (OS) for FOLFOX patients within the PRIME study was 20.2 months (Douillard et al, 2013); 27% of these patients received subsequent anti-EGFR therapy, which they would not currently do within the NHS, and hence OS is likely to be reduced.

Similarly, the conclusions around extension to life are clinically implausible. Based on robust RCT evidence, the FOLFOX combination offers at least an additional 3 month OS gain. The median OS gain of 5.6 months (PRIME study) has been accepted by the European Medicines Agency (EMA) as providing credible evidence to support its license indication. The robustness and maturity of data (82% of patients had died when this assessment was conducted) and given that the impact of subsequent treatments would likely attenuate OS gains, all provide strong reasons why panitumumab in combination with FOLFOX offers at least an additional 3 months of life, compared with FOLFOX, the current NHS treatment. Therefore, the increased life expectancy results presented in Tables 13-14 in the Addendum are clinically inconsistent and implausible as they result in flawed conclusions:

- Only panitumumab+FOLFOX meets the EoL criterion of increased life expectancy when no stopping rules (or when stopping rules with PFS/OS unchanged) are applied whereas cetuximab+FOLFOX does not, under this scenario, even though cetuximab and panitumumab are recognised as being similar.
- However, panitumumab+FOLFOX does not meet the EoL criterion of increased life expectancy when stopping rules are applied with PFS/OS changed. In contrast, in the same scenario, cetuximab+FOLFOX meets the EoL criterion of increased life expectancy even though cetuximab and panitumumab are recognised as being similar. Additionally, this suggests that stopping cetuximab treatment earlier results in improved survival which seems clinically implausible.

We have serious concerns about these conclusions. We believe that the clinically relevant and plausible approach would be to assume similarity between panitumumab and cetuximab including equivalence around key assumptions (such as resection rates). Indeed, this is the approach taken by the EMA which pragmatically used the strength of panitumumab data (PRIME study) to augment the evidence base in patients with RAS WT tumours for cetuximab stating *"cetuximab data by RAS status are only derived from the randomised phase II study OPUS, the biological rationale supporting the efficacy in patients with RAS wild type tumours only is strong and the conclusions are supported by data related to panitumumab"* (European Medicines Agency, 2013).

A possible determination that only cetuximab+FOLFIRI meets EoL, and therefore could be deemed cost effective, but not panitumumab+FOLFIRI or indeed any of the FOLFOX anti-EGFR combinations, seems implausible. This may lead to a clinically suboptimal recommendation, restricting clinician and patient choice and preventing the tailoring of treatments to optimise patient outcomes.

Given the clinical evidence which shows similiarity between cetuximab and panitumumab and also between panitumumab+FOLFOX and panitumumab+FOLFIRI, it would be unreasonable to conclude that of the four FOLFOX or FOLFIRI combinations with the anti-EGFRs, only the cetuximab+FOLFIRI is potentially cost effective (driven by meeting EoL criteria).

Furthermore, the AG has not formally considered the cost effectiveness of panitumumab with FOLFIRI, although this combination is licensed and currently recommended by the CDF which considers panitumumab and cetuximab to be similar in terms of efficacy and side-effect profiles with no known biological difference (see Section 3 for more detail).

Therefore if cetuximab+FOLFIRI combination therapy is cost effective within the EoL threshold, then other combinations with the anti-EGFR agents (including panitumumab+FOLFIRI) should also be cost effective. Additionally the less frequent licensed dosing regimen for panitumumab should further improve the ICERs.

The assumption of differential resection rates for the anti-EGFR agents is inconsistent with clinical expert opinion and does not reflect the Committee's preferred assumptions. Resection rates for cetuximab and panitumumab should be assumed to be equivalent.

At the second NICE Appraisal Committee meeting, clinical experts commented that the two anti-EGFR agents were generally considered to be clinically equivalent and confirmed that resection rates for these agents should be approximately 20%. Following this meeting, NICE (in the Committee's specification for further work) directed the AG to use the same resection rates for both agents:

"The Committee preferred assumptions (to be incorporated in above analyses):

- The Assessment Group's resection rates associated with cetuximab and panitumumab
    - Total population, resection rate of 20.7%
    - Subgroup of people with metastases confined to the liver, resection rate of 31.3%"

In contrast, in the Addendum, cetuximab is attributed with a much higher resection rate of 20.7% versus 12.6% for panitumumab, resulting in significantly worse life expectancy (and likely contributing to significantly worse ICERs) as seen in Tables 13-15 of the Addendum for panitumumab compared to cetuximab. We are concerned that the additional analyses conducted by the AG do not follow the Committee specification and use clinically implausible inputs and assumptions to inform the model. This inevitably leads to clinically implausible conclusions that are unlikely to help the Committee's decision making.

We believe that the clinical and cost effectiveness case for panitumumab is sufficiently robust. Further, the PAS we have offered mitigates the risk to the NHS regarding any residual uncertainty.

Access to panitumumab and cetuximab through the Cancer Drugs Fund (CDF) has delivered critical improvements in outcomes for previously untreated mCRC patients. This appraisal presents an opportunity to move panitumumab into baseline commissioning and provide patients with the first ever NICE approved targeted treatment in this life limiting condition.

We therefore propose that NICE recommends panitumumab in combination with FOLFOX or FOLFIRI for use in previously untreated metastatic colorectal cancer patients.

2. Consideration of panitumumab in combination with FOLFIRI

The Addendum does not formally consider the cost effectiveness of panitumumab with FOLFIRI, however panitumumab, like cetuximab, is licensed in combination with FOLFIRI. Evidence from four studies (ASPECCT, PLANET, Study 20060314 and PRIME) formed the basis of the EMA approval of the first-line indication of panitumumab in combination with FOLFIRI. This evidence is summarised in Table 1 and was presented in Appendix 7 of our submission.

Table 1: Studies underpinning the approval of panitumumab+FOLFIRI in 1st-line

Study	Treatment and Design	Population	Results
ASPECCT (Price et al, 2014)	Panitumumab versus cetuximab Phase III RCT	KRAS WT ≥3rd line study	Panitumumab demonstrated non-inferiority to cetuximab in terms of OS with a similar tolerability profile.
PLANET (Abad et al, 2014)	Panitumumab + FOLFOX versus panitumumab + FOLFIRI Phase II RCT	Liver limited disease KRAS WT RAS WT 1st line study	FOLFIRI arm had similar if not better results (OS and PFS) than the FOLFOX arm.
20060314 (Amgen, 2014)	Panitumumab + FOLFIRI Single arm study	All patients RAS WT 1st line study	<u>RAS WT population</u> ORR and PFS were similar to the cetuximab+FOLFIRI arm of the CRYSTAL study: • 20060314: 59% ORR and 11.2 months PFS • CRYSTAL: 66% ORR and 11.4 months PFS (Van Cutsem et al, 2015)
PRIME (Douillard et al, 2013)	Panitumumab + FOLFOX versus FOLFOX	All patients RAS WT 1st line study	<u>RAS WT population</u> Median PFS 10.1 months in the panitumumab+FOLFOX arm. OS gain of 5.6 months (HR 0.77 [95% CI 0.64 to 0.94]; p=0.009)

WT, wild-type; PFS, progression-free survival; OS, overall survival; ORR, overall response rate; RCT, randomised controlled trial

The key evidence considerations were:

- Panitumumab is non-inferior to cetuximab (in the monotherapy setting in terms of OS, with a similar tolerability profile). The premise of equivalence between the two anti-EGFR agents has also been acknowledged by the EMA who stated that the evidence base for cetuximab in patients with RAS WT tumours was augmented by data related to panitumumab (European Medicines Agency, 2013). Similarly, the CDF listing notes that *"there was no known biological difference between panitumumab and cetuximab in terms of efficacy and that side-effect profiles were also very similar"*. (Cancer Drugs Fund, 2014)
- Panitumumab+FOLFIRI patients in the 20060314 study are similar to those cetuximab+FOLFIRI patients in CRYSTAL (pivotal phase III study) with similar outcomes in terms of PFS and response rates.

- Panitumumab+FOLFIRI is at least similar to panitumumab+FOLFOX based on the PLANET study as well as the similarity in the results between the 20060314 and the PRIME trials. This is supported by EMA considerations which state *"The comparison of the two panitumumab combinations (to FOLFOX and FOLFIRI) used as first line treatment in the PLANET trial and the cross-study comparison between the efficacy results of Study 20060314 with FOLFIRI and Study 20050203 with FOLFOX support the proposed extension of indication for the FOLFIRI combination."* (European Medicines Agency, 2015)
- Panitumumab+FOLFIRI combination does not result in additional safety concerns with the EMA stating that *"The safety of the combination of panitumumab with FOLFIRI has been well characterised from clinical trials and post-marketing experience. No new safety concern has arisen from the new data submitted."* (European Medicines Agency, 2015)

The above considerations support the conclusion that panitumumab+FOLFIRI is equivalent to panitumumab+FOLFOX and also lends support to the conclusion that panitumumab+FOLFIRI is also likely to be similar to cetuximab+FOLFIRI. We believe this should satisfy the Committee that the clinical and cost effectiveness of panitumumab+FOLFOX combination therapy gives a good indication of the clinical and cost effectiveness of panitumumab+FOLFIRI combination therapy.

3. Assessment Group's concerns regarding Amgen additional analyses

AG concern: *"The interpretation of the hazard ratios is not clear. Amgen say they represent the scenario "when subsequent anti EGFR therapy is taken in to account". Does this mean the counterfactual state in which no patients subsequently receive CET or PAN?"*

Amgen response:

The various statistical techniques represent methods for estimating survival times that would have been observed if patients had not gone on to receive subsequent treatments i.e. in which no patients subsequently receive cetuximab or panitumumab.

The Inverse Probability of Censoring Weights (IPCW) method presented specifically addresses the informative censoring issue and does not use survival data after subsequent therapy is received (i.e. censored) for subjects that received subsequent therapy. It censors data for switchers at the point of switch and weights the remaining observations with the aim of removing any censoring-related selection bias.

AG concern: *"We are not convinced that it is appropriate to perform some of the statistical techniques on the data from PRIME. For example, the RPSFT method estimates the treatment effect (in terms of an acceleration factor) of subsequent treatments based on its effect first line. However, the subsequent treatment CET was not taken 1st line in PRIME. Also, the impact of subsequent treatments may be largely unknown because only a proportion of patients received each subsequent treatment in both arms, and these may be a biased sample of all patients."*

"As discussed in the DSU Technical Support Document 16 (http://www.nicedsu.org.uk/Treatment-switching-TSD(2973293).htm), it is important to discuss and justify the method of adjustment, e.g. IPCW, rank preserving structural failure time models (RPSFTM) or Two-Stage method. However, Amgen have not done this. Instead, they have used the IPCW method without justification. This is important, as cost-effectiveness can be very sensitive to the method."

Amgen response:

We acknowledge that each statistical technique has its own assumptions and limitations. We focused on the IPCW method as it specifically addresses the informative censoring issue referred to by the AG above and does not use the survival data after subsequent therapy was received (for patients that received subsequent therapy). Patients who did not receive subsequent therapy are therefore essential in the final weighted analysis using this method. IPCW aims to produce an unbiased estimate of the causal effect of treatment in the presence of time-dependent confounding (Robins et al, 2000) and may be particularly suited for detecting OS benefits beyond those detected with an ITT approach that ignores selective crossover/drop-in bias.

We agree with the AG that it is important to discuss and justify the method selected as the cost effectiveness can be sensitive to the method. **In order to explore this uncertainty and to reassure the Committee that the impact of subsequent therapies would only serve to attenuate OS gains for panitumumab, we now provide results using the Two-Stage and RPSFTM methods (in addition to IPCW presented previously) to assess the impact of subsequent therapy on the OS treatment effect in the WT RAS population (Table 2 and Table 3). Regardless of the method used to address subsequent anti-**

EGFR or bevacizumab use, results consistently suggest a more favourable panitumumab OS treatment effect than that observed in the ITT analysis. The RPSFTM method assumes that the treatment received after switching has the same effect on survival as the treatment started at randomisation and may be less appropriate than the other methods presented since it is questionable whether this assumption holds (see detail in Table 2 and Table 3). Furthermore, the methods in the counterfactual framework (RPSTM and the stage 1 model for the Two-Stage method) assume a parametric accelerated failure time model for the treatment effect on OS. This assumption is untestable and unlikely to be true in practice. With the comprehensive list of baseline covariates and time-dependent covariates used in the IPCW analysis, this method may produce an estimate with the least bias.

Table 2: Impact of subsequent anti-EGFR therapy on OS in PRIME (WT RAS)

Analysis	OS HR (95% CI) Panitumumab + FOLFOX vs FOLFOX (N=512)	Comments
Intent to treat[a]	0.77 (0.64, 0.94)	
IPCW[a]	0.69 (0.50, 0.95)	Key assumptions: • No unmeasured confounders: data must be available on all baseline and time-dependent prognostic factors for mortality that independently predict informative censoring (switching). • Correctly specified models for switching and survival. Implementation (covariates used): • Baseline covariates: age, sex, race, region, disease location, number of metastatic sites, liver-only disease. • Time-dependent covariates: ECOG (worst within a treatment cycle) and disease progression status.
Two-Stage method[b]	[redacted]	Key assumptions: • Appropriate secondary baseline exists. • No unmeasured confounders at secondary baseline. • Switching must occur soon after secondary baseline time point; otherwise the method is prone to time-dependent confounding. Implementation: • Recensoring is applied by actual censor date for censored cases and by cut-off date for events when stage 1 HR>1. • Rebaseline is defined as the last dose date plus 2 weeks for dosed subjects; othewise the decision date to end treatment. • Covariates include worst grade of AE, worst grade of lab, worst grade of ECOG, and disease progression status within 30 days before or on secondary rebaseline • Stage 1 HR (95% CI) = [redacted]
RPSFTM[b]	[redacted]	Key assumptions: • The failure rank of any two patients following a treatment will be preserved following any other treatment. • Treatment has a multiplicative effect on a patient's lifetime. • The treatment received after switching has the same

Analysis	OS HR (95% CI) Panitumumab + FOLFOX vs FOLFOX (N=512)	Comments
		effect on survival as the treatment started at randomization and the counterfactual HR is 1.00. Implementation: • The counterfactual survival time are re-censored at the earlier of the two: the total follow-up time and the total follow-up time multiplying the factor for counterfactual survival. • The assumption that the treatment received after switching has the same effect on survival as the treatment started at randomisation was informally assessed by the two-stage method. The stage 1 HR=[redacted] while the final HR=[redacted]. The difference in stage 1 and stage 2 HRs suggests this assumption may not be valid.
CI, confidence interval; HR, hazard ratio; IPCW, inverse probability of censoring weighted; OS, overall survival; RPSFTM, rank preserving structural failure time model; WT, wild-type. Based on OS update analysis (data cut-off 24 January 2013). Analysis based on 'excluding codon 59'. [a] Source: (Peeters et al, 2013); [b] Source: Amgen data on file		

Table 3: Impact of subsequent bevacizumab therapy on OS in PRIME (WT RAS)

Analysis	OS HR (95% CI) Panitumumab + FOLFOX vs FOLFOX (N=512)	Comments
Intent to treat[a]	0.77 (0.64, 0.94)	
IPCW[b]	0.76 (0.61, 0.94)	
Two-Stage method[b]	[redacted]	Stage 1 HR (95% CI) =[redacted]
RPSFTM[b]	[redacted]	The assumption that the treatment received after switching has the same effect on survival as the treatment started at randomisation was informally assessed by the two-stage method. The stage 1 HR=[redacted]while the final HR=[redacted]. The difference in stage 1 and stage 2 HRs suggest this assumption may not be valid.
CI, confidence interval; HR, hazard ratio; IPCW, inverse probability of censoring weighted; OS, overall survival; RPSFTM, rank preserving structural failure time model; WT, wild-type. Based on OS update analysis (data cut-off 24 January 2013). Analysis based on 'excluding codon 59'. [a] Source: (Peeters et al, 2013); [b] Source: Amgen data on file.		

AG concern: *"Amgen have still not addressed our concern that the underlying data was not based on the latest data cut."*

Amgen response:

As stated in our response to the request for additional data (February 2016), the underlying data and **all analyses presented are based on the latest data cut, i.e. the most recent OS update analysis (data cut-off 24 January 2013).**

4. Other issues

Implementation of stopping rules for panitumumab and cetuximab

We note that the AG has conducted additional analyses applying 8 and 16 week treatment stopping rules for all patients. This approach does not align with the licensed indication for panitumumab which does not specify stopping rules according to a set time period. In the PRIME study (panitumumab+FOLFOX versus FOLFOX) treatment was continued until disease progression or unacceptable toxicity and treatment stopping rules may not be an appropriate strategy for all patients.

Unit costs of drug administration

The AG noted the application of a substantial reduction in unit costs of drug administration for cetuximab. Where the reduction in unit costs affects both treatments, then the reduction should be consistently applied in the model to both treatments.

5. References

Abad A, Massuti B, Gravalos C, et al. Panitumumab plus FOLFOX-4 or pantiumumab plus FOLFIRI in subjects with wild-type KRAS (exon 2) colorectal cancer and multiple or unresectable liver-limited metastases: data from the randomized, phase II PLANET study. Poster presented at World Congress on Gastro-Intestinal Cancer & ESMO 16th World Congress on Gastrointestinal Cancer; 25–28 June 2014, Barcelona, Spain. Available from: http://www.postersessiononline.eu/pr/congreso.asp?cod=502056300 (Accessed 23 February 2015). 2014.

Amgen. Data on file. Supplemental CSR 20060314, 16 October 2014. 2014.

Cancer Drugs Fund. National Cancer Drug Fund Prioritisation Scores - Panitumumab. http://www.england.nhs.uk/wp-content/uploads/2014/02/panitum-rasmcrc-jan14.pdf (access date 28 September 2015). 2014.

Douillard JY, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. *N Engl J Med*. 2013;369:1023–1034.

European Medicines Agency. Assessment Report - Erbitux. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000558/WC500160158.pdf (access date 28 September 2015). 2013.

European Medicines Agency. European Public Assessment Report: Vectibix. 26 February 2015. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000741/WC500187313.pdf (Accessed 18 August 2016). 2015.

Peeters M, Douillard JY, Siena S ea, et al. Impact of post-protocol anti-epidermal growth factor receptor therapy on survival in wild-type KRAS/NRAS metastatic colorectal cancer: Data from the PRIME study. Poster presented at Markers in Cancer - a joint meeting by ASCO, EORTC and NCI, Brussels, 7-9 November 2013. 2013.

Price TJ, Peeters M, Kim TW, et al. Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study. *Lancet Oncol*. 2014;15:569–579.

Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology*. 2000;11:550-560.

Seymour MT, Maughan TS, Ledermann JA, et al. Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial. *Lancet*. 2007;370:143–152.

Van Cutsem E, Lenz HJ, Kohne CH, et al. Fluorouracil, leucovorin, and irinotecan plus cetuximab treatment and RAS mutations in colorectal cancer. *J Clin Oncol*. 2015;33.

Multiple Technology Appraisal (MTA): Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer [ID794]

Merck's response to PenTAG's assessment of additional analyses

Executive Summary

Colorectal cancer remains the UK's second most common cause of cancer death, highlighting that patients with this disease still have a high unmet need. Without access to targeted therapies, treatment options will return to what clinicians and charities have described as "the dark ages".

Merck have demonstrated that, under a set of reasonable evidence-based assumptions and with a revised PAS, cetuximab – licensed for metastatic colorectal cancer patients with RAS wt tumours – is a cost-effective use of NHS resources for all patients in this indication. While acknowledging that in any modelling process uncertainties remain, Merck believes that the Committee can feel confident in the robustness of these conclusions. In responding to PenTAG's comments on revised assumptions and analyses provided to NICE, Merck wishes to emphasise the following key points:

1. The analyses require a consistent set of assumptions around resection rates across chemotherapy backbones for both the overall population and LLD population. PenTAG have a different interpretation of NICE's stated preferred assumptions for the analyses, unfortunately resulting in clinically illogical scenarios, with divergences in resection rates between chemotherapy backbones and agents which lack scientific or clinical basis. It is illogical to apply one approach to one chemotherapy backbone but not to the other. Merck have addressed this challenge through the application of a standardised resection rate as proposed by the Committee, and amended model functionality to account for this.

2. In adjusting for the effects of later line treatments on overall survival, recognised academics in this area have confirmed that the RPSFTM method and Merck's application of it represent a legitimate and appropriate technique to address this challenge. Further they corroborate that an IPCW analysis would be less appropriate in this case (see detailed response below). Merck strongly asserts that the adjusted OS HR of [redacted] for cetuximab/FOLFIRI represents a reasonable approximation of the benefit of treatment when the confounding due to post-study anti-cancer treatment is taken into account.

3. The use of *actual* trial doses of cetuximab represents the most robust approach, as it reduces the need for unnecessary extrapolations and assumptions. When adopting this approach, Merck confirms that PenTAG – who instead *estimate* the trial doses – overestimate the average monthly cost of cetuximab by around 15%.

4. In a revised base case, when Merck follow PenTAG's method of implementing the adjusted OS hazard ratio, using actual trial doses (dose intensity input set at 100%) and the Committee's preferred resection rates, the ICER for cetuximab/FOLFIRI versus FOLFIRI alone is [redacted] confirming the cost-effectiveness of this treatment in all RAS wt mCRC patients.

5. Cetuximab is routinely administered fortnightly in the UK. Both Merck and PenTAG analyses in this appraisal are based on weekly administration of cetuximab. However this introduces "phantom cost" of an additional [redacted] per patient as the treatment is not routinely administered in this way. This assumption of weekly dosing increases the ICER by [redacted] relative to the reality of fortnightly dosing.

6. Merck can confirm that the treatment durations previously provided represent the actual means from the CRYSTAL and OPUS studies.

7. Cetuximab/FOLFOX would not be cost-effective in PenTAG's model even with cetuximab at zero cost. The challenges in modelling cost effectiveness with FOLFOX are related to the selection of the OS model as the base case, and the specific study under consideration (OPUS), rather than the clinical profile of the drug itself. Cetuximab in combination with FOLFOX has consistently demonstrated similar outcomes to cetuximab in combination with FOLFIRI across a variety of RCTs involving active comparators. It is administered in the same fortnightly dosing schedule in the UK and so in this model has a similar excess treatment cost profile relative to chemotherapy alone. The revised Merck PAS applies irrespective of backbone. Merck urges the Committee to take a pragmatic approach with its recommendation to maximise clinician's choice of either FOLFIRI or FOLFOX at no financial impact to the NHS.

8. The analysis of cetuximab's cost-effectiveness in the LLD patient population has been overcomplicated. Merck has demonstrated that cetuximab is cost-effective in the all patient population. This analysis *includes* the LLD subgroup, precluding further discussion.

9. Furthermore, in TA176 cetuximab was found to be cost-effective in the LLD patient population for patients who were KRAS wild-type. The only relevant changes since TA176 are:

    a. further restriction of the patient population (KRAS wt to RAS wt) to exclude patients unlikely to benefit from treatment,

    b. an improved PAS.

    Both of these changes should improve cost effectiveness and therefore cetuximab in the LLD patient population would remain cost-effective. We urge pragmatism in this area.

10. Following the introduction of new CDF guidelines from 31st July 2016, new EOL criteria are in place. Application of these new criteria result in cetuximab in 1st line treatment of RAS wt mCRC meeting EOL criteria. The requirement that the total indicated population for a drug be fewer than 7000 patients no longer applies. Merck urges the Committee to apply these criteria in its evaluation.

Throughout this process Merck have engaged proactively, positively and transparently with all stakeholders. Information and data have been shared in a timely, clear and expeditious fashion. Cetuximab is routinely used for treating colorectal cancer in the UK and we are committed to continuing this positive engagement with NICE to ensure that mCRC patients can continue to access life extending medicines.

Background

In July 2016, PenTAG provided commentary around the additional analyses that Merck had provided in response to NICE's request after the second Appraisal Committee meeting. In this document, Merck responds to PenTAG's assessment of our analyses.

1.1. Resection rates

The economic model is sensitive to the resection rate inputs. Merck and PenTAG have a different interpretation of NICE's stated preferred assumptions for resection rates for the economic modelling; PenTAG's approach unfortunately result in an illogical set of assumptions.

In the specification of additional analyses received from NICE on 27th January 2016, the Appraisal Committee clearly set out a preferred assumption set to be implemented by PenTAG in the model (see Table 1 below).

Table 1: Committee's preferred assumptions

The Committee preferred assumptions (to be incorporated in above analyses):

• The Assessment Group's resection rates associated with cetuximab and panitumumab
  o Total population, resection rate of 20.7%
  o Subgroup of people with metastases confined to the liver, resection rate of 31.3%
• The Assessment Group's estimates for duration of progression-free survival for patients whose liver metastases were most plausible
• The Assessment Group's updated estimate of drug administration
• Assessment Group's Average body surface area 1.85 m^2
• Including FOLFOX6 rather than FOLFOX4
• Mean duration of treatment from the trials

Merck have interpreted this to mean that the resection rate for cetuximab/FOLFIRI and cetuximab/FOLFOX should be 20.7% for the total population and 31.3% for the liver-limited subgroup of patients, as outlined in Table 2.

Table 2: Resection rates implemented by Merck

R0 resection rates	**Chemotherapy only (No figures provided by NICE, Merck estimates)**	**Cetuximab/chemotherapy (NICE committee preferred assumptions)**
All patients	6%	20.7%
LLD subgroup	12%	31.3%

In order to calculate an appropriate estimate for patients treated with chemotherapy only (not provided by the Committee but required in the model), Merck applied the relative effect from CRYSTAL in each setting. Relative to the Committee's preferences, this leads to assumptions of a 6% R0 resection rate for FOLFIRI alone in the overall mCRC population, and 12% for FOLFIRI alone in the LLD population. These estimates align with the literature for patients treated with chemotherapy only and are appropriate (Adam R, 2004), (Ye, 2013).

In contrast to this, it appears that the ERG have instead assumed the resection rates of 20.7% should apply only to the cetuximab/FOLFOX 'all patient' analysis and 31.3% should apply only to the panitumumab/FOLFOX LLD analysis. In the cetuximab/FOLFIRI analysis, the ERG use R0 rates from the CRYSTAL trial for the cetuximab/FOLFIRI arm (although we are unclear why they state this as 6.5% in the cetuximab/FOLFIRI arm when the result was 7.3% - a value which PENTAG had used in their previous model). In Table 3 we outline the most recent full set of assumptions about resection rates that PenTAG applied, as far as we can determine it based upon the redacted ERG report and our version of PenTAG's economic model. As can be seen in Table 3, NICE's preferred assumption of 31.3% in the LLD group has not been implemented by PenTAG in cetuximab analyses.

Table 3: Resection rates applied to cetuximab by PenTAG.

R0 resection rates	Chemotherapy only (No figures provided by NICE)	Cetuximab/chemotherapy
All patients group		
- FOLFIRI	2.1%	6.5%*
- FOLFOX	6.3%	20.7% (NICE preferred)
LLD subgroup		
- FOLFIRI	6.5%	16.3%
- FOLFOX	17.1%	26.9%

PenTAG's interpretation of NICE's specification presents three clinical problems:

- *Applying the Committee's preferred resection rates only to the cetuximab + FOLFOX arm (and utilising CRYSTAL rates for the cetuximab/FOLFIRI arm) results in a clinically illogical set of assumptions for cetuximab, i.e. significantly higher for cetuximab/FOLFOX compared to cetuximab/FOLFIRI. This is contrary to clinical evidence which we have previously referenced which shows comparable resection rates with both chemotherapy backbones (38% for cetuximab/FOLFOX and 30% for cetuximab/FOLFIRI in the LLD group).* (Folprecht, 2014)
- *It is logically inconsistent to assume a higher resection rate in the all-patients group with cetuximab/FOLFOX (20.7%) than in the LLD subgroup with cetuximab/FOLFIRI (16.3%); resection rates are always higher in a liver-limited selected patient population than an all comer group.*
- *In the previous appraisal of cetuximab/chemotherapy (TA176), "The Committee considered the most plausible liver resection rate for cetuximab in combination with chemotherapy to use in the analysis to be 35%". This is in line with the guidance from the Committee in this appraisal*

* PenTAG reference this value incorrectly to the CRYSTAL study; the actual resection rate in the intervention arm in CRYSTAL is 7.3%.

of 31.3% for the LLD subgroup. Merck is unclear why the ERG have chosen to use an alternative figure of 16.3% for cetuximab/FOLFIRI and instead finds the Committee's recommendation of 31.3% for cetuximab/FOLFIRI and cetuximab/FOLFOX more plausible.

The rates that Merck proposed in the response to NICE's request for additional analyses have greater clinical relevance in the context of this decision problem than PenTAG's. Given the important impact of this assumption set, we ask the Committee to consider the clinical plausibility of the different approaches. Merck's proposed assumptions are shown in Table 2.

To implement Merck's recommended assumptions around resection rates, a minor amendment to the PenTAG model functionality is required. This is because there is currently an artificial link between the proportion of resected patients and the modelled mean survival of unresected patients (due to the way the model implements the separation of the CRYSTAL survival data into the resected patient and the unresected patient's survival).

In the PenTAG model, changing the percentage of patients who are resected results in a change in the modelled mean survival time of the unresected patients. Changing the percentage of patients who are resected would not affect the survival time of patients who are not resected; therefore Merck revised the model delinking this relationship to ensure the correct survival times are maintained.

1.2. Adjustment of overall survival for confounding due to post-study anti-cancer therapies

PenTAG suggest that Merck have not defended the RPSFTM sufficiently (versus the IPCW method) and that there is an error in our application of the re-censoring methodology; Merck clarifies our position on these two analyses – confirming that RPSFTM is a reasonable analysis, whilst IPCW may be less so. We address the application of the re-censoring method. We propose that the RPSFTM adjusted HR that PenTAG implement in the model ([redacted]) is the most appropriate reflection of cetuximab/FOLFIRI's benefit.

In the adjustment of overall survival for confounding due to post-study anti-cancer therapies, Merck applied two methods, the inverse-probability-censoring weighting method (IPCW) and the rank-preserving structural failure time model (RPSFTM).

The IPCW model was deemed to be a less reliable method for our data. It results in unbiased estimates only if a number of conditions are met. Howe et al, (2011;) write that the ability of IPCW to yield an unbiased estimated is dependent on whether the assumption of *exchangeability* is met. This (exchangeability) assumption only holds under the following three conditions. First that all common predictors are appropriately measured and accounted for in the analysis. Second that that there are a sufficient number of participants under follow-up at all relevant times. Third, the common predictors

cannot be deterministic or nearly deterministic in relation to both the outcome of interest and the artificial censoring mechanism among participants over time.

It is this first assumption that is likely violated in the data from the CRYSTAL trial. The decision to retreat or to switch treatment is likely to be based on how the patient has responded to earlier treatments, the availability of treatment (which is centre specific) and to his/her quality of life at the moment of the decision. Data about quality of life are somewhat incomplete in CRYSTAL and are available only until the end of study-treatment. Treatment switching happens after ending study treatment, sometimes months after. As such one can safely state that not all common predictors are appropriately measured and accounted for in the analysis and that as such the IPCW analysis leads to biased outcomes.

We do not understand the intention of the following comment from PenTAG "*If no observed variables predict switching, this does not tell us whether any unobserved variables predict switching. Therefore, we do not accept Merck Serono's reasoning for rejecting the IPCW method as inappropriate. They provide no further critique of the suitability of the IPCW method."*

Of course we agree that we learn nothing about *unobserved* variables through our conclusion that no *observed* variables predict switching. It must follow that since we haven't measured the variables that predict switching then the ones that do are unmeasured. Unmeasured variables, of course, cannot be accounted for in the analysis and as such the IPCW analysis is likely to lead to a biased result. We let the reader decide what is illogical here.

In relation to the RPSFTM, the ERG writes:

"As explained above, DSU is clear that the suitability of adjustments methods should be considered carefully. However, Merck Serono do not justify the use of this method. For example, they do not consider the key assumption of the method of the constancy of treatment effect for switcher and non-switchers."

This is an inevitable point of critique for this randomisation-based method. As the DSU guidelines explicitly describe, the underlying assumption of common treatment effect, i.e. that the effect of treatment is a function of the duration of treatment cannot be tested on the basis of the type of trial data as is available here. One may find some assurance in the fact that doctors start to retreat with cetuximab under the assumption of a similar effect and the better the expectation the longer a patient may receive the drug. Further support for this assumption in the CRYSTAL dataset may be found in Figure 1 where survival is depicted as a function of the duration of treatment. The causality of this relationship can be challenged, but this again confirms that the underlying assumption is difficult to test.

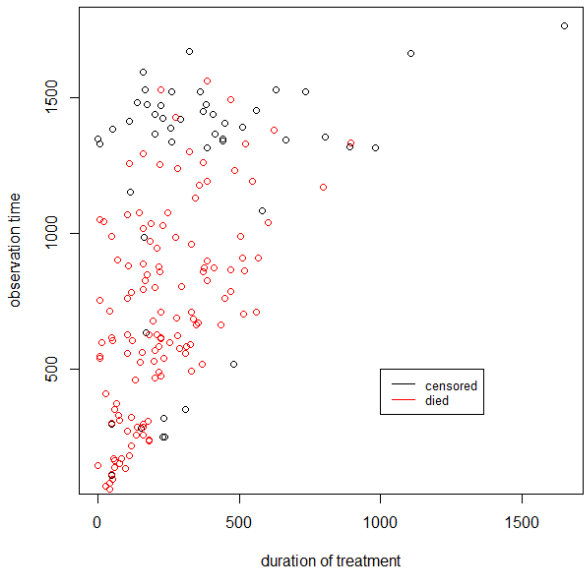


Figure 1: Survival and duration of treatment

In order to avoid bias due to the fact that counterfactual survival times could be linked to prognosis (i.e. could be informative), the RPSFTM method requires recensoring of the control group survival times. PenTAG have questioned Merck's approach to recensoring, suggesting that it may have been implemented incorrectly, saying "Let C_i be the censoring time for person i, on the observed time scale. Is the first option to recensor at min_i C_i? If so it is inappropriate as the recensoring time for one person should not depend on censoring times for other people. The correct recensoring time is person-specific and is usually min(C_i, C_i*exp(psi))."

Merck is aware of the advice to recensor at min(C_i, C_i*exp(psi)). Regrettably, we did not make it clear previously that the estimate of exp(psi) equals 0.08 in CRYSTAL's counterfactual control dataset and that if one applies this approach to recensoring, the maximum observed follow up time decreases from 56 months to 4.6 months. In **Error! Reference source not found.** (academic in confidence), the difference between no recensoring and PenTAG's suggested approach is shown. In our view the application of the alternative method results in such a significant loss of information so as to render the method unhelpful.

[redacted]

[redacted]

If we consider the reason why we recensor at all, it is to avoid informative censoring. We chose to do this by artificially using a new cut-off date, at min(C-i, Cut/off/date – randomisation/date-i). This too is person specific. The selection of a cut-off date is somewhat arbitrary. The shorter the chosen cut off, the less effect re-treatments have. We chose three new cut off dates and the shortest – as advised by Latimer et al (Latimer, 2013) – showed the most beneficial hazard ratio when applied to the CRYSTAL data set. We elected instead to utilise a more conservative estimate, the HR derived from recensoring at the second earliest censoring time to strike a balance between the fear of bias and loss of information.

In summary, Merck's position is that the pattern of treatments received post-study do not reflect the way patients would be treated in the NHS and it is appropriate to attempt to adjust for this. Given the imbalance between the study arms in post-study therapies, particularly in receipt of post-study cetuximab (with the control arm receiving proportionately more), the ITT result from CRYSTAL is an underestimate of relative treatment effect that may be experienced were these post-study therapies not received. The assumption of the IPCW (unmeasured confounders) is not satisfied in our data. It is not possible to test whether or not the assumption of the RPSFTM (common treatment effect) is satisfied in this dataset.

Merck, following advice from Pharmerit and Latimer, selected the RPSFTM as the more appropriate of the two methods to be used for this analysis.

1.3. Use of actual trial doses

PenTAG have elected to <u>model</u> the monthly doses of cetuximab used in the trials. Merck contends that there is no need to model these and instead the <u>actual</u> trial doses can be used. PenTAG's approach unfairly (and unnecessarily) penalises cetuximab.

Both PenTAG and Merck agree that to estimate monthly costs of cetuximab in the model, we simply need to multiply the cost per mg by the dose per month (accounting for likely treatment exposure). The main difference between the methods applied by both is in the approximation of the likely treatment exposure. Here, we make an assessment of the way that PenTAG has estimated this compared to Merck and discuss which of the two approaches is reasonable.

As described in the original ERG report (p. 320), PenTAG approximate monthly cetuximab acquisition costs by the following formula:

(cost per mg) X (*expected* total dose [mg] per month) X (*mean* Tx duration) X (*median* dose intensity)

By utilising dose intensities from the trial, PenTAG appear to agree that the CRYSTAL trial is the right source of data on treatment exposure. The question then is why does PenTAG estimate 10-15% higher monthly drug use than the trial shows? Both PenTAG's and Merck's estimates take into account wastage and body surface area is not the driver (monthly costs with PenTAG's method are the same whether a BSA of 1.79m^2 or 1.85m^2 is assumed).

In Merck's assessment it is because PenTAG's preliminary assumption that the *median* dose intensities (provided by Amgen and Merck in their original submissions) are a good approximation of the *mean* is likely flawed as it doesn't account for outliers.

Merck's approach to the same calculation is as follows:

(cost per mg) X (mean Tx duration) X (actual trial mean monthly dose)

Merck's approach uses **actual** trial doses, and is therefore a more accurate quantifier of the potential treatment exposure as it better reflects the likely distribution of treatment exposures across the trial population. This is a more robust approximation than PenTAG's which relies on the assumption that median equals mean. We urge the Committee to rely on actual rather than estimated trial doses, otherwise the average monthly costs of cetuximab are overestimated by approximately 15%.

We recognise that in our prior calculations, we did not fully appreciate PenTAG's implementation of dose intensities (which in part corrects for the inaccuracy of their approach), but when we correct for this – i.e. use actual trial doses at 100% dose intensity (rather than the ~92% current in PenTAG's model) our base case ICER is only marginally changed (ICER for cetuximab+FOLFIRI vs FOLFIRI = [redacted] at weekly dosing assumption), i.e. PenTAG's approach unnecessarily penalises cetuximab resulting in an additional [redacted] to the ICER. When we use PenTAG's recommended approach at implementing our adjusted OS HR, the ICER improves significantly (see Section 1.5).

1.4. Weekly vs fortnightly

Comment from PENTAG, pg 14 of report:

- Given that NICE have previously judged that we should assume weekly administration, we continue to make this assumption in all analyses in this report. We believe that it is NICE's decision as to whether modelling a process outside of licence constitutes a recommendation outside of the marketing authorisation.

As discussed at the previous Appraisal Committee Meetings, cetuximab is typically administered intravenously every two weeks in combination with chemotherapy in first line mCRC in England. This pattern of usage has emerged during the many years that cetuximab has been available and makes pragmatic sense for patients and physicians and financial sense for the NHS given the dosing schedule of the chemotherapy backbone. With this schedule, clinic visits are reduced by half and quality of life is likely to be improved for the patient.

The scenarios being discussed in the base case of this appraisal assume weekly administration of cetuximab and therefore include a 'phantom' cost as the treatment is not delivered in this way in current practice in the NHS and is not likely to be in the future. The impact of such an assumption is significant (an additional [redacted] of administration cost per patient is inappropriately attributed to treatment with cetuximab plus FOLFIRI versus FOLFIRI alone when weekly dosing is assumed). This assumption of weekly dosing increases the ICER by [redacted] relative to the reality of fortnightly dosing.

Merck would like to remind the Committee that the value (cost-effectiveness) of cetuximab to the NHS is underestimated in the scenarios which assume it will be administered weekly.

1.5. Revised base case from Merck

In a revised base case we incorporate the following assumptions:

- PSACT adjusted OS HR ([redacted] from the RPSFTM method) implemented using PenTAG's method as described on page 15 of the "Addendum: between 2nd and 3rd NICE Appraisal Committee meetings"
- Actual (trial) total monthly dose of cetuximab (rather than PenTAG's approximated doses) with corrected dose intensities (on *'1st line treatment duration CRYSTAL'!* worksheet)
- Committee's stated preferred resection rates for cetuximab in combination, and Merck's estimated resection rate for chemotherapy only
- A minor amendment to the PenTAG model functionality.[†]

[†] Currently, increasing the proportion of patients who are resected drives a reduction in the modelled mean survival of unresected patients because of the way the model implements the separation of the CRYSTAL survival data into the resected patient and the unresected patient's survival. This is artificial and in order to appropriately incorporate the Committee's preferred resection rates, it is necessary to delink the resection rate inputs from the modelled OS in unresected patients.

The following table presents the results of the analysis using PenTAG's economic model, under the assumptions set out above.

Table 4: Results of cost-effectiveness analysis under main assumptions

	Total cost (£)	Incremental cost (£)	Total QALYs	Incremental QALY	ICER (£/QALY)
Overall population / CRYSTAL study					
Cetuximab/FOLFIRI	[redacted]	[redacted]	2.17	0.81	[redacted]
FOLFIRI	[redacted]		1.36		

The results of the base case analysis show that cetuximab/FOLFIRI is a cost-effective treatment for patients with RAS wt metastatic colorectal cancer.

1.6. Mean treatment durations

The treatment durations that Merck have provided previously to PenTAG (response to ACD – dated 8th December 2015; response to request for additional analyses – dated April 2016) are directly from the OPUS and CRYSTAL Clinical Study Reports. It is fully appropriate that PenTAG have utilised these values in the economic model and we reject any suggestion that we have not been 100% transparent with these figures, their source and how they are calculated.

Tables 2 and 3 in our submission of additional analyses (April 2016) were copies of tables from the CSR showing the mean cetuximab treatment duration (in weeks) in the cetuximab/FOLFIRI arm and of irinotecan treatment in the FOLFIRI arms of the CRYSTAL study ([redacted]). In Section 6.3.2 we also provided treatment exposure data from the CSR of the OPUS study, confirming a mean cetuximab treatment duration of [redacted] for cetuximab/FOLFOX and of [redacted] for FOLFOX.

For convenience we repeat the relevant CSR tables in the document's Appendix.

1.7. Cetuximab + FOLFOX

Cetuximab is licensed in combination with either FOLFOX or FOLFIRI. The clinical evidence for cetuximab/FOLFOX in the RAS wt population is limited (phase II OPUS study, n=87 RAS wt patientsWith the current evidence base and the chosen decision making framework, cetuximab/FOLFOX cannot be cost-effective even at price zero. Merck highlights that the efficacy of cetuximab in combination with FOLFOX has been established in a number of RCTs, and is similar to that shown with FOLFIRI. Merck are offering the proposed PAS for cetuximab combined with either FOLFIRI or FOLFOX backbones, and we urge the Committee to take a pragmatic approach in this area.

Efficacy with both FOLFOX and FOLFIRI

Merck highlights that the clinical data supports the efficacy of cetuximab in combination with either FOLFOX or FOLFIRI chemotherapy backbones.

Examination of first line studies supports that cetuximab in combination with FOLFOX or FOLFIRI can extend median overall survival to in excess of 30 months (FIRE3 – 33.1 months (Stintzing, 2014), CALGB-80405 - 32 months (Lenz, 2014), CECOG/CORE2 – 28.5 months (Brodowicz, 2014).

Cetuximab in combination with FOLFOX has repeatedly demonstrated clinical benefit compared to FOLFOX alone. In addition to the OPUS study, the use of cetuximab with FOLFOX is supported by clinical trial data:

- FOLFOX group from the CALGB-80405 study - cetuximab/FOLFOX mOS – 32.5 months (Lenz, 2014),
- FOLFOX arm from the APEC study - cetuximab/FOLFOX mOS – 27.8 months
- The CORE2 study - cetuximab/FOLFOX mOS – 28.5 months (Brodowicz, 2014)

These studies consistently show strong efficacy data of 28 to 32 months median OS for cetuximab in combination with FOLFOX.

Similar efficacy with both Cetuximab/FOLFOX and Cetuximab/FOLFIRI

These data are consistent with the outcomes seen for cetuximab in combination with FOLFIRI reflecting similar outcomes for cetuximab/FOLFOX as cetuximab/FOLFIRI.

- In the CALGB-80405 study, in the RAS wild-type analysis, PFS for patients for cetuximab/FOLFOX was 11.3 months and 12.7 months for cetuximab/FOLFIRI and OS was 32.5 months and 32 months respectively for cetuximab/FOLFOX vs cetuximab/FOLFIRI.
- In the APEC study in RAS wild-type patients, outcomes for cetuximab/FOLFOX vs cetuximab/FOLFIRI on a 2-weekly schedule were comparable; PFS 13.3 vs 12.8 months and OS 27.8 vs 28.7 months respectively.

These studies reinforce that there are similar outcomes whether cetuximab is used in combination with either FOLFOX or FOLFIRI.

Therefore, although OPUS is the study used to represent the clinical data section for cetuximab/FOLFOX in this submission due to it having been the only head-to-head trial against FOLFOX alone at the time of the original submission, other studies with larger sample sizes support there being comparable outcomes when cetuximab is administered with either FOLFOX or FOLFIRI.

1.8. Patients with disease limited to the liver

The population of interest in this MTA is all patients with previously untreated RAS wt metastatic colorectal cancer, i.e. cetuximab's label. This patient group by definition includes a proportion of patients in whom disease is limited to the liver. Given the benefit that all patients receive with palliative use of cetuximab, it is unnecessary to isolate a group of patients with disease limited to the liver. Merck wish to remind the Committee that two key elements have changed subsequent TA176 – guidance which previously recommended cetuximab in combination with chemotherapy for LLD patients, namely Merck have further reduced the price of cetuximab to the NHS and secondly – in 2013 – cetuximab's indication was restricted to patients with wild-type RAS tumours (a smaller population in whom efficacy of anti-EGFRs is greater). Merck asks that the Committee consider the logic of the decision making in this appraisal given these changes which in principle should result in greater value of this medicine to the NHS and patients.

In TA176 cetuximab was evaluated in the LLD subgroup. It was appraised based upon data from the CELIM study which specifically evaluates the sub-population of patients that have metastasis confined to the liver. At that time, cetuximab was found to be cost effective in this patient group with the application of a 16 week stopping rule. In this current appraisal, the cost of cetuximab has been reduced (i.e. the simple discount increased) and the patient population has been both reduced in size (KRAS wt to RAS wt), a reduction in the number of patients by approximately 15%, and refined to a patient group which benefits more.

PenTAG have performed additional analyses in which they reduce PFS and OS (changed group, Tables 7-10), to account for the possible reduction in benefit of stopping cetuximab treatment earlier. In additional analyses requested by NICE, PenTAG assume that when cetuximab treatment stops at either week 8 or week 16, then so does the PFS and OS benefit seen with cetuximab. In other words, in the PenTAG model, patients treated at week 16 will reflect the additional benefit seen when cetuximab is added to chemotherapy, whereas those same patients at week 17 will show no benefit above that seen with chemotherapy alone, despite 16 weeks of treatment. It seems implausible that 16 weeks of treatment with a targeted treatment would not provide some additional benefit to

patients beyond chemotherapy alone when treatment is stopped. PenTAG purport that there is a rebound effect, and that it is feasible to assume that progression accelerates at this time. This has not been shown clinically.

Cetuximab in combination with FOLFIRI or FOLFOX provides benefits to patients with metastatic colorectal cancer, whether or not their disease is limited to the liver. The 'all-patient' analysis in this appraisal therefore represents the appropriate population for this decision problem. It *includes* patients with liver-limited disease as well as those with more widespread metastases and provides benefit for both patient groups. For this reason, Merck consider the LLD subgroup as a redundant analysis.

Cetuximab was previously recommended in the LLD patient population in TA176 and it is illogical that it wouldn't be recommended following a price cut and a smaller, more selected patient group in which cetuximab is more efficacious. Thus, Merck contends that with an additional price cut and an increase in benefit due to refined patient population, cetuximab remains cost-effective in the LLD patient group.

Stopping rule in all patient group

PenTAG, at the request of the NICE committee, have implemented stopping rules at 8 and 16 weeks in the 'all patient' analysis (Tables 7 & 9). It is not therapeutically meaningful to implement a stopping rule for patients who are being treated palliatively and continue to benefit from cetuximab treatment for their metastatic disease.

References

Adam R, D. V. (2004). Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. *Annals of Surgery, 240*(4), 644-57.

Brodowicz, T. (2014). FOLFOX4 plus cetuximab administered weekly or every two weeks in first-line treatment of patients with KRAS and NRAS wild-type (wt) metastatic colorectal cancer (mCRC). *J Clin Oncol*, LBA391.

Folprecht, G. E. (2014). (2014). Survival of patients with initially unresectable colorectal liver metastases treated with FOLFOX/cetuximab or FOLFIRI/cetuximab in a multidisciplinary concept (CELIM study). . *Ann Oncol*, 1018-25.

Howe, C., Cole, S., Chmiel, J., & Munoz, A. (2011;). Limitation of Inverse Probability-of-Censoring Weights in Estimating Survival in the Presence of Strong Selection Bias. *Am J Epidemiol*, 173(5):569-577.

Latimer, N. e. (2013). *Adjusting survival time estimates to account for treatment switching in randomised controlled trials - a simulation study.* Retrieved from www.shef.ac.uk: https://www.shef.ac.uk/polopoly_fs/1.259501!/file/HEDSDP1306.pdf

Lenz, H.-J. (2014). CALGB/SWOG 80405: PHASE III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with untreated metastatic adenocarcinoma of the colon or rectum (MCRC): RAS. *ESMO*, Abstract 929.

Stintzing, S. (2014). Independent radiological evaluation of objective response, early tumor shrinkage, and depth of response in FIRE-3 (AIO KRK-0306) in the final RAS evaluable population. *ESMO Congress, Oral Presentation and abstract*, LBA11.

Tabernero, J. (2008). Administration of Cetuximab Every 2 Weeks in the Treatment of Metastatic Colorectal Cancer: An Effective, More Convenient Alternative to Weekly Administration? *The Oncologist*, 113-119.

Ye, L. (2013). Randomized controlled trial of cetuximab plus chemotherapy for patients with KRAS wild-type unresectable colorectal liver-limited metastases. . *J Clin Oncol ;31(16),*, 1931-8.

Appendix: Mean treatment durations

[redacted]

[redacted]

Error! Reference source not found. presents the mean duration of irinotecan treatment in the chemotherapy arm. This was [redacted].

[redacted]

[redacted]

[redacted]

[redacted]

The mean duration of cetuximab treatment in the treated arm in this study is [redacted]. The mean duration of oxaliplatin treatment in the combination arm is [redacted].

Sir Andrew Dillon
Chief Executive
NICE

23 August 2016

Dear Sir Andrew

Re: The clinical effectiveness and cost effectiveness of cetuximab (review of TA176) and panitumumab (partial review of TA240) for previously untreated metastatic colorectal cancer. A systematic review and economic evaluation

At present both cetuximab and panitumumab are available via the Cancer Drug Fund in England for the treatment of patients with metastatic colorectal cancer. We would like to support their continued use in the future throughout the UK.

As more drugs have been made available over the last 20 years, we have seen a major improvement in the median survival rate for patients with advanced bowel cancer when treated with chemotherapy (from 8 months to almost 2 years). For those with wild type RAS tumours, 50% are now living longer than 30 months when treated with 1st line cetuximab or panitumumab based chemotherapy. This has made a huge difference to thousands of patients and has given them hope and more importantly a longer life with their families.

We are aware of the on-going review of both cetuximab and panitumumab in the first line setting. If NICE decide to stop funding these drugs, then we will only be able to offer our patients treatments that we had a decade ago. This could also potentially have an impact on patients in the devolved nations, particularly Wales and Scotland. These targeted drugs are also routinely available to patients in much of Western Europe and North America. Reducing their availability in the UK would be a tragic and retrograde step.

Another indirect consequence would be that we will not be able to participate in international clinical trials since we will no longer able to provide “gold standard” chemotherapy. This will further isolate the UK research community.

We would like you to consider our plea and continue to fund both of these drugs in the future.

Yours sincerely

[redacted]

Please see co-signatories overleaf.

/…..

Beating Bowel Cancer
Harlequin House | 7 High Street | Teddington | TW11 8EE | Main Tel 020 8973 0000 |
Nurse Advisor 020 8973 0011 | info@beatingbowelcancer.org | beatingbowelcancer.org
Registered Charity Nos. 1063614 (England & Wales) SCO43340 (Scotland) | Registered Company Number 3377182

Dr Nooreen Alam	Consultant Clinical Oncologist	The Christie NHS Foundation Trust
Dr Alan Anthoney	Honorary Consultant in Medical Oncology	Leeds Teaching Hospitals NHS Trust
Dr Seema Arif	Consultant Clinical Oncologist	Velindre Cancer Centre
Mr Tan Arulampalam	Consultant Colorectal Surgeon	Beating Bowel Cancer Medical Board
Dr Ashraf Azzabi	Consultant Medical Oncologist	Newcastle upon Tyne Hospitals NHS FT
Dr Michael Braun	Consultant Medical Oncologist	The Christie NHS Foundation Trust
Prof John Bridgewater	Professor of Medical Oncology	University College London
Dr Mark Churn	Consultant Clinical Oncologist	Worcestershire Acute Hospitals NHS Trust
Dr Susan Clenton	Consultant Clinical Oncologist	Sheffield Teaching Hospitals NHS FT
Prof David Cunningham	Consultant Medical Oncologist	The Royal Marsden NHS Foundation Trust
Dr Alice Dewdney	Consultant Clinical Oncologist	Sheffield Teaching Hospitals NHS FT
Dr Tony Dhillon	Consultant Medical Oncologist	Royal Surrey County Hospital
Dr Richard Ellis	Consultant Clinical Oncologist	Royal Cornwall Hospital
Dr Daniel Epurescu	Consultant in Medical Oncology	Norfolk & Norwich University Hospital
Dr Stephen Falk	Consultant Oncologist	Bristol Cancer Institute
Dr Maxine Flubacher	Consultant Clinical Oncologist	Poole Hospital NHS Foundation Trust
Dr Ian Geh	Consultant Clinical Oncologist	University Hospitals Birmingham NHS FT
Dr Rob Glynne-Jones	Consultant Clinical Oncologist	Mount Vernon Centre for Cancer Treatment
Dr Janet Graham	Consultant Medical Oncologist	Beatson West of Scotland Cancer Centre
Dr Sarah Gwynne	Consultant Oncologist	Abertawe Bro Morgannwg University HB
Dr Mark Harrison	Consultant Oncologist	Mount Vernon Cancer Centre
Dr Mark Hill	Consultant Medical Oncologist	Maidstone & Tunbridge Wells
Dr Timothy Iveson	Consultant in Medical Oncology	University Hospital Southampton
Dr Andrew Jackson	Consultant Clinical Oncologist	University Hospital Southampton
Dr Fiona Lofts	Consultant Oncologist	St Georges University Hospitals FT
Dr Kalena Marti	Consultant Medical Oncologist	The Christie NHS Foundation Trust
Dr Vivek Misra	Consultant Clinical Oncologist	The Christie NHS Foundation Trust
Dr Saifee Mullamitha	Consultant in Medical Oncology	The Christie NHS Foundation Trust
Dr Nishanth Murukesh	Consultant Medical Oncologist	Worcestershire Acute Hospital NHS Trust
Dr Sethupathi Muthuramalingam	Consultant Medical Oncologist	Portsmouth Hospitals NHS Trust
Dr Luke Nolan	Consultant Medical Oncologist	University Hospital Southampton NHS FT
Dr Ann O'Callaghan	Consultant in Medical Oncology	Portsmouth Hospitals NHS Trust
Mr Daniel O'Leary	Consultant Colorectal Surgeon	Portsmouth Hospitals NHS Trust
Dr Ian Pedley	Consultant Clinical Oncologist	Newcastle upon Tyne NHS FT
Dr Vanessa Potter	Consultant Medical Oncologist	Nottingham University Hospitals NHS Trust
Dr Sheela Rao	Consultant Medical Oncologist	The Royal Marsden NHS Foundation Trust
Dr Sherif Raouf	Consultant Clinical Oncologist	Barking, Havering & Redbridge Hosp NHS T
Dr Pippa Riddle	Consultant Oncologist	Imperial College Healthcare NHS Trust
Dr Robert Rulach	ST4 Clinical Oncology	NHS Greater Glasgow & Clyde
Dr Leslie Samuel	Consultant Oncologist	Aberdeen Royal Infirmary
Dr Mark Saunders	Consultant Oncologist	The Christie NHS Foundation Trust
Dr Alaaeldin Shablak	Consultant Medical Oncologist	University Hospitals Southampton NHS FT

/…

Dr David Sherriff	Consultant Gastrointestinal Oncologist	Plymouth Hospitals NHS Trust
Dr Bruce Sizer	Consultant Clinical Oncologist	Colchester General Hospital
Dr Naureen Starling	Consultant Medical Oncologist	The Royal Marsden NHS FT
Dr Jeff Summers	Consultant Oncologist	Maidstone & Tunbridge Wells
Dr John Wagstaff	Director	South West Wales Cancer Institute
Dr Harpreet Wasan	Reader in Medical Oncology	Imperial College Healthcare NHS Trust
Dr Gregory Wilson	Consultant Medical Oncologist	The Christie NHS Foundation Trust
Prof Richard Wilson	Consultant Medical Oncologist	Belfast HSC Trust
Dr Kathryn Wright	Consultant Clinical Oncologist	Newcastle upon Tyne NHS FT
Dr Robin Young	Consultant Medical Oncologist	Sheffield Teaching Hospitals NHS FT

For further information please contact [redacted]

Bowel Cancer UK response to the NICE consultation on the Addendum to the Assessment Group report on cetuximab and panitumumab for previously untreated metastatic colorectal cancer [ID794]

Bowel Cancer UK welcomes the opportunity to respond to this consultation on the addendum to the Assessment Group Report on the use of cetuximab and panitumumab as a first line treatment for people diagnosed with advanced bowel cancer. After consultation with clinical experts we would urge NICE to approve cetuximab and panitumumab for use on the NHS.

Survival rates for advanced bowel cancer are poor with less than one in ten people surviving more than five years. These patients deserve access to the best quality treatment and care. Progress has been made in improving survival rates for patients with advanced bowel cancer. A key part of this progress can be attributed to the availability of precision medicines. For some patients these drugs can be life-saving, while for others they improve survival resulting in more time to spend with loved ones.

We would urge NICE to consider the following points in relation to duration of treatment, dosing frequency and the end of life criteria.

Duration of treatment

TA176 recommended cetuximab for 16 weeks as pre-operative treatment for patients with metastatic colorectal cancer who have unresectable liver disease in the hope that the liver metastases becomes resectable and therefore extend the life of a patient and the time they have to spend with their loved ones. However in practice, as the vast majority of these patients their liver metastases do not become resectable, cetuximab or panitumumab is typically given until disease progression or until the side-effects becomes intolerable. The justification for this approach is that for RAS Wildtype patients we would now aim for >30 months survival with EGFR inhibition given as first line therapy with chemotherapy based on latest trial data (compared to 20 months with chemotherapy alone).

Dosing frequency

Although the clinical trial studies used weekly dosing, we now believe fortnightly dosing is as effective, is more convenient for the patient and helps chemotherapy capacity problems. This frequency of dosage is now used widely in UK hospitals. Because of this we urge NICE to use this dosage when considering the cost-effectiveness of cetuximab.

End of Life

Bowel Cancer UK believe that End of Life criterial is met for patients with metastatic colorectal who do not have a liver resection as the life expectancy for these patients if they receive chemotherapy alone is under 24 months (Tournigand, 2004). Cetuximab and panitumumab have been shown to increase overall survival by at least three months. Most recent trial evidence suggests that patients with metastatic colorectal cancer that are RAS wild type and receive chemotherapy and an EGF receptor antibody (either cetuximab or panitumumab) their survival is in excess of 30 months. We urge NICE to consider cetuximab and panitumumab under the end of life criteria.

Conclusion

Access to effective treatment is essential to prolonging and enhancing quality of life. It is therefore necessary patients gain timely access to treatments that have been proven to be safe and effective and which their clinicians believe could benefit them. We understand that technologies appraised by NICE need to meet cost effectiveness criteria. However the availability of effective treatments to people with advanced bowel cancer is currently limited and has been further limited with recent changes to the Cancer Drugs Fund. A negative recommendation would decrease the choice that patients and clinicians have when deciding what course of treatment to opt for. It would mean that there would be no first line precision therapy for patients who have advanced bowel cancer. Consequently patients will have to rely on Individual Funding Requests, which are only successful in exceptional cases, or pay for the drugs themselves. The impact of this on patients in terms of both survival and psychologically would be detrimental, with many patients will be unable to access a treatment that could prolong their life and give them the best possible outcome.

Royal College of Physicians
11 St Andrews Place
Regent's Park
London NW1 4LE
Tel: +44 (0)20 3075 1560

www.rcplondon.ac.uk

[redacted]

National Institute for Health and Care Excellence
10 Spring Gardens
London
SW1A 2BU
TACommB@nice.org.uk

11 August 2016

Dear [redacted]

Re: Cetuximab and panitumumab for previously untreated metastatic colorectal cancer ID794

The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 32,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

The NCRI-ACP-RCP-RCR are grateful for the opportunity to respond to the above consultation. Due to the degree of redaction it is difficult to fully interpret this new analysis but we would like to make the following comments.

Liver resection rates
There are considerable differences in the stated resection rates of 20.7% in all metastatic patients treated with cetuximab and 31.3% in liver limited disease patients treated with panitumumab (section 3.7). These are clearly two very different populations of patients, so it is difficult and potentially misleading to make direct comparisons.
We also note that in Section1.2.2 the addendum states the resection rates selected in the original report were used for the analysis, but it is not clear what these are.

Stopping rules
TA176 has a stopping rule for cetuximab (but not for chemotherapy) at 16 weeks for patients with liver limited disease. Clearly the length of treatment using the 16 or 8 week stopping rule is significantly shorter than the mean duration of treatment in the relevant clinical trials. Section 4.6.3 discusses the impact of stopping on PFS and OS. It is not clear if this relates only to the liver limited disease patients or to the broader metastatic CRC population. If liver limited disease only, a significant proportion of these patients would progress to resection and so shortening the duration of treatment would not necessarily impact as greatly on PFS and OS as suggested. However, if this relates to all patients then clearly there will be an impact on PFS and potentially OS.
We have concerns that in section 4.7.1 the 16 week/8 week stopping rule appears to be applied to all metastatic patients, not just those with liver limited disease. This would be a very difficult condition of use to discuss with patients who have widespread metastatic disease, who are continuing to respond to

treatment and who have potentially had very significant improvements in disease-related symptoms and in quality of life. Current practice would be to continue treatment in this group of patients until disease progression, unacceptable toxicity or patient and physician choice.

End of Life criteria
Cetuximab/FOLFIRI appears to fulfil the overall survival and the greater than 3 month benefit in survival criteria but not the patient population criterion. As previously stated this figure if 7000 also seems to include patients with head and neck cancer. The bundling together of SCCHN patients with metastatic CRC patients makes no sense and is very misleading. The new CDF end of life criteria suggests removal of this patient population criterion.
In the original report by PenTAG both cetuximab and panitumumab met the first two criteria but not the population criterion (Table 19). It does not seem clinically plausible that this is now not the case.

Clinical recommendations
In practice, as we have previously stated, the number of patients offered triple therapy (chemotherapy doublet and anti-EGFR antibody) is relatively small and limited to those with good performance status and high tumour burden and who accept the risk of additional toxicities particularly acneiform rash.
It is clear to colorectal oncologists throughout the UK that the addition of anti-EGFR antibodies has played a very significant role in improving outcomes for patients with metastatic colorectal cancer, and that a NICE decision not to allow use of these drugs in this setting will have a very significant and negative impact on the survival and quality of life of UK patients with metastatic CRC. The colorectal oncology community feel that it is vital that our patients continue to have access to these drugs.

In addition, we are very concerned that an inability to use these drugs in the first-line setting will have a major impact on the future of UK colorectal cancer clinical trials, as global studies all require patients to have received anti-EGFR antibodies if appropriate. This will hence have a negative impact on trials in patients with RAS wild type metastatic CRC not only in first-line but in all subsequent lines of therapy.

We feel that there is very little clinically relevant difference between the two antibodies and having the option of using either antibody with the FOLFIRI or FOLFOX chemotherapy backbones would be ideal. While the stopping rule is appropriate for patients with liver limited disease, we do not feel this should be applied to patients with more widespread metastatic disease.

Yours sincerely

[redacted]

[redacted]

NHS England submission to NICE re the appraisals of 1st line cetuximab and panitumumab in advanced /metastatic colorectal cancer

1. NHS England recognises that the evidence base that supports the efficacy of these drugs has shifted in line with use of a sequential change in biomarkers: from being trialled in and given to all patients, first the KRAS biomarker allowed identification of greater benefit and more recently the RAS biomarker has further defined the population of patients which gain greatest benefit with cetuximab/panitumumab.
2. The consequence of this shift in the key evidence base is that the best evidence to be assessed currently relies on retrospective analysis of bowel cancer tissue samples from patients entered into trials performed a considerable time ago. Allowances have to be made therefore for this shifting evidence base, now reliant on retrospective analyses of prospectively performed clinical trials.
3. The first issue is that NHS England regards cetuximab and panitumumab as being identical in terms of efficacy and toxicity. A large head to head comparison of these 2 drugs as single agent therapy in chemotherapy-refractory colorectal cancer demonstrated identical efficacy and toxicity. In addition, there is no biological plausibility for considering that their contribution to 1st line combination chemotherapy will be any different.
4. Cetuximab has been in the CDF since 2010. When NHS England took over the CDF and it became national in 2013, it stipulated the use of 2-weekly cetuximab as there was then sufficient evidence of equivalence and widespread use of 2-weekly cetuximab rather than the weekly licensed schedule of administration of cetuximab. This stipulation of course had the bonus for patients of much greater convenience and for hospitals of significantly reducing congestion and waiting times in chemotherapy units. NHS England thus urges NICE to only consider 2-weekly schedules of cetuximab as that is the schedule used now and that is what will only be used in the future in colorectal cancer.
5. NHS England knows that the best evidence for the use of cetuximab in combination with 1st line chemotheraoy for colorectal cancer lies with an irinotecan-based combination. This evidence comes from the CRYSTAL trial and a retrospective analysis for RAS status. The improvement in median overall survival from 20 to 28 months is impressive in itself but also in a disease in which other treatment options follow for most patients and thus potentially blur the benefit in survival of earlier lines of treatment.
6. NHS England also knows that the evidence for the use of cetuximab in combination with 1st line oxaliplatin-based chemotherapy is weak. This because the retrospective RAS analysis of the OPUS trial has few patients and thus no robust conclusions can be made from this evidence alone.
7. NHS England knows that the benefit of adding panitumumab to 1st line chemotherapy lies in the PRIME trial which employed an oxaliplatin-based regimen.

This evidence base also required a retrospective analysis for RAS and resulted in an improvement in overall survival of just under 6 months, again an impressive result in the context of bowel cancer and a setting which usually witnesses several lines of chemotherapy.

8. There is no robust evidence base for the use of panitumumab in combination with 1st line irinotecan-based chemotherapy.
9. In its CDF considerations, NHS England was aware of:
    i) Oxaliplatin-based or irinotecan-based combination chemotherapy regimens offer similar efficacy but differing toxicity (see relevant NICE bowel cancer appraisals). Hence patients and clinicians can debate and choose the most appropriate regimen to use as 1st line chemotherapy
    ii) There is no difference in efficacy and toxicity between cetuximab and panitumumab
    iii) The robust evidence base for cetuximab plus 1st line chemotherapy lies with an irinotecan-based regimen
    iv) The robust evidence base for panitumumab plus 1st line chemotherapy lies with an oxaliplatin-based regimen
    v) As a consequence of i) to iv), when the CDF assessed the retention of cetuximab and panitumumab in the CDF, it recognised the impressive survival benefit of these drugs and was happy to translate the evidence base for both drugs to both oxaliplatin-based and irinotecan-based 1st line chemotherapy regimens. It thus approved the use of either cetuximab or panitumumab In combination with either chemotherapy regimen. In this way, it did not want to impose on patient choice and clinician recommendation but considered this to be a reasonable, practical and relevant interpretation of the evidence base reliant on retrospective analyses of older trials.
10. If NICE approves the use of cetuximab or panitumumab or both, NHS England urges NICE to also adopt similar considerations in order to keep NICE guidance relevant and practical, this to also include use of the 2-weekly schedule of administration of both cetuximab and panitumumab.

[redacted]

[redacted]

[redacted]

Many thanks for providing us a slightly redacted copy of report by the Assessment Group (AG). They have carried out further analysis subsequent to the NICE committee meeting earlier this year. Due to the degree of redaction it has been difficult for us to fully interpret this new analysis.

I am not sure what points might need to be teased out at your meeting; so at risk of repetition I am grateful for the opportunity to re highlight some of the salient points or observations made at those earlier meetings

a) A lot has been said by the AG about the 'FOLFIRI network' and the 'FOLFOX network'. This methodology is obviously needed to enable carrying out objective statistical analysis of various anti –EGFR interventions. Nevertheless from clinical & evidence based stand point we would again reiterate that these 2 regimes are considered equivalent in terms of efficacy and only differ in their toxicities. Whilst each of these chemotherapy backbones have their preferred anti – EGFR partners (FOLFOX with panitumumab and FOLFIRI with cetuximab) as per international guidelines (and indeed UK Cancer Drug Fund guidelines) any permutation and combination is a bonafide choice and subject to acceptable toxicity.

b) Liver resection rates

Further to above from the efficacy point of view the 2 anti EGFR antibodies in question are considered to be broadly equivalent. There is no data which attests to the seemingly different resection rates that are being attributed to cetuximab and panitumumab. As discussed at the earlier meeting – in palliative setting the conversion rate (resection rate) is probably in order of 20% or so for both the anti –EGFR antibodies.

In previous NICE documents (TA176) experts at the time had quoted higher resection rates from trials in order of ~ 35%. This however is more applicable to trials looking at patients with liver limited population only i.e. there is a huge element of patient pre-selection going on.

c) Stopping Rules: More work has been done in this regard but quite a few figures are redacted. Just to clarify clinically how stopping rules operate:

a. In patients being treated under TA176 the stopping rule of 16 weeks is indeed true. Cetuximab or panitumumab is not continued beyond **maximum** of 16 weeks (as is stipulated by NICE guidelines). If patient becomes operable at any stage- they go for liver operation. If the liver disease remains inoperable, the cetuximab is discontinued and chemotherapy maybe continued on its own.

Section 4.6.3 discusses the impact of stopping on PFS and OS. It is not clear if this relates only to the liver limited disease patients or to the broader metastatic CRC population. If liver limited disease only, a significant proportion of these patients would progress to resection and so shortening the duration of treatment would not necessarily impact as greatly on PFS and OS as suggested. However, if this relates to all patients then clearly there will be an impact on PFS and potentially OS.

In contrast, in the population being treated palliatively, there is NO stopping rule for either of the anti EGFR antibodies. They are continued fortnightly until disease progression (i.e. much beyond 8 weeks and 12 weeks). CDF guidelines infact do not allow treatment breaks (in excess of 4 weeks) unless there are exceptional circumstances. This clinical practice is therefore in line with what transpires in clinical trials.

We have concerns that in section 4.7.1 the 16 week/8 week stopping rule appears to be applied to all metastatic patients, not just those with liver limited disease. This would be a very difficult condition of use to discuss with patients who have widespread metastatic disease, who are continuing to respond to treatment and who have potentially had very significant improvements in disease-related symptoms and in quality of life. As previously noted the current practice would be to continue treatment in this group of patients until disease progression, unacceptable toxicity or patient and physician choice.

Finally, it's always difficult and frustrating when two diverse groups of patients namely (a) the liver limited disease population - wherein the aim is cure & (b) the truly palliative group of patients- wherein the majority are by definition palliated – only a fraction go for potentially curative surgery. Almost everything such as resection rates; duration of treatment (critical) and treatment outcome will be completely different.

Trial designs and inclusion / exclusion criteria for these 2 groups of patients tend to be different and consequently outcomes from same should not be extrapolated to one another.

d) End of life criteria / provision:

Cetuximab/FOLFIRI appears to fulfil the overall survival and the greater than 3 month benefit in survival criteria but not the patient population criterion. As previously stated this figure of 7000 also seems to include patients with head and neck cancer. The bundling together of SCCHN patients with metastatic CRC patients makes no sense and is very misleading. The new CDF end of life criteria suggests removal of this patient population criterion.

In the original report by PenTAG both cetuximab and panitumumab met the first two criteria but not the population criterion (Table 19). It does not seem clinically plausible that this is now not the case.

Consensus statement

In practice, as we have previously stated, the number of patients offered triple therapy (chemotherapy doublet and anti-EGFR antibody) is relatively small and limited to those with good performance status and high tumour burden and have extended Ras status (50% of patients with advanced bowel cancer).

It is clear to colorectal oncologists throughout the UK that the addition of anti-EGFR antibodies has played a very significant role in improving outcomes for patients with metastatic colorectal cancer, and that a NICE decision not to allow use of these drugs in this setting will have a very significant and negative impact on the survival and quality of life of UK patients with metastatic CRC.

In addition, we are very concerned that an inability to use these drugs in the first-line setting will have a major impact on the future of UK colorectal cancer clinical trials; as global studies require patients to necessarily receive anti-EGFR antibodies if appropriate. This will hence have a negative impact on ability for the United Kingdom to participate and lead in major international clinical trials in bowel cancer.

We feel that there is very little clinically relevant difference between the two antibodies and having the option of using either antibody with the FOLFIRI or FOLFOX chemotherapy backbones would be ideal.

Finally, the care of patients with advanced bowel cancer is at risk of being rolled back by a decade if the use of these targeted drugs is curtailed. As experts called in by NICE we would be aghast and horrified at such a prospect. **We hope that the industry and NICE continue to work constructively and collegiately to find a mutually acceptable way of providing these potentially lifesaving and life prolonging treatments in one of the commonest cancers afflicting the UK population.**

Electronically signed by

Dr Saifee Mullamitha, Consultant Medical Oncology

Dr Vanessa Potter, Consultant Medical Oncology

PS_ no new conflict of interests to declare since the ones declared at last NICE meeting in Jan 2016

The clinical effectiveness and cost-effectiveness of cetuximab (review of TA176) and panitumumab (partial review of TA240) for previously untreated metastatic colorectal cancer: a systematic review and economic evaluation

Addendum:

Between 2nd and 3rd NICE Appraisal Committee meetings

5th Sept 2016

Confidential information that is academic-in-confidence is redacted [redacted]

Confidential information that is commercial-in-confidence is redacted [redacted]

Contents

1 Background to this MTA

1.1 Analyses requested by NICE

After the 2nd NICE committee meeting on 6th January 2016, NICE asked us, the Assessment Group, to estimate cost-effectiveness separately on each of the following 20 = 2 x 2 x 5 bases:

- All patients and Liver mets subgroup (2 bases).
- With and without adjustment for OS for subsequent treatments (2 bases).
- Treatment stopping rules (5 bases):
    1. No treatment stopping modelled
    2. 8 week treatment stopping rule with no change in PFS or OS
    3. 8 week treatment stopping rule with adjusted PFS and OS
    4. 16 week treatment stopping rule with no change in PFS or OS
    5. 16 week treatment stopping rule with adjusted PFS and OS.

On 18th May 2016, we submitted an Addendum to our original report in response to these requests.

1.2 Responses from Merck Serono and Amgen

On 25th August 2016, we received responses from Merck Serono and Amgen to our Addendum. Here, we comment on these responses.

2 Reply to Amgen responses of 25th August 2016

2.1 End of Life criteria

In our Addendum of 18th May 2016, we claimed that we find the EoL criteria for life expectancy of the comparator < 2 years and incremental life expectancy of treatment > 3 months is satisfied only for CET+FOLFIRI vs. FOLFIRI for all scenarios in which OS is adjusted for subsequent treatments.

Amgen do not agree. Instead, they believe that all treatments meet the revised EoL criteria. We maintain that our discussion of End of Life in our previous Addendum remain valid.

2.2 Resection rates

In our base case, we have always assumed the following resection rates for the all patients group:

- CET+FOLFIRI: 7.3%
- FOLFIRI: 2.1%
- CET+FOLFOX: [redacted]
- PAN+FOLFOX: [redacted]
- FOLFOX: [redacted]

We explained the derivation of these rates in Section 6.1.4.1 of our original report. In short, all rates are based on data from the CRYSTAL, PRIME and OPUS RCTs. The rates for:

- CET+FOLFIRI and FOLFIRI are taken directly from the CRYSTAL RCT.
- PAN+FOLFOX and FOLFOX are taken directly from the PRIME RCT.
- CET+FOLFOX is calculated as follows (p257 our original report). The logit of the value of [redacted] for CET+FOLFOX was calculated by first estimating the values for CET+FOLFOX and for FOLFOX for *RAS* WT patients from OPUS. Unfortunately, we are not aware of this value being reported. Therefore, we were forced to estimate them from the corresponding values for *KRAS* WT patients from OPUS, which are reported. Specifically, the estimated rate for *RAS* patients for CET+FOLFOX = 9.8% / 83% = 11.9%, and we assume that 83% of *KRAS* WT patients are also RAS WT. The estimated rate for *RAS* patients for FOLFOX was estimated as 4.1% * ([redacted] / 7.6%) =

[redacted], where the [redacted] / 7.6% are the rates for FOLFOX from OPUS for *RAS* and *KRAS* WT patients respectively.

In their response of August 2016, Amgen state: "*The assumption of differential resection rates for the anti-EGFR agents is inconsistent with clinical expert opinion and does not reflect the Committee's preferred assumptions. Resection rates for cetuximab and panitumumab should be assumed to be equivalent*." They then claimed that NICE instructed us to assume equal resection rates for CET and PAN. We acknowledge that NICE's instructions were rather ambiguous. As explained in Section 3.7 of our Addendum of 18th May 2016, we therefore asked NICE early in 2016 to clarify their request. They replied that they wanted us to continue to assume our trial-based resection rates.

Similarly, in their response of August 2016, Merck Serono understood that the NICE committee required the same resection rates for CET as for PAN (Section 3.1, p11).

Further to these comments, on 31st August 2016, NICE instructed us to perform the following scenario analyses for the all patients group:

- Resection rate CET+FOLFOX = PAN+FOLFOX = [redacted].
- Resection rate PAN+FOLFOX = CET+FOLFOX = [redacted].

We are grateful to Merck Serono for highlighting that a minor amendment is required to correctly implement these changes in our model. In the model, mean PFS and OS for unresected patients are estimated in part from the resection rate. It is therefore necessary to hold the mean PFS and OS for unresected patients constant when changing the resection rates.

NICE instructed us not to perform scenario analyses on the resection rates for the liver metastases subgroup, because the values for CET+FOLFOX and PAN+FOLFOX are very similar, at [redacted] and [redacted] respectively.

In our opinion, if resection rates are to be set equal, they should be set to [redacted], as this is taken directly from a large RCT, PRIME. The value of [redacted] for CET+FOLFOX is informed by data from OPUS, but this RCT was far smaller and the value was estimated from other data from OPUS.

We are wary about these scenario analyses, because they are not evidence based. Also, if we are to assume equal resection rates, then logically, one could argue also to assume equal PFS and OS.

We now give the results on each of these two bases in addition to our base case values.

2.2.1 Resection rates CET+FOLFOX = [redacted]

This is part of our base case.

Table 1. ICERs (£/QALY) for CET+FOLFOX vs. FOLFOX: All patients

Stopping rule	PFS / OS	OS not adjusted for subsequent treatments	OS adjusted for subsequent treatments
None	n/a	[redacted]	n/a
16 weeks	**unchanged**	[redacted]	n/a
8 weeks	**unchanged**	[redacted]	n/a
16 weeks	**changed**	[redacted]	n/a
8 weeks	**changed**	[redacted]	n/a

2.2.2 Resection rates CET+FOLFOX = [redacted]

Table 2. ICERs (£/QALY) for CET+FOLFOX vs. FOLFOX: All patients

Stopping rule	PFS / OS	OS not adjusted for subsequent treatments	OS adjusted for subsequent treatments
None	n/a	[redacted]	n/a
16 weeks	**unchanged**	[redacted]	n/a
8 weeks	**unchanged**	[redacted]	n/a
16 weeks	**changed**	[redacted]	n/a
8 weeks	**changed**	[redacted]	n/a

2.2.3 Resection rates PAN+FOLFOX = [redacted]

This is part of our base case.

Table 3. ICERs (£/QALY) for PAN+FOLFOX vs. FOLFOX: All patients

Stopping rule	PFS / OS	OS not adjusted for subsequent treatments	OS adjusted for subsequent treatments
None	n/a	[redacted]	[redacted]
16 weeks	**unchanged**	[redacted]	[redacted]
8 weeks	**unchanged**	[redacted]	[redacted]
16 weeks	**changed**	[redacted]	[redacted]
8 weeks	**changed**	[redacted]	[redacted]

2.2.4 Resection rates PAN+FOLFOX = [redacted]

Table 4. ICERs (£/QALY) for PAN+FOLFOX vs. FOLFOX: All patients

Stopping rule	PFS / OS	OS not adjusted for subsequent treatments	OS adjusted for subsequent treatments
None	n/a	[redacted]	[redacted]
16 weeks	**unchanged**	[redacted]	[redacted]
8 weeks	**unchanged**	[redacted]	[redacted]
16 weeks	**changed**	[redacted]	[redacted]
8 weeks	**changed**	[redacted]	[redacted]

2.3 Panitumumab + FOLFIRI

Amgen correctly say that we do not estimate the cost-effectiveness of PAN+FOLFIRI vs. FOLFIRI. They claim that there is evidence that the effectiveness of PAN+FOLFIRI is similar to that of PAN+FOLFOX.

As stated in our original report of 7th August 2015 (p39), we found no trials of PAN+FOLFIRI vs. FOLFIRI in the patient population relevant to the current HTA.

They further claim that the effectiveness of PAN+FOLFIRI is likely to be similar to that of CET+FOLFIRI. However, they provide no evidence to justify this assertion.

2.4 Adjustment for subsequent treatments

Amgen previously stated that the intention-to-treat (ITT) OS hazard ratio (HR) of 0.77 between PAN+FOLFOX and FOLFOX reduced to 0.69 given IPCW adjustment for subsequent anti-EGFR treatment, and was virtually unchanged given adjustment for subsequent bevacizumab.

In our Addendum of 18th May 2016, we said we were still concerned about the following issues concerned with the statistical adjustment used by Amgen.

- The interpretation of the hazard ratios is not clear. Amgen say they represent the scenario "when subsequent anti EGFR therapy is taken in to account". Does this mean the counterfactual state in which no patients subsequently receive CET or PAN ?
- As Amgen admit, the underlying data was not based on the latest data cut.
- We are not convinced that it is appropriate to perform some of the statistical techniques on the data from PRIME. For example, the RPSFT method estimates the treatment effect (in terms of an acceleration factor) of subsequent treatments based on its effect first line. However, the subsequent treatment CET was not taken 1st line in PRIME. Also, the impact of subsequent treatments may be largely unknown because only a proportion of patients received each subsequent treatment in both arms, and these may be a biased sample of all patients."
- As discussed in the DSU Technical Support Document 16 (http://www.nicedsu.org.uk/Treatment-switching-TSD(2973293).htm), it is important to discuss and justify the method of adjustment, e.g. IPCW, rank preserving structural failure time models (RPSFTM) or Two-Stage method. However, Amgen have not done this. Instead, they have used the IPCW method without justification. This is important, as cost-effectiveness can be very sensitive to the method.

In response, Amgen now confirm that their HRs do indeed represent the counterfactual state in which no patients subsequently receive CET or PAN.

They also say that the underlying data and all analyses presented are based on the latest data cut (24 January 2013).

Concerning the last two bullet points, Amgen now present analyses based on the RPSFT and 2-Stage methods. We still do not see how the RPSFT method can be used, given that CET was not taken 1st-line in PRIME. Nonetheless, given that the IPCW remains their method of choice, we do not dwell on this.

The data presented in Tables 2 and 3 of Amgen's response suggest that the HR adjusted for subsequent treatments (CET, PAN and BEV) is likely to be similar for the IPCW and 2-stage methods, but worse for the RPSFT method. Amgen suggest that the IPCW method is

preferable by saying that it is not possible to test the assumptions underlying the RPSFT method. However, they do not adequately critique the appropriateness of the IPCW method.

Two important assumptions of the IPCW include that (1) there are no unmeasured confounders and (2) the method is sensitive to the proportion of patients that switch. Whilst we do appreciate that it is very difficult to assess the appropriate of the methods, concerning (1), Amgen claim that the IPCW method uses a comprehensive list of baseline covariates, and Amgen do not address (2).

2.5 Stopping rules

Amgen correctly observe that, in our Addendum of May 2016, we conducted scenario analyses applying 8 and 16 week treatment stopping rules for all patients. These analyses were requested by NICE on advice of the NICE committee of January 2016.

Amgen now respond: "*this approach does not align with the licensed indication for panitumumab which does not specify stopping rules according to a set time period. In the PRIME study (panitumumab+FOLFOX versus FOLFOX) treatment was continued until disease progression or unacceptable toxicity and treatment stopping rules may not be an appropriate strategy for all patients.*"

Merck Serono likewise comment: "*It is not therapeutically meaningful to implement a stopping rule for patients who are being treated palliatively and continue to benefit from cetuximab treatment for their metastatic disease*."

This is also our understanding. Indeed, we note the consultation comments from Dr Saifee Mullamitha, Consultant Medical Oncologist and Dr Vanessa Potter, Consultant Medical Oncologist:

"*We have concerns that in section 4.7.1 the 16 week/8 week stopping rule appears to be applied to all metastatic patients, not just those with liver limited disease. This would be a very difficult condition of use to discuss with patients who have widespread metastatic disease, who are continuing to respond to treatment and who have potentially had very significant improvements in disease-related symptoms and in quality of life. As previously noted the current practice would be to continue treatment in this group of patients until disease progression, unacceptable toxicity or patient and physician choice*."

2.6 Unit costs of drug administration

As part of our 4th January 2016 Addendum to our report, we substantially reduced our estimated unit costs of drug administration for CET.

Amgen now say: "where the reduction in unit costs affects both treatments, then the reduction should be consistently applied in the model to both treatments.".

We confirm that the error applied only to administration of CET, not PAN. Therefore, no further action is necessary.

3 Reply to Merck Serono responses of 25th August 2016

3.1 Resection rates

Merck Serono argue that we have misinterpreted the resection rates preferred by the NICE committee. In response, please see Section 2.2, p5.

3.2 Adjustment for subsequent treatments

Merck Serono previously reported that they believed the IPCW method to be inappropriate as they found that none of the explanatory variables were significantly associated with switching. In our Addendum of May 2016, we replied that this does not necessarily invalidate the method.

Merck Serono originally preferred the RPSFT method. In our Addendum of May 2016, we noted that they did not defend this choice. Further, Dr Ian White, an expert on statistical methods to adjust for switching, suggested that Merck Serono may have incorrectly implemented the statistical technique of recensoring.

Merck Serono now defend their choice of the RPSFT method, saying that "*recognised academics in this area have confirmed that the RPSFTM method and Merck's application of it represent a legitimate and appropriate technique*", and that the academics suggest the RPSFT method is more appropriate than the IPCW method.

Merck Serono now justify the inappropriateness of the IPCW method by saying that it is unlikely that the no unmeasured confounders assumptions is satisfied. If this argument were to be believed, then this would also invalidate Amgen's choice of the IPCW method.

Merck Serono admit that it is difficult to test the assumption of the RPSFT method that the treatment effect is independent of the line of treatment, and we are sympathetic to this. Next, Merck Serono say that if they were to apply the approach to recensoring as recommended by Dr Ian White, the maximum observed follow up time decreases dramatically, from 56 to 4.6 months. Merck Serono claim that this would result in such a significant loss of information so as to render the method unhelpful. We have not had time to critique their defence of their method of recensoring.

3.3 Total cost of acquisition of cetuximab

Merck Serono correctly say that we estimate the total acquisition cost of CET using the formula they give in their response document:

(cost per mg) X (expected total dose [mg] per month) X (mean Tx duration) X (median dose intensity)

They then say that we estimate 10-15% higher monthly drug use then was the case in the trial. They believe this is accounted for by the fact that we use median, rather than mean,

dose intensities. However, given that Merck Serono do not explain how they derive the figure 10-15%, we consider this no further.

3.4 Frequency of administration of cetuximab

Merck Serono have consistently argued that we should model fortnightly, rather than weekly administration of CET. We have nothing further to add to this debate.

3.5 Merck Serono revised ICERs

In their previous addendum, Merck Serono adjusted their version of our model and found ICERs for CET+FOLFIRI vs. FOLFIRI of approximately:

- [redacted] per QALY, assuming weekly dosing of cetuximab, and
- [redacted] per QALY, assuming fortnightly dosing of cetuximab.

In our Addendum of May 2016, we said that our corresponding value for weekly dosing of CET (without stopping rule) is approximately [redacted] per QALY, which was similar to Merck Serono's value of [redacted].

Now Merck Serono report an ICER for CET+FOLFIRI vs. FOLFIRI of approximately [redacted] per QALY. Merck Serono do not say whether this represents weekly or fortnightly dosing of cetuximab.

3.6 Mean treatment durations

Merck Serono say it is correct that we are using the treatment durations they have provided. They maintain that they are reported correctly from their RCTs. We have nothing further to say on this matter.

3.7 Effectiveness of CET+FOLFOX

Merck Serono maintain that the effectiveness of CET+FOLFOX is similar to that for CET+FOLFIRI. Throughout this HTA, we have repeated that we have taken the effectiveness evidence for CET+FOLFOX only from the OPUS RCT, as this is the only RCT in the patient population relevant to the current appraisal.

3.8 Liver mets subgroup

For the first time in this appraisal, Merck Serono now claim that it is unnecessary to consider the liver mets subgroup. They say this is because all patients receive benefit with CET. It may be true that non liver mets patients and liver mets patients all get benefit from CET. However, the magnitude of the benefit may differ. In which case, it is reasonable to consider the liver mets subgroup.

3.9 Stopping Rule

As discussed above, Merck Serono now say: "*It is not therapeutically meaningful to implement a stopping rule for patients who are being treated palliatively and continue to benefit from cetuximab treatment for their metastatic disease*."

NICE asked us to consider scenario analyses in which treatment stopping rules are applied. In some analyses, we assumed no impact on PFS and OS of stopping rules. In other analyses, we assumed equal rates of progression and mortality between treatments after treatment stops.

Merck Serono now say: "*It seems implausible that 16 weeks of treatment with a targeted treatment would not provide some additional benefit to patients beyond chemotherapy alone when treatment is stopped. PenTAG purport that there is a rebound effect, and that it is feasible to assume that progression accelerates at this time. This has not been shown clinically*."

In response, we are presenting these analyses as scenarios only. Further, we did not say that we believed there is a rebound effect, only that such an effect is one of many possibilities.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cetuximab and panitumumab for previously untreated metastatic colorectal cancer

Response to Assessment Group's Addendum (28 Nov 2016)

Prepared by:

19 December 2016

Confidential information that is commercial-in-confidence is highlighted and underlined

1. Summary

We welcome the opportunity for further consideration of this appraisal, following withdrawal of the FAD and the issue of the subsequent AG Addendum Report.[1,2] We are confident that our response will now allow NICE to make a positive recommendation for panitumumab in the overall population.

In the withdrawn FAD, the ICER for panitumumab in the overall population (using the appraisal committee's preferred assumptions) was [redacted] including a [redacted] PAS.[1-3] The committee concluded that panitumumab plus chemotherapy fulfilled the criteria to be considered a life-extending, end of life treatment in the overall population; however given that the ICER exceeded the EoL threshold of £50,000, it did not consider panitumumab to be a cost-effective use of NHS resources.[2]

In its considerations, the committee noted that the cost-effectiveness of panitumumab in the overall population combined those patients with liver limited disease (LLD) and those with widespread metastases (non-LLD), raising concerns that the patients in the LLD subgroup were more likely to have resection, leading to improved prognosis.[2] However, we believe that it is not robust or clinically plausible to separate out LLD and non-LLD subgroups, that the ICER of [redacted] generated using the committee's preferred assumptions is not unduly influenced by the LLD subgroup and consequently any uncertainty around estimates of the cost-effectiveness of panitumumab in the overall population is limited. Therefore the **overall population should be used as the basis for decision-making in this appraisal**.

We consider it important to create a simple route forward for recommendation and avoid revisiting the considerations which underpin the overall population ICER; the result of an appraisal process lasting over 18 months. We have therefore taken the important step to further increase the PAS discount, to [redacted], which ensures that the overall population ICER remains below £50,000; even in the worst-case scenario when exploring uncertainty by varying resection rates.

Table 1 presents ICERs for the overall population based on the committee's preferred assumptions with the [redacted] PAS and with the revised PAS of [redacted] for panitumumab, exploring upper and lower bound ICERs by varying resection rates from 0% to 20%.

Table 1 ICERs in the overall population (panitumumab+FOLFOX versus FOLFOX)

	ICER (£/QALY) ([redacted] PAS)	ICER(£/QALY) (revised [redacted] PAS)
Committee preferred assumptions OS adjusted for subsequent treatments, trial resection rates, no treatment stopping rule	[redacted]	[redacted]
Scenario analysis (lower bound for ICER) Resection rate of 20% assumed for panitumumab+FOLFOX and 10.7% for FOLFOX	[redacted]	[redacted]
Scenario analysis (upper bound for ICER) Resection rate of 0% assumed for panitumumab+FOLFOX and 0% for FOLFOX	[redacted]	[redacted]

With the increased PAS discount, panitumumab is safely cost-effective below the EoL threshold, producing a final decision-making ICER of [redacted], notably lower than previously [redacted]. The lower bound ICER (with a 20% resection rate for panitumumab) is highly cost-effective at [redacted], and the upper bound ICER (with resection rates set to 0%) still remains below the EoL threshold at [redacted].

We believe that the clinical and cost effectiveness case for panitumumab in the overall population is robust. The further increased PAS we have offered mitigates the risk to the NHS regarding any residual uncertainty.

Access to panitumumab and cetuximab through the Cancer Drugs Fund (CDF) has delivered critical improvements in outcomes for previously untreated mCRC patients. This appraisal presents an opportunity to move panitumumab into baseline commissioning and provide patients with the first ever NICE approved targeted treatment in this life limiting condition.

We therefore propose that NICE recommends panitumumab in combination with FOLFOX or FOLFIRI for use in the overall population.

2. Detailed response to key issues

The overall population should be used for decision-making and it is neither clinically appropriate nor robust to separate out subgroups:

- It is common in randomised controlled trials (RCTs), including PRIME, for there to be patient sub-populations that potentially confer improved prognosis (e.g. age, gender, ECOG status, primary tumour and site of metastases - LLD or elsewhere). Panitumumab has clearly demonstrated a robust OS gain in the overall population (hazard ratio [HR] 0.77, 95% confidence interval [CI] 0.64, 0.94[4]) regardless of patient sub-populations. In addition, panitumumab remains clinically effective in the non LLD sub-population, with a similar HR to the overall population that is nominally significant (HR 0.79, 95% CI 0.64, 0.98).[5] The interaction between treatment and site of metastases (LLD or elsewhere) was not statistically significant with a p-value of 0.71. Therefore there is no strong clinical rationale to separate out subgroups (such as LLD and non-LLD subgroups).
- In the LLD subgroup, improved prognosis is driven largely by those patients who have resection, whilst all other LLD patients will be treated palliatively to progression. Separating the whole LLD subgroup is therefore not a robust way of addressing the committee's concerns regarding the improved prognosis conferred by resection. We believe it is better to address this issue using the overall population for panitumumab and to conduct scenario analyses varying resection rates, rather than separating out clinically implausible subgroups.
- Importantly, the proportion of LLD patients is only 17.6% of the overall population in the PRIME RCT and any impact on the ICER due to improved survival is small. Indeed, the significantly lower ICER for the LLD subgroup presented in the AG assessment report (around [redacted][1]) is driven by the 16 week treatment stopping rule for panitumumab. Without the stopping rule, the ICER for the LLD subgroup is not markedly lower than the overall population ICER, further supporting the case that the overall population ICER is robust and should be used for decision-making.[1,3]

The impact of resection on the overall population ICER (based on committee's preferred assumption for resection) is likely to be small and any uncertainty limited:

- The committee noted that patients in the LLD subgroup were more likely to have resection, leading to improved prognosis.[2]
- However, the resection rates (taken from the PRIME RCT) and used in the NICE cost-effectiveness analysis to generate the ICER in the overall population, based on the committee's preferred assumptions*, were low (12.6% for panitumumab+FOLFOX and 10.7% for FOLFOX), with negligible differences between treatment arms. Consequently, the impact of resection rates on the overall population ICER for panitumumab is likely to be small.

* committee preferred assumptions for the overall population in the withdrawn FAD: OS adjusted for subsequent treatments, trial resection rates, no treatment stopping rule

The committee deemed panitumumab to meet the EoL criteria for the overall patient population after full consideration of the criteria,[2] consequently the £50,000 threshold for EoL medicines applies to the overall population regardless of the inclusion of people with liver-limited disease:

- The LLD subgroup (which makes up 17.6% of the overall population in the PRIME RCT) is just one of many subpopulations (e.g. age, gender, ECOG status, primary tumour) within the overall population that may confer improved prognosis.
- Regardless of the presence of the LLD subgroup, it is clear that in the overall population panitumumab meets the EoL considerations for average life expectancy and average survival gain.

We propose to create a simple route forward for recommendation using the committee's preferred assumptions for panitumumab in the overall population and mitigate any additional uncertainty through a further increased PAS discount:

- The committee acknowledged that the overall population ICERs, based on the committee's preferred assumptions, are likely to be lower in practice.[2] However to create a simple route forward, we continue to use, conservatively, the committee's preferred assumptions in the overall population, to generate revised ICERs.
- To address concerns regarding the uncertainty in the overall population, we have explored scenarios around the ICER generated using the committee's preferred assumptions [redacted], based on different resection rates for panitumumab in place of the committee's preferred assumption of 12.6% (PRIME resection rate)
    - Increase in the resection rate to 20% for panitumumab+FOLFOX: This reflects clinical expert opinion that the estimates of resection for panitumumab (and cetuximab) could be higher in practice (around 15% to 20%), and results in a potential lower bound ICER of [redacted]; providing reassurance that the ICER generated using the committee's preferred assumptions in the overall population [redacted] is conservative.
    - Reduction in the resection rate to 0% for both the panitumumab+FOLFOX and FOLFOX arms: This resection rate, although clinically implausible, results in a potential upper bound ICER of [redacted] and serves to explore concerns regarding uncertainty.
- Although the upper bound scenario is clinically implausible, we have further increased the PAS discount ([redacted]) to mitigate any additional uncertainty and ensure that the overall population ICER remains below £50,000, even in this worst-case scenario. Results based on the [redacted] PAS and the revised [redacted] PAS are presented in Table 2.
- With the increased PAS discount, panitumumab is safely cost-effective below the EoL threshold producing a final decision-making ICER of [redacted], notably lower than previously [redacted] using the committee's preferred assumptions. The lower bound ICER (with 20% resection rate for panitumumab) is highly cost-effective at [redacted], and the upper bound ICER (with resection rates set to 0%) still remains below the EoL threshold at [redacted].

Table 2 ICERs in the overall population (panitumumab+FOLFOX versus FOLFOX)

	ICER (£/QALY) ([redacted] PAS)	ICER(£/QALY) (revised [redacted] PAS)
Committee preferred assumptions OS adjusted for subsequent treatments, trial resection rates[a], no treatment stopping rule	[redacted][b]	[redacted]
Scenario analysis (lower bound for ICER) Resection rate of 20% assumed for panitumumab+FOLFOX and 10.7% for FOLFOX	[redacted]	[redacted]
Scenario analysis Resection rate of 15% assumed for panitumumab+FOLFOX and 10.7% for FOLFOX	[redacted]	[redacted]
Scenario analysis (upper bound for ICER Resection rate of 0% assumed for panitumumab+FOLFOX and 0% for FOLFOX	[redacted]	[redacted]
All ICERs presented in our response are based on the AG model using mean body surface area and weight.[1]		
[a] Resection rates from PRIME RCT (12.6% for panitumumab+FOLFOX, 10.7% for FOLFOX)[2] [b] Source: AG addendum report 28 Nov 2016 (ICER rounded to [redacted]),[1] AG addendum report 26 July 2016[3] AG, assessment group; ICER, incremental cost effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year; RCT, randomised controlled trial.		

We believe that the clinical and cost effectiveness case for panitumumab in the overall population is sufficiently robust. The further increased PAS we have offered mitigates the risk to the NHS regarding any residual uncertainty. We therefore propose that NICE recommends panitumumab in combination with FOLFOX or FOLFIRI for use in the overall population.

3. References

1. National Institute for Health and Care Excellence. Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer - Assessment Group Addendum Report. 28 Nov 2016.
2. National Institute for Health and Care Excellence. Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer - Final Appraisal Determination (withdrawn). 14 Oct 2016.
3. National Institute for Health and Care Excellence. Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer - unredacted ICERs from 26 July 2016 Assessment Group Addendum Report. Received via email on 18 Oct 2016.
4. Douillard JY, Oliner KS, Siena S *et al.* Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. *N Engl J Med* 2013;369:1023–34.
5. Data on file. Analysis based on OS update analysis (data cut-off 24 Jan 2013).
6. National Institute for Health and Care Excellence. Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer - Amgen response to request for additional data. Feb 2016.

[redacted]

5 January 2017

National Institute for Health and Care Excellence
1st Floor, 10 Spring Gardens
London, SW1A 2BU

By email to: Melinda.Goodall@nice.org.uk, Meindert.Boysen@nice.org.uk, Jeremy.Powell@nice.org.uk

Dear [redacted]

Cetuximab in metastatic colorectal cancer (NICE MTA [ID794])

Today we have submitted our response to PenTAG's latest addendum and the withdrawn FAD for this MTA.

We would be grateful for NICE's ongoing support in ensuring that the key messages within our response are a clear and consistent foundation for the Committee's discussions in both the public and private sessions of the Appraisal Committee meeting on January 25th. They are as follows:

1. During the course of this appraisal, the Committee have explicitly accepted several key assumptions (e.g. using trial resection rates, OS adjusted for post-study therapies, a distribution of BSAs, EOL for all-patients, comparability of FOLFOX and FOLFIRI backbones) and they need not be revisited.

2. The clinical paradigm within the UK setting is described and illustrated graphically. This highlights the fact that the vast majority of patients receive EGFRis with life-extending intent. We provide reassurance that the all-patient model fully represents this.

3. LLD patients are an intrinsic part of the all-patient population. Some of them may experience a better prognosis because they go on to receive resection. However, as these patients cannot be identified *a priori*, it is inappropriate to modify the cost-effectiveness threshold on the basis of the presence of LLD patients.

Merck KGaA
Merck Serono Ltd | Bedfont Cross | Stanwell Rd |
Feltham | Middlesex | TW14 8NX | UK
Tel: +44 791 861 8983
ceilidh.stapelkamp@merckgroup.com

www.merckgroup.com

4. In the LLD model, the stopping rule drives the cost-effectiveness of the LLD patients. Without this, they are no more or less cost-effective than the all-patient group. Consequently, in themselves LLD patients are not a more cost-effective group nested in the all-patient model and it is inappropriate to remove them from it.

[redacted]

Merck continues to be committed to this ongoing appraisal and to maintaining access to cetuximab for all RAS-wt metastatic colorectal cancer patients. We look forward to the remaining steps in the process.

With kind regards,

[redacted]

Merck KGaA
Address line one
Address line two
Tel: +00 (0)00 0000 0000
Fax: +00 (0)00 0000 0001
Email address

www.merckgroup.com

Multiple Technology Appraisal (MTA): Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer [ID794]

Merck's response to Committee B's withdrawn FAD

Merck welcomes the opportunity for ongoing discussions with NICE and Committee B about cetuximab's value proposition.

We respect the Committee's efforts and deliberations to date through which many of the key assumptions within this appraisal have been debated and decided. It is our view that several key preferred assumptions should not be revisited in the scheduled meeting, namely the LLD treatment paradigm, comparability of FOLFOX and FOLFIRI backbones, preference for OS modelling adjusted for subsequent therapy, clinical trial resection rates, weight based distribution and that the all patient group of mCRC patients meet end of life criteria. We have not further addressed these areas.

In this short response we would like to take the opportunity to reflect on some of the remaining issues of discussion for the Committee.

The clinical paradigm in this disease area is complex, particularly in light of the two economic models that are being used to represent it in this MTA. The description of the way in which patients with mCRC are treated in the UK should reassure the Committee that the current all-patient economic model appropriately represents the decision problem. We also discuss those patients whose disease is limited to their liver and the role of the stopping rule in the economic model. Through this, we hope to reassure the Committee that these patients are not influencing the results seen for the overall population.

We welcome the Committee's willingness to "take into account the potentially cheaper costs in clinical practice" of fortnightly dosing of cetuximab, and have provided further information to help the Committee factor this into their deliberation of cost effectiveness.

In addition, we have revised the level of discount available through the existing confidential simple patient access scheme for cetuximab from [redacted] to [redacted] to underwrite remaining uncertainties in the cost-effectiveness case. We therefore present results following a re-run of PenTAG's latest model, using the Committee's preferred assumptions and changing only the price of cetuximab in accordance with the new discount. In summary, the base case ICER for cetuximab versus chemotherapy alone is [redacted].

Cetuximab remains a cost-effective treatment alternative for all RAS-wt patients with metastatic colorectal cancer. Merck continues to be fully committed to working with NICE to appropriately represent the value that first line treatment with cetuximab in combination with FOLFIRI or FOLFOX offers to patients with RAS wt mCRC, and to ensuring that patients in England and Wales continue to benefit from access to this life-extending medicine.

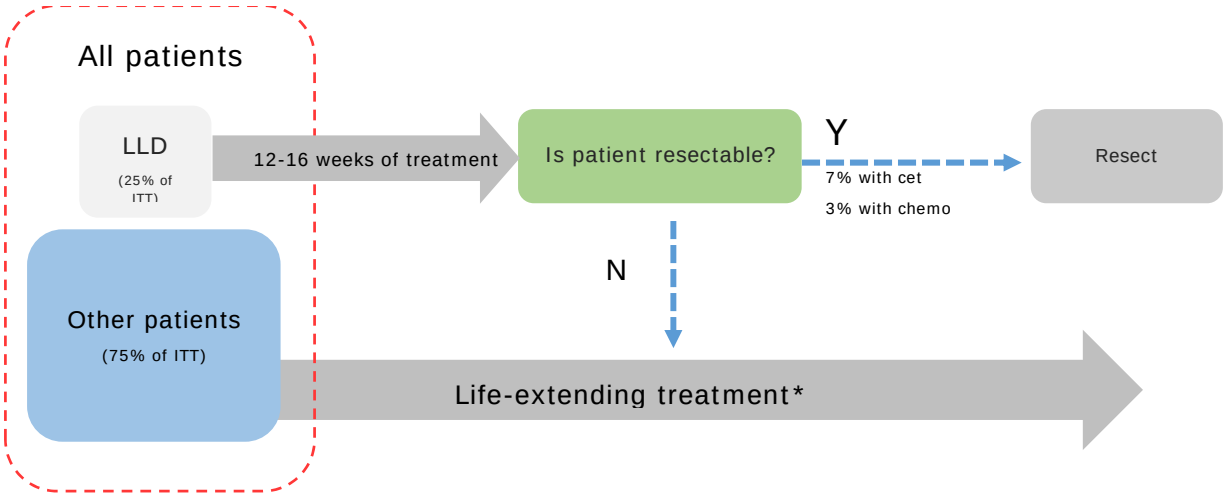
Multiple Technology Appraisal (MTA): Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer [ID794]

Contents

1.1. The current all patient model reflects the UK treatment paradigm in colorectal cancer

The decision problem in this MTA, as set out in its original scope, reflects the drugs' licences, namely the use of cetuximab and panitumumab in RAS wt metastatic colorectal cancer. Figure 1 below illustrates this treatment paradigm, reflecting the way in which the EGFR inhibitors are used in the UK, as life-extending medicines for all metastatic colorectal cancer patients. As a total population, these patients have high unmet need and, as confirmed by the Committee, meet end of life criteria.

Figure 1: Treatment of mCRC patients in the UK



* In the CRYSTAL study, 93% of patients received life-extending treatment

Patients with *extra* hepatic metastases, who represent 75-80% of patients, receive life-extending treatment from the outset. Of the remaining 20-25% patients who have metastases limited to the liver, a proportion may undergo resection following a short course of treatment; however, only a small minority become resectable, and enjoy improved prognosis. It is not possible to prospectively identify these patients and is therefore inappropriate to modify the cost-effectiveness threshold in the all-patient population on the basis of the presence of LLD patients.

Further, a stopping rule is artificial. The majority of patients who are not eligible for liver resection continue to receive life-extending treatment if they are deriving benefit from the medicine. That is to say, for patients who are not resected (the vast majority, e.g. 93% in the CRYSTAL trial) no 'stopping rule' is applied in real life. Patient prognosis in this unresected population is comparable irrespective of location of the metastases.

The all-patient model represents this clinical paradigm exactly and is therefore the relevant model for the decision problem set out by NICE in the scope of this appraisal.

1.2. LLD patients do not drive cost effectiveness in the all patient model

The cost-effectiveness of LLD patients in the LLD model is driven by the stopping rule. Without a stopping rule, LLD patients are no more or less cost-effective than the all patient group. This is evidenced by PenTAG's own analyses where in the addendum between the 2nd and 3rd meetings, the ICER for the overall population (assuming weekly dosing and OS correction) is the same as seen in the LLD model without a stopping rule ([redacted])*.

1.3. Revised confidential patient access scheme

Merck have revised the level of the discount to cetuximab's list price that we previously agreed with the Department of Health. The level of the discount remains commercial in confidence. We have received confirmation from the Department that they are content with the revision and that this can be considered as part of this ongoing appraisal. There is little doubt that cetuximab is a clinically effective medicine and all parties in this appraisal have acknowledged the need for EGFRi treatments for all patients with metastatic colorectal cancer; there are no alternative treatment options. Merck is extremely committed to maintaining access for these patients. The revised cetuximab price, from [redacted] discount to [redacted] further underwrites the uncertainties that remain in the economic case.

1.4. Cost-effectiveness of cetuximab (PenTAG's model incorporating cetuximab's revised discount)

We acknowledge PenTAG's recent additional analyses as laid out in their most recent addendum†. The results presented therein are little different to their previous analyses, and they reflect the base case ICERs, at cetuximab's previous price, now including results when 100% fortnightly dosing is assumed.

The incorporation of a distribution of BSA values reduces the ICERs by approximately [redacted]. We thank PenTAG for including this element and demonstrating this. Although PenTAG describe its impact as marginal it is nevertheless more accurate.

---

* Tables 9 and 12; PenTAG Addendum between 2nd and 3rd Appraisal Committee Meetings

† PenTAG. Addendum: Between 3rd and 4th NICE Appraisal Committee meetings. 28th Nov 2016.

PenTAG's addendum, however, is overcomplicated by the inclusion of numerous LLD analyses and a series of analyses which do not reflect the Committee's preferred assumptions outlined in the withdrawn FAD. These add an unnecessary level of complexity to the addendum and risk distracting the Committee from the key remaining subject of discussion, namely cost effectiveness in the all-patient population, applying the Committee's preferred assumptions (i.e. trial resection rates, OS values adjusted for post-study treatments, PenTAG's distribution of BSA values (rather than means) and a consideration of fortnightly dosing).

The Committee have indicated a willingness to take into account the cost of fortnightly dosing, which is routine clinical practice in the UK. In Table 1, results of the economic model are presented alongside the full range of assumptions about the proportion of patients receiving cetuximab fortnightly.

In Appendices 1 and 2 we have provided supportive data to reassure the Committee regarding the extent of fortnightly dosing in England and Wales. This appears to be [redacted] compared to [redacted] weekly dosing. It is Merck's understanding that this can be ratified by analysis of SACT data. When these real world dosing patterns are factored into the economic model using a weighted average of fortnightly and weekly results, the ICER for cetuximab plus FOLFIRI vs FOLFIRI alone is [redacted].

[redacted]

As can be seen above, cetuximab is cost effective even under extremely conservative dosing assumptions. The Committee can be reassured that they are not being asked to make a decision at the margins of cost-effectiveness. In summary, the base case ICER - which incorporates the Committee's preferred assumptions and real world dosing patterns – is [redacted].

Conclusion

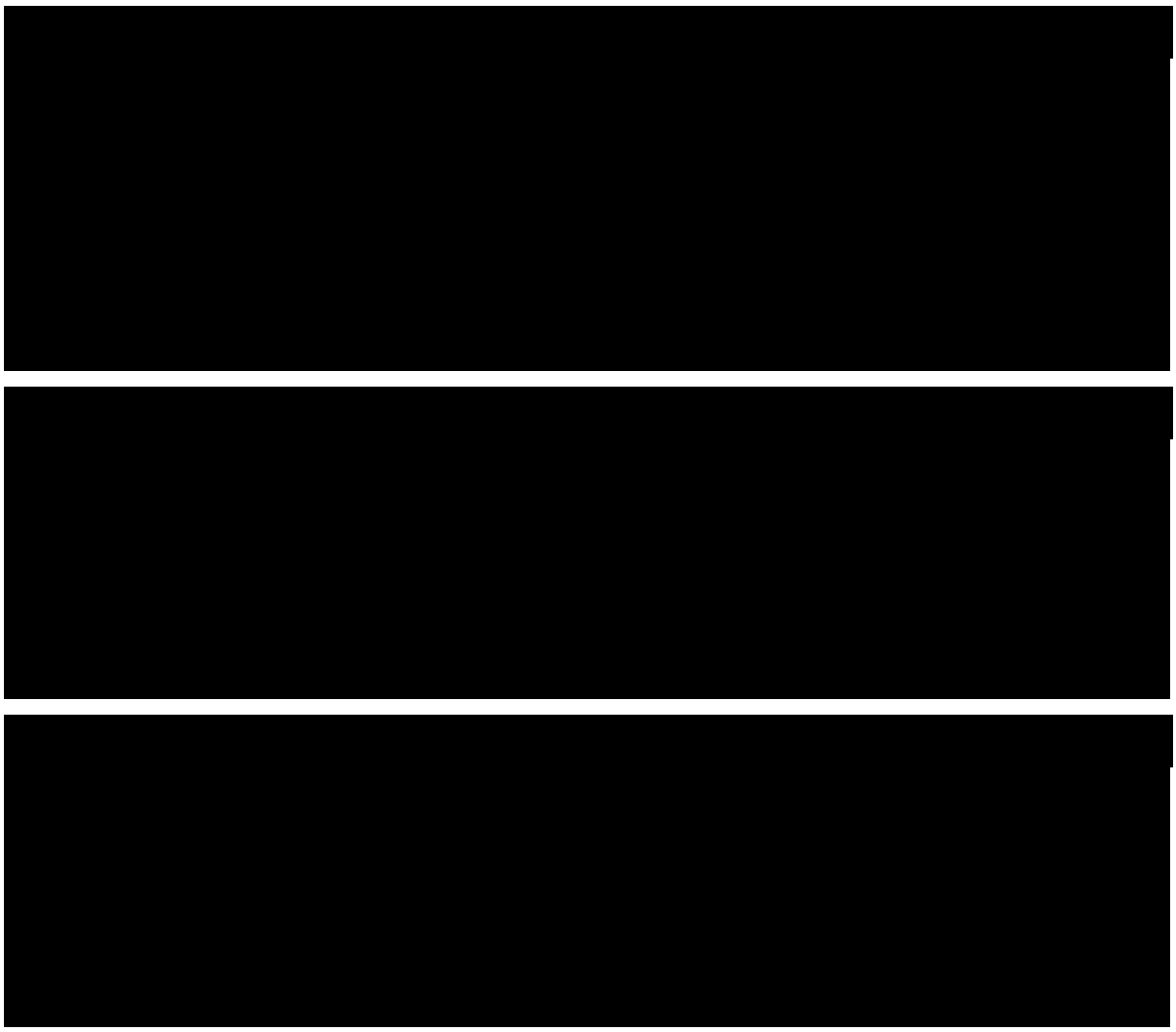
Targeted therapies have been available in the UK to mCRC patients since 2011, and without access to them, the chemotherapies in use a decade ago would be the only alternatives. The clinical evidence for cetuximab as a treatment for RAS-wt mCRC is strong. The CRYSTAL study shows a significant overall survival gain versus chemotherapy alone; 8 month median survival gain. Throughout the course of this MTA, Merck have remained fully committed to working with NICE to appropriately represent the economic value of the treatment to the NHS, and to ensuring that patients in England and Wales continue to benefit from access to this life-extending medicine. We have summarised the Committee's deliberations in this document and additionally we hope that by revisiting the clinical paradigm, the model structure and by revising the cetuximab discount, we have addressed any remaining areas of uncertainty in the Committee's mind. Under the preferred assumptions that the Committee previously agreed, cetuximab is a cost-effective use of NHS resources for all patients in this indication.

Appendix 1: Real world evidence of dosing frequency

A: Market research (date: 12-19th December 2016) on administration of cetuximab

The results of this assessment confirm that the vast majority of patients being prescribed cetuximab in the first line setting for mCRC received the treatment on a fortnightly schedule.

B. Market research (date: June 2016) on administration of cetuximab



Appendix 2: Data on File (Oncologist feedback regarding dosing schedule of cetuximab)

UK Cetuximab Dosing Schedule Used in mCRC and reason

This data on file is to provide information on oncologists' feedback to Merck in 2016 regarding dosing frequency of cetuximab in 1st line mCRC and the rationale.

Institution	Dose used	Reason
[redacted]	500 mg/m2 D1 every 14 days with FOLFIRI or FOLFOX	Data shows equivalent PK to 400 mg/m2 loading dose then weekly 250 mg/m^2. It is much more convenient for patients as it halves their visits, is significantly less resource intensive (and hence more cost-effective) for the pharmacists who make it up, the nurses who administer it in our SACT delivery suites and the clinician who assesses the patients and authorises treatment at each visit. This answer is for all the GI oncologists working in the 5 HSC Trusts across N. Ireland and reflects our regional guidelines.
[redacted]	400mg/m(2) as first dose and then 500 mg/m(2) every 2 weeks to co-ordinate with fortnightly administration of FOLFIRI	This reduces patient visits and also reduces the need for chemotherapy chairs. It was shown by Tabernero to be effective and have similar PK to the registered schedule/dose.
[redacted]	500mg/m2 2 weekly	Convenience and as effective
[redacted]	500 bi weekly	

[redacted]	500mg/m2 every 2 weeks	We use a 2 weekly regimen as it is more convenient to patients compared with weekly
[redacted]	500mg/m2 every 2 weeks in combination with FOLFIRI	Mandated by the CDF
[redacted]	2 weekly	1. Pharmacologically proven similarity 2. Patient convenience and preference 3. Increased efficiency
[redacted]	5mg/Kg 2-weekly	The reason is that there are patient benefits in reduced attendance as this is administered alongside FOLFOX or FOLFIRI. Clearly this also has a benefit in managing day unit capacity. The justification is the Tabernero data on bi-weekly cetuximab.
[redacted]	2 weekly schedule 500mg/m2 either in combination with folfiri or folfox	Based on the CDF regulations, it is also a lot easier for patients
[redacted]	2 weekly 500mg/mq	Patient convenience. PK and PD data demonstrate equivalence to weekly dosing. Ref: Tabernero et.al. 2008. the Oncologist

Multiple Technology Appraisal (MTA): Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer [ID794] – a joint response from Bowel Cancer UK and Beating Bowel Cancer

As the two leading bowel cancer charities we welcome the decision to withdraw the final appraisal determination document (FAD) for the appraisal of cetuximab and panitumumab for previously untreated metastatic colorectal cancer. We are pleased that the Committee is re-evaluating this appraisal and has provided us with the opportunity to present our view on the FAD and further evidence. In this brief submission we outline our reasons for disagreeing with the previous FAD and provide further evidence that demonstrate cetuximab is administered 2-weekly in the UK.

While we were pleased that the end of life criteria had been met and would be applied to this appraisal, we disagreed with the FAD for the following reasons:

1. **The criteria are too restrictive**. The proposed recommendation for the use of cetuximab and panitumumab severely restricts the population who can benefit from these targeted therapies. Overall approximately 50% of people with bowel cancer will either be diagnosed with metastatic disease or go on to develop it and half of these will be RAS wild type. Of these patients, those with liver-limited disease make up a small proportion of this population. NICE's own costing template estimates that this figure is 10%. This means the vast majority, 90%, will be denied the potential benefit of this targeted therapy.

2. **The guidance is a significant departure from clinical practice and opinion**. A recommendation for all RAS wild type patients has wide clinical support. Furthermore both treatments were recommended under the Cancer Drugs Fund for a wider indication. The NICE final guidance decreases the choice that both patients and clinicians have when deciding what course of treatment to opt for. It would mean that there would be no first line precision therapy for RAS wild type patients who have widespread metastases. We know that chemotherapy given with an EGFR antibody, such as cetuximab or panitumumab, can lead to a median survival rate in excess of 30 months. A letter to Sir Andrew Dillon signed by the Chairs of the Medical Advisory Boards of Bowel Cancer UK and Beating Bowel Cancer, along with the signatories of over 40 oncologists supporting the continued use of both cetuximab and panitumumab is attached in Appendix 1.

3. **The guidance will have a detrimental impact on the whole of the UK**. Both Scotland and Wales have recommended cetuximab as a first line treatment for all RAS wild type patients for some time now – in Scotland this guidance has been in place since January 2015 and in Wales since December 2015. However as NICE TA guidance supersedes AWMSG guidance and NICE MTAs also usually supersede SMC advice consequently the FAD risks putting the whole of the UK back in terms of access to medicines for people with widespread metastases.

4. **Cetuximab is administered fortnightly in the UK**. In the FAD the Committee set out a willingness to take into consideration that in clinical practice cetuximab is administered fortnightly rather than weekly. Appendices 2 and 3 set out supporting evidence on the extent of this practice in the UK. The raw data has been from two sources: first, the SACT database and second, from a survey of prescribing practices carried out by Beating Bowel Cancer.

a. SACT Dataset[1] (Appendix 2)

A request was made to SACT for the number of doses of cetuximab administered at different dose-levels. The weekly dose is 250mg/m2 and the 2-weekly dose is 500mg/m2. SACT also provided the median surface area for male (1.98m2) and female (1.76m2) patients (enclosed – appendix 2), Therefore the weekly dose would be around 400-500mg and the 2-weekly dose will be double this (800-1000mg). The SACT data attached shows that in England only 25% of patients received the lower dose via the weekly schedule whereas, 75% received the higher dose via the 2-weekly schedule (slide 2). The data has not been filtered by line of treatment. This means that some of the cetuximab may have been given 3rd or 4th line setting, as continuation of treatment that was commenced when this was available via the Cancer Drugs Fund (CDF). However, as cetuximab was only approved for use on the CDF as a first line treatment during 2016, we believe that this is a good representation of the first line prescribing practices of oncologists in England. This information has been generated from nearly 34,000 administrations of cetuximab (slide 3) and therefore we would say is robust evidence for the use of 2-weekly cetuximab in England.

b. A survey of oncologists, carried out by Beating Bowel Cancer[2] (Appendix 3)

During a 2-week period between the 21st December 2016 and the 4th January 2017 a number of oncologists in the UK were sent a short survey via email on whether they prescribe cetuximab on a weekly or 2-weekly basis. A total of 64 replies were received. The results show that an overwhelmingly 98% of clinicians prescribe it in the 2-weekly schedule and only one Oncologist prescribes weekly cetuximab. The CDF only allowed a 2-weekly schedule. However, even though this was the case, there were no statements regretting that clinicians were not able to administer cetuximab weekly. Some of the other comments were recorded in the raw data that is enclosed with this submission. These include references for evidence and statements that the 2-weekly schedule is preferable for busy chemotherapy units and halves the number of visits that patients would have to make to hospitals. It is therefore efficacious and saves hospital and patient time and is therefore cheaper because of this.

It is for these reasons that we believe that cetuximab and panitumumab should be recommended as a first line treatment option for all RAS wild type patients. It would be a tragedy if the Committee did not recommend these two treatments and would be in contrast not only to other parts of the UK but the rest of Europe and North America. This will lead to a real crisis for bowel cancer patients and the treatment of metastatic disease across the UK.

This would be a disastrous step, which will take us backwards and bring to a halt the progress in patient care that was achieved by the Cancer Drugs Fund, as well as significantly shorten survival rates of people with metastatic colorectal cancer in England. The Medical Advisory Board members of both charities also fully support this position.

[1] The data from SACT was generated by Michael Wallington within 24 hours of our request. We would like to thank him for his prompt response and support the excellent use of SACT data.

[2] We would like to thank all of the clinicians who replied to the survey, which was carried out over the Christmas and New Year break. The fact that so many replied so quickly emphasises the strong feeling that cetuximab is best administered 2-weekly. Even though the survey did not ask whether clinicians support the continuation of 1st-line use of EGFR inhibitors, Appendix 1 confirms this.

APPENDIX 1

Sir Andrew Dillon
Chief Executive
NICE

23 August 2016

Dear Sir Andrew

Re: The clinical effectiveness and cost effectiveness of cetuximab (review of TA176) and panitumumab (partial review of TA240) for previously untreated metastatic colorectal cancer. A systematic review and economic evaluation

At present both cetuximab and panitumumab are available via the Cancer Drug Fund in England for the treatment of patients with metastatic colorectal cancer. We would like to support their continued use in the future throughout the UK.

As more drugs have been made available over the last 20 years, we have seen a major improvement in the median survival rate for patients with advanced bowel cancer when treated with chemotherapy (from 8 months to almost 2 years). For those with wild type RAS tumours, 50% are now living longer than 30 months when treated with 1st line cetuximab or panitumumab based chemotherapy. This has made a huge difference to thousands of patients and has given them hope and more importantly a longer life with their families.

We are aware of the on-going review of both cetuximab and panitumumab in the first line setting. If NICE decide to stop funding these drugs, then we will only be able to offer our patients treatments that we had a decade ago. This could also potentially have an impact on patients in the devolved nations, particularly Wales and Scotland. These targeted drugs are also routinely available to patients in much of Western Europe and North America. Reducing their availability in the UK would be a tragic and retrograde step.

Another indirect consequence would be that we will not be able to participate in international clinical trials since we will no longer able to provide “gold standard” chemotherapy. This will further isolate the UK research community.

We would like you to consider our plea and continue to fund both of these drugs in the future.

Yours sincerely

Dr Mark Saunders
Chair, Beating Bowel Cancer Medical Advisory Board

Dr Rob Glynne-Jones
Chair, Bowel Cancer UK Medical Advisory Board

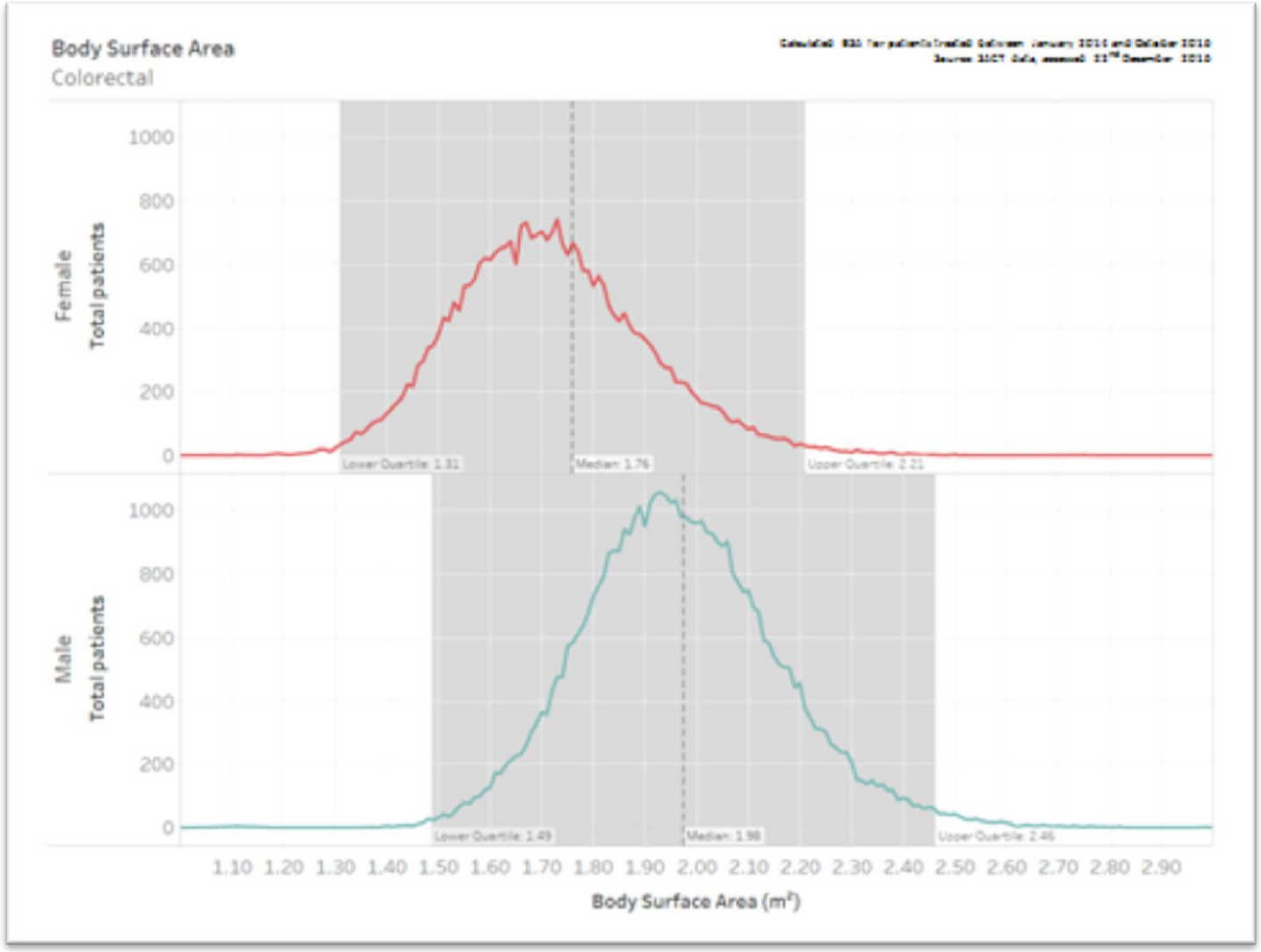
Please see co-signatories overleaf.

Dr Nooreen Alam	Consultant Clinical Oncologist	The Christie NHS Foundation Trust
Dr Alan Anthoney	Honorary Consultant in Medical Oncology	Leeds Teaching Hospitals NHS Trust
Dr Seema Arif	Consultant Clinical Oncologist	Velindre Cancer Centre
Mr Tan Arulampalam	Consultant Colorectal Surgeon	Beating Bowel Cancer Medical Board
Dr Ashraf Azzabi	Consultant Medical Oncologist	Newcastle upon Tyne Hospitals NHS FT
Dr Michael Braun	Consultant Medical Oncologist	The Christie NHS Foundation Trust
Prof John Bridgewater	Professor of Medical Oncology	University College London
Dr Mark Churn	Consultant Clinical Oncologist	Worcestershire Acute Hospitals NHS T
Dr Susan Clenton	Consultant Clinical Oncologist	Sheffield Teaching Hospitals NHS FT
Prof David Cunningham	Consultant Medical Oncologist	The Royal Marsden NHS FT
Dr Alice Dewdney	Consultant Clinical Oncologist	Sheffield Teaching Hospitals NHS FT
Dr Tony Dhillon	Consultant Medical Oncologist	Royal Surrey County Hospital
Dr Richard Ellis	Consultant Clinical Oncologist	Royal Cornwall Hospital
Dr Daniel Epurescu	Consultant in Medical Oncology	Norfolk & Norwich University Hospital
Dr Stephen Falk	Consultant Oncologist	Bristol Cancer Institute
Dr Maxine Flubacher	Consultant Clinical Oncologist	Poole Hospital NHS Foundation Trust
Dr Ian Geh	Consultant Clinical Oncologist	University Hospitals Birmingham NHS FT
Dr Rob Glynne-Jones	Consultant Clinical Oncologist	Mount Vernon Centre for Cancer Treatment
Dr Janet Graham	Consultant Medical Oncologist	Beatson West of Scotland Cancer Centre
Dr Sarah Gwynne	Consultant Oncologist	Abertawe Bro Morgannwg University HB
Dr Mark Harrison	Consultant Oncologist	Mount Vernon Cancer Centre
Dr Mark Hill	Consultant Medical Oncologist	Maidstone & Tunbridge Wells
Dr Timothy Iveson	Consultant in Medical Oncology	University Hospital Southampton
Dr Andrew Jackson	Consultant Clinical Oncologist	University Hospital Southampton
Dr Fiona Lofts	Consultant Oncologist	St Georges University Hospitals FT
Dr Kalena Marti	Consultant Medical Oncologist	The Christie NHS Foundation Trust
Dr Vivek Misra	Consultant Clinical Oncologist	The Christie NHS Foundation Trust
Dr Saifee Mullamitha	Consultant in Medical Oncology	The Christie NHS Foundation Trust
Dr Nishanth Murukesh	Consultant Medical Oncologist	Worcestershire Acute Hospital NHS Trust
Dr Sethupathi Muthuramalingam	Consultant Medical Oncologist	Portsmouth Hospitals NHS Trust
Dr Luke Nolan	Consultant Medical Oncologist	University Hospital Southampton NHS FT
Dr Ann O'Callaghan	Consultant in Medical Oncology	Portsmouth Hospitals NHS Trust
Mr Daniel O'Leary	Consultant Colorectal Surgeon	Portsmouth Hospitals NHS Trust
Dr Ian Pedley	Consultant Clinical Oncologist	Newcastle upon Tyne NHS FT
Dr Vanessa Potter	Consultant Medical Oncologist	Nottingham University Hospitals NHS Trust
Dr Sheela Rao	Consultant Medical Oncologist	The Royal Marsden NHS FT
Dr Sherif Raouf	Consultant Clinical Oncologist	Barking, Havering & Redbridge NHS Trust
Dr Pippa Riddle	Consultant Oncologist	Imperial College Healthcare NHS Trust
Dr Robert Rulach	ST4 Clinical Oncology	NHS Greater Glasgow & Clyde
Dr Leslie Samuel	Consultant Oncologist	Aberdeen Royal Infirmary
Dr Mark Saunders	Consultant Oncologist	The Christie NHS Foundation Trust
Dr Alaaeldin Shablak	Consultant Medical Oncologist	University Hosp Southampton NHS FT

/…

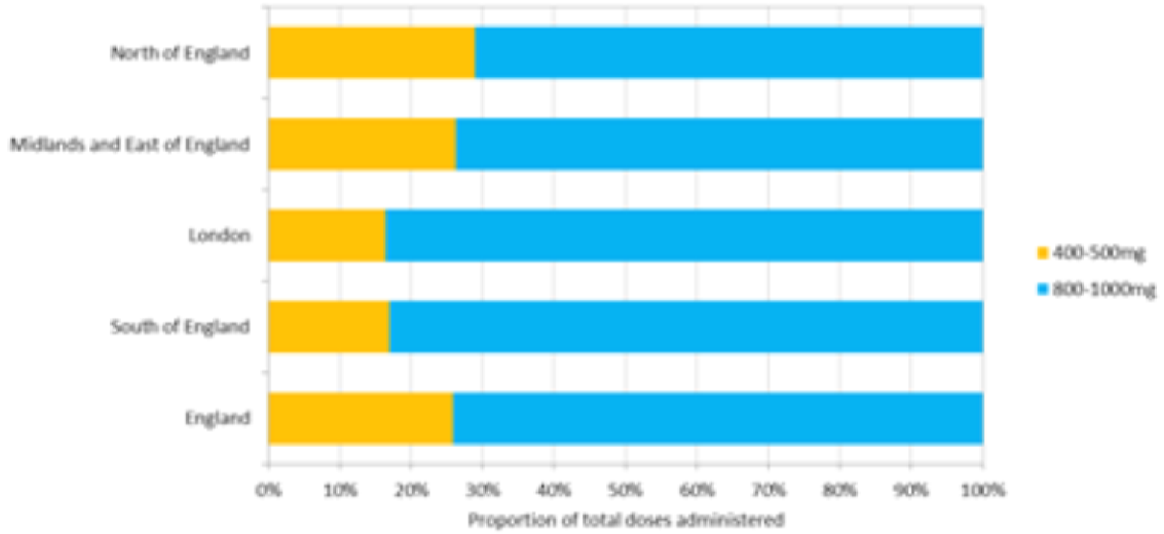
Dr David Sherriff	Consultant Gastrointestinal Oncologist	Plymouth Hospitals NHS Trust
Dr Bruce Sizer	Consultant Clinical Oncologist	Colchester General Hospital
Dr Naureen Starling	Consultant Medical Oncologist	The Royal Marsden NHS FT
Dr Jeff Summers	Consultant Oncologist	Maidstone & Tunbridge Wells
Dr John Wagstaff	Director	South West Wales Cancer Institute
Dr Harpreet Wasan	Reader in Medical Oncology	Imperial College Healthcare NHS Trust
Dr Gregory Wilson	Consultant Medical Oncologist	The Christie NHS Foundation Trust
Prof Richard Wilson	Consultant Medical Oncologist	Belfast HSC Trust
Dr Kathryn Wright	Consultant Clinical Oncologist	Newcastle upon Tyne NHS FT
Dr Robin Young	Consultant Medical Oncologist	Sheffield Teaching Hospitals NHS FT

APPENDIX 2


Body Surface Area
Colorectal
Female
Total patients
1000
800
600
400
200
0
Lower Quartile: 1.31
Median: 1.76
Upper Quartile: 2.21
Male
Total patients
1000
800
600
400
200
0
Lower Quartile: 1.49
Median: 1.98
Upper Quartile: 2.46
1.10 1.20 1.30 1.40 1.50 1.60 1.70 1.80 1.90 2.00 2.10 2.20 2.30 2.40 2.50 2.60 2.70 2.80 2.90
Body Surface Area (m²)

CETUXIMAB

Administered doses between January 2014 and October 2016



Source: SACT data, accessed 22nd December 2016
National Cancer Registration and Analysis Service, Public Health England

Administered doses of CETUXIMAB between January 2014 and October 2016

Source: SACT data, accessed 22nd December 2016

National Cancer Registration and Analysis Service, Public Health England

Number of records	Dose range				
Region	<400mg	400-500mg	500-800mg	800-1000mg	>1000mg
England	1,944	6,192	5,263	17,787	2,784
South of England	301	976	1,409	4,798	718
London	60	510	810	2,601	500
Midlands and East of England	990	2,195	1,584	6,182	599
North of England	593	2,533	1,765	6,205	1,556

APPENDIX 3

Dear oncologists

We have heard from our Medical Advisory Board that the NICE decision about the 1st line use of cetuximab in metastatic colorectal cancer is at a critical stage. One of the sticking points is whether Trusts give cetuximab weekly or 2-weekly. The originally licenced way and financial data that NICE have used is from the weekly trials. However many oncologists give it 2-weekly (easier for patients / hospitals and considered just as effective), but we just can't provide evidence for this. Therefore we would be grateful if you could answer the following question by TUESDAY 4 JANUARY as the deadline is 6 January.

Replies received by 6.1.17 – 64 replies (63 respondents give cetuximab 2-weekly and only one respondent weekly who is planning to change to 2-weekly)

ENGLAND

Consultant / Hospital	Weekly	2 Weekly	Comments
Dr Fiona McDonald QE Gateshead		✓	
Dr Alexandra Stewart Royal Surrey County Hospital Guildford		✓	Two weekly exclusively
Dr Bruce Sizer Colchester General Hospital		✓	
Dr Rob Glynne-Jones Mount Vernon Cancer Centre		✓	Safety/efficacy established by Barcelona group
Ashraf Azzabi Chair, North East of England colorectal site specific group		✓	The funding for cetuximab with the preoperative TAG637 (not sure what number it was, but it's the 16 weeks one) is for two weekly dosing so I can confirm that the north east of England uses cetuximab as a two weekly regimen

James Gildersleve Royal Berkshire		✓	
Dr Kalena Marti The Christie NHS Foundation Trust		✓	
Dr Melanie Osborne Royal Devon & Exeter		✓	I can confirm that we use Cetuximab 2 weekly – it's well tolerated and much more convenient for patients
Dr Mark Churn Worcestershire Acute Hospitals		✓	We give Cetuximab two-weekly in almost all cases
Dr Paul Ross Guy's & St Thomas' NHS FT / Guy's Cancer Centre		✓	
Dr Vanessa Potter University Hospital Coventry and Warwickshire		✓	2-weekly as per CDF. Also using 2 weekly for the TAG176/ I can also speak for Nottingham University Hospitals NHS Trust as have recently moved from there.
Dr Gregory Wilson The Christie NHS Foundation Trust		✓	We give it two weekly, normally with IrMdg. This was based on a Spanish phase one trial showing higher peak blood levels and similar trough levels. The initial researcher is a famous Spanish oncologist called Tabanero. Everyone accepts that two weekly is as efficacious and easier.
Dr Ultan McDermott Addenbrooke's Hospital		✓	
Dr Sheela Rao /Royal Marsden Hospital		✓	Given 2 weekly for some time now –as effective and less day unit issues with capacity
Dr Sethupathi Muthuramalingam Portsmouth Hospitals NHS Trust		✓	Agreed at the network level
Dr Saifee Mullamitha The Christie NHS Foundation Trust		✓	Always 2 weekly
Dr Michael Braun The Christie NHS Foundation Trust		✓	All patients receive 2 weekly rather than weekly given convenience to patients and capacity issues with chemotherapy units.

Dr Fiona Lofts St Georges		✓	Fits in with FOLFIRI protocol
Dr Kathryn Connolly Aberdeen Royal Infirmary		✓	
Dr Alice Freebairn Royal Berkshire NHS FT		✓	
Prof David Cunningham Royal Marsden		✓	
Dr Seema Arif Velindre Cancer Centre		✓	
Dr Nishanth Murukesh Worcestershire Acute Hospital		✓	
Dr Pippa Riddle Imperial NHS Foundation Trust		✓	
Dr Naureen Starling The Royal Marsden		✓	
Prof Tim Maughan Oxford		✓	Based on PK data of equivalence
Dr Tim Simmons / Newcastle upon Tyne Hospitals NHS Foundation Trust (Freeman Hospital) / County Durham Darlington NHS Foundation Trust (UHND)		✓	The evidence for this should come from the CDF database itself. We only have access to Cetuximab under the CDF, and can only give it 2 weekly according to the CDF rules in the above screenshot taken from the CDF database. Massively frustrating if NICE is using financial data from weekly administration, ignoring how the CDF mandates cetuximab to be administered. I probably could give cetuximab weekly for the very small number of neoadjuvant treatments for liver mets, but this indication is tiny compared to the palliative treatments we give, and to avoid confusion I always give it fortnightly. Needless to say, this colorectal oncologist thinks cetuximab is a useful drug and would not wish to see it taken off the CDF.

Dr Ian Chau The Royal Marsden		✓	Evidence: Ann Oncol. 2010 Jul;21(7):1537-45. doi: 10.1093/annonc/mdp549. Epub 2009 Nov 25. Cetuximab administered once every second week to patients with metastatic colorectal cancer: a two-part pharmacokinetic/pharmacodynamic phase I dose-escalation study. Tabernero J1, Ciardiello F, Rivera F, Rodriguez-Braun E, Ramos FJ, Martinelli E, Vega-Villegas ME, Roselló S, Liebscher S, Kisker O, Macarulla T, Baselga J, Cervantes A. Oncologist. 2008 Feb;13(2):113-9. doi: 10.1634/theoncologist.2007-0201. Administration of cetuximab every 2 weeks in the treatment of metastatic colorectal cancer: an effective, more convenient alternative to weekly administration? Tabernero J1, Pfeiffer P, Cervantes A.
Dr Mark Saunders The Christie NHS Foundation Trust		✓	Never give weekly out of trials
Dr Maxine Flubacher / Poole Hospital NHS Foundation Trust		✓	
Dr Fiona Minear Royal Cornwall Hospitals		✓	
Prof Robert Thomas Bedford and Addenbrooke's Cambridge University Hospitals		✓	Often day 1 day 8 then a week off easier and better tolerated
Dr Charlotte Rees Southampton & Hampshire Hospitals Foundation Trust		✓	
Dr Ann O Callaghan Portsmouth Hospitals NHS Trust		✓	

Dr Nick Brown Calderdale & Huddersfield		✓	
Dr Mark Hill Kent Oncology Centre		✓	European evidence base
Dr Joanne Hornbuckle Sheffield Teaching Hospitals NHS Trust (Weston Park Hospital)		✓	
Dr Stephen Falk Bristol Oncology Centre		✓	
Prof Rachel Kerr Churchill Hospital		✓	We give it first line in combination with chemo. Always two-weekly.
Dr Luke Nolan Hampshire Hospitals FT		✓	I am unaware of any sites giving weekly cetuximab
Dr Sherif Raouf Barking Havering & Redbridge		✓	
Dr David Sherriff Derriford Hospital Plymouth		✓	We give Cetuximab in combination every 2 weeks – as per CDF guidance. It is well tolerated, appears just as effective as the published trial data and is far more convenient for patients to receive in 2-weekly.
Prof John Bridgewater UCLH, North Middlesex, Princess Alexandra		✓	

SCOTLAND

Consultant / Hospital	Weekly	2 Weekly	Comments
Dr Leslie Samuel Aberdeen Royal Infirmary		✓	With first cycle we give loading dose & a maintenance dose week 2, & then onto 2 weekly with subsequent cycles
Dr Lesley Dawson NHS Lothian		✓	2-weekly in Edinburgh & SCAN.

Dr Nicholas MacLeod Beatson West of Scotland		✓	We give all 1st line cetux 2 weekly now in Ayrshire and Arran.
Dr Alec McDonald Crosshouse University Hospital Beatson West of Scotland Cancer Centre		✓	
Dr Janet Graham		✓	All consultants in Glasgow give it fortnightly as per the CDF rules. All English centres, I think, follow the CDF stipulation of fortnightly
Dr Grainne Dunn Beatson West of Scotland		✓	
Dawn Storey Beatson Oncology Centre		✓	(I also treat patients at Inverclyde Royal Hospital, Greenock (Greater Glasgow & Clyde) and Forth Valley Royal Hospital, Larbert (Forth Valley NHS Trust)
Dr David McIntosh Forth Valley Stirling		✓	Mainly 2 weekly for patient and clinic ease
Dr Sally Clive Western General Edinburgh		✓	Only approved by SMC for 2-weekly use in 1st line setting

WALES

Consultant / Hospital	Weekly	2 Weekly	Comments
Dr Richard Adams Velindre Cancer Centre		✓	In my experience this is in common with all practice in Wales, representing over 3 million population
Dr Sarah Gwynne ABM University Health Board	✓		We give mainly weekly. We are looking at changing to 2 weekly for the reasons of the advantages that you have already stated.

N. IRELAND

Consultants / Hospital	Weekly	2 Weekly	Comments
Dr Vicky Coyle, Dr Robert Harte, Dr Richard Park and Prof Richard Wilson. Belfast City Hospital, Belfast HSC Trust.		✓	In N. Ireland, we all use 500 mg/m2 D1 every 14 days with either FOLFIRI or FOLFOX. Published data shows equivalent PK of this fortnightly schedule to 400 mg/m2 loading dose then weekly 250 mg/m2 [Tabernero J et al, Ann Oncol 2010;21 (7):1537-1545 and Tabernero J et al, The Oncologist 2008; 13 (2): 113-119.]
Dr David Conkey and Dr Colin Purcell. Antrim Area Hospital, Northern HSC Trust.		✓	Fortnightly use is much more convenient for patients as it halves their visits, is significantly less resource intensive (and hence more cost-effective) for the pharmacists who make it up, the nurses who administer it in our SACT delivery suites and the clinician who assesses the patients and authorises treatment at each visit. This is the agreed pattern of usage for all the GI medical and clinical oncologists working in the 5 HSC Trusts across N. Ireland and also reflects our current regional SACT guidelines for colorectal cancer. Our only use of weekly Cetuximab is where this is mandated as the licensed schedule within a clinical trial.
Dr Robert Harte and Dr Richard Park. Craigavon Area Hospital, Southern HSC Trust.		✓	
Dr Paul Henry and Dr Bode Oladipok. Ulster Hospital Dundonald, Southeastern HSC Trust.		✓	
Dr Darren Brady and Dr Sonali Dasgupta. Altnagelvin Hospital, Western HSC Trust.		✓	

Royal College of Physicians
11 St Andrews Place
Regent's Park
London NW1 4LE
Tel: +44 (0)20 3075 1560

www.rcplondon.ac.uk

From [redacted]

Dr Melinda Goodall,
NICE - National Institute for Health and Care Excellence
1st Floor
10 Spring Gardens
London
SW1A 2BU
tacommb@nice.org.uk

12 January 2017

Dear Dr Goodall

Re: FAD from NICE for cetuximab and panitumumab for previously untreated metastatic colorectal cancer [ID794]

The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 33,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

The NCRI-ACP-RCP-RCR are grateful for the opportunity to respond to the above consultation. Many thanks for your recent email about our formal letter sent to you on 19 October 2016 which detailed our concerns in relation to the recommendations in this FAD for ID794. We are very grateful that NICE took the decision not to publish this FAD, but to allow time for wider consultation prior to discussing this topic again on January 25 2017, and also for your invitation asking us to convey our concerns in writing to the committee.
This reply is from the NCRI Colorectal Cancer Clinical Studies Group who are acting on behalf of the Royal College of Physicians as regards this FAD.

As stakeholders, we were very surprised and very saddened when we read through the NICE FAD whose recommendation in October 2016 was to allow Cetuximab or Panitumumab in combination with either 5-fluorouracil, folinic acid and oxaliplatin (FOLFOX) or with 5-fluorouracil, folinic acid and irinotecan (FOLFIRI) are recommended as options for previously untreated epidermal growth factor receptor (EGFR)-expressing, RAS wild type metastatic colorectal cancer in adults, only if:

- the metastases are confined to the liver and are unresectable without treatment
- the person is fit enough to have surgery after treatment with cetuximab or panitumumab
- treatment lasts no longer than 16 weeks, at which point the liver is assessed for resection, and
- the companies provide cetuximab and panitumumab with the discounts agreed in the patient access scheme.

As colorectal clinicians, we strongly believe that the anti-EGFR antibodies Cetuximab and Panitumumab have made an enormous and beneficial impact in the management of patients with widespread metastatic colorectal cancer in the first-line setting, particularly those who are symptomatic with a high volume disease

burden. The FIRE-3 and CALGB 80405 trials (which were not analysed in this assessment) have clearly shown significant benefits in terms of depth and duration of response and improved overall survival for the biomarker-selected group of patients with KRAS/NRAS wild-type disease who received anti-EGFR antibodies along with FOLFIRI or FOLFOX chemotherapy. These trials were started many years ago, involve several thousands of patients, and subsequent analyses of treatment post-progression in second and third-line and beyond have included patients who only received an anti-EGFR antibody in first-line, and neither anti-VEGF treatments nor repeat exposure to anti-EGFR treatments subsequently. These trial populations fit with current use of Cetuximab and Panitumumab as has been permitted in the CDF in the UK. The data from these subsequent analyses of these trials fits very well with our experience as UK colorectal oncologists. There is clear benefit to our patients who receive these drugs in first-line therapy. Optimal treatment in the first line setting is absolutely essential as only 45-60% of patients commence second line treatment, even in the most specialist centres in the UK, and only 20-35% commence third-line treatment.

We are concerned that there may have been some confusion in the committee between the benefits of first-line palliative use of EGFR inhibitors in RAS wild type metastatic colorectal cancer with chemotherapy (which represents approximately 90% of their use) and the liver only setting where we are allowed up to 16 weeks of Cetuximab with combination chemotherapy in TA176 to try to downstage to allow potentially curative surgery (which represents approximately 10% of use). In the draft FAD, a broadened liver-only metastatic colorectal cancer indication is permitted by the addition of Panitumumab to Cetuximab for use with either FOLFIRI or FOLFOX. We welcome the potential to best match the specific EGFR inhibitor to the chemotherapy backbone with which it will be given. However, and much more importantly, this recommendation ignores the clear benefit seen in first-line palliative use of these EGFR antibodies with chemotherapy in the vast majority of our RAS wild type metastatic colorectal cancer patients. The life extension (as seen in both published and presented data from clinical trials and from 'real world' audits and data collections) is very significant, as is the improved symptom control and quality of life overall. We believe that the key indication in first-line use of these drugs for our patients must be to improve the quantity and quality of life of those whose metastatic tumours will never become curable via surgery. In all respects other than that of cost, these patients meet end of life criteria. We hope that a new level of discount will be made available by the companies involved through the NICE confidential patient access scheme that will deal with this one unmet criterion.

The CELIM trial demonstrated a favourable long-term survival for patients with initially sub-optimal or unresectable RAS wild type colorectal liver-only metastases who respond to conversion therapy with Cetuximab and either FOLFIRI or FOLFOX chemotherapy and undergo secondary resection. Patients who underwent R0 resection achieved a better median overall survival of 53.9 months than the 21.9 months seen those who did not. The median disease-free survival for R0 resected patients was 9.9 months, and the 5 year overall survival rate was 46.2%. The maximum permitted usage of 16 weeks of EGFR inhibitors when attempting to downstage to resection ignores this CELIM trial data (on which TA176 was based) where complete R0 resections were done in 35 of 105 patients (33%) with the median number of treatment cycles before surgery being 8 (range 4–27). This excludes ongoing use to allow surgery in about half of patients who may ultimately become resectable. We suggest that NICE should allow ongoing use of these drugs with chemotherapy, and do not limit this, with resection attempted when this has become technically possible on repeat imaging, whether that be after 8, 12, 16, 24 or more weeks of combination treatment. Our practice as colorectal oncologists working in a multi-disciplinary fashion with our liver surgeons is not to try to maximally downstage, but to downstage to a point where surgery becomes possible while trying to minimise the degree of liver toxicity from these drugs, and so we limit our duration of use to the least doses of EGFR inhibitors and chemotherapy needed. This stopping rule in TA176 use of 16 weeks affects the outcomes of the whole population with metastatic colorectal cancer treated - we know that the overall survival of patients with liver only metastatic colorectal cancer receiving EGFR inhibitors with chemo who are unable to be resected is the same as those who are receiving palliative intent treatment for more widespread metastatic colorectal cancer from the outset, and hence the cost-effectiveness of their treatment will also be the same.

This FAD will also impact very negatively on the ability of the UK to participate in global clinical trials (where use of anti-EGFR treatments in RAS wildtype metastatic colorectal cancer is assumed to be standard care) in

all of first, second and third line settings and beyond and so further deny UK patients the opportunity to receive novel agents, and minimise innovation across the NHS.
We realise that the NICE assessment of these drugs is based on their current licensed indication, but note that there are other practical issues relevant to their use which impact on this guidance that we feel should be further considered:

(i) In this era of precision medicine, we have sufficiently robust data that the presence of activating mutations in BRAF impact on effectiveness of anti-EGFR antibodies. There is no evidence of that survival outcomes are worse from the use of EGFR inhibitors in patients with BRAF mutant metastatic colorectal cancer (unlike their use in patients with RAS mutant metastatic colorectal cancer), but there is evidence of dysbenefit through exposure to EGFR inhibitor toxicities, inconvenience for patients, additional use of staffing resource and additional drug costs. Hence, as clinicians we advise use in patients with BRAF mutant metastatic colorectal cancer only in the context of clinical trials. This group represents 8-10% of metastatic colorectal cancer patients overall, but are enriched to the higher proportion of 15-20% in the RAS wild type population that this guidance applies to. A recommendation from NICE about use in the BRAF mutant group being restricted to clinical trials would further reduce the population of patients with RAS wild type tumours receiving these drugs, hence further improving cost effectiveness and avoiding unnecessary toxicities.

(ii) Patients whose tumours do not express EGFR on immunohistochemistry (~10% overall) are excluded from use of EGFR inhibitors in this recommendation although we have known from multiple clinical, translational and basic science reports that EGFR expression has no bearing on the probability of response or any other outcome from use of these drugs. This is an old and outdated piece of data in the drug licence, but would exclude metastatic colorectal cancer patients who could potentially benefit if this was applied.

(iii) Our clinical standard of 2 weekly use of Cetuximab (not weekly) reduces costs, chair time and other resource utilisation and positively impacts again on cost effectiveness. In this FAD, NICE modelled cost effectiveness using weekly dosing and not 2 weekly dosing. This reflects the licensed schedule but not our real world practice, including use with combination chemotherapy via the CDF. Historically over the period 2014 – 2016, SACT data shows that three quarters of patients in England and Wales received 2 weekly Cetuximab in first, second and third line. We also know from a poll in December 2016 with responses from 64 consultant colorectal oncologists (including representation from England, Wales, Scotland and N. Ireland) that nowadays over 95% of specialists prescribe Cetuximab in the 2 weekly schedule in the first-line setting for metastatic colorectal cancer.

We strongly and respectfully urge NICE to consider the points we raise in this letter at the forthcoming committee meeting. We passionately wish to optimise the outcomes for our current and future patients with metastatic colorectal cancer in both the palliative and potentially curative settings. We also want to ensure that NICE continues to command the full confidence of the colorectal cancer community in the UK of patients and their families, clinicians and cancer charities. This would be achieved through a recommendation to allow use of both EGFR antibodies with chemotherapy in the whole population of patients with RAS wild type metastatic colorectal, irrespective of potentially curative or definitely palliative intent of treatment. We feel that such a recommendation is critically important given the impact that NICE guidance has not only on our four UK devolved nations, but also widely outside these islands.

Yours sincerely

NHS England submission to NICE re the appraisals of 1st line cetuximab and panitumumab in advanced /metastatic colorectal cancer

January 2017

1. The evidence base has shifted very significantly over the past 10 years for better identifying advanced colorectal cancer patients who are most likely to benefit from cetuximab/panitumuab and this has resulted in narrowing the use of these two drugs in patients according to their tumour RAS status. In the same time frame however, the numbers of patients selected for liver surgery and other types of surgery (eg resection of lung metastases) have increased substantially as imaging and surgical techniques improve, new types of dealing with liver metastases evolve and the morbidity of surgery lessens. Many more patients with metastatic colorectal cancer are thus having radical approaches to their metastatic disease than was evident when the cetuximab/panitumumab trials were performed.
2. The current selection of patients for liver surgery is now much more performed once the maximal response to chemotherapy has been achieved. Thus a definition of operable or inoperable liver metastases prior to the start of chemotherapy is no longer as clinically relevant as it was. As a consequence, NHS England regards this upfront separation of 'inoperable but may become operable' as not being helpful in the current management of patients, especially if there is a cap on treatment duration with cetuximab and panitumumab when the degree of response at that time may not be maximal.
3. A further issue is that chemotherapy in patients even with operable colorectal cancer liver metastases is being used as primary treatment before surgery as surgeons recognise that the ease of surgery and local control of liver disease are augmented by the response to treatment, let alone the benefits of chemotherapy in terms of potentially impacting on any microscopic disease elsewhere.
4. As has been alluded to in paragraph 2 above, a stopping rule is difficult to implement for a treatment that has definitely worked and shrunk liver metastases but has not delivered the opportunity for surgery. Such patients ask the obvious question as to why treatment is being stopped when it is working and a maximal response (and thus the assessment as to radical intervention) has not yet definitely occurred.
5. NHS England thus regards the upfront separation of patients into having disease that is operable/inoperable/inoperable but may become operable as currently artificial and of much less use and relevance than it may have been when TA 176 was produced. It thus urges the NICE Technology Appraisal Committee to consider the patients with metastatic colorectal cancer as a whole rather than splitting the patients up into categories which have changed and are likely to further change as imaging and surgery evolve.

September 2016

1. NHS England recognises that the evidence base that supports the efficacy of these drugs has shifted in line with use of a sequential change in biomarkers: from being trialled in and given to all patients, first the KRAS biomarker allowed identification of greater benefit and more recently the RAS biomarker has further defined the population of patients which gain greatest benefit with cetuximab/panitumumab.
2. The consequence of this shift in the key evidence base is that the best evidence to be assessed currently relies on retrospective analysis of bowel cancer tissue samples from patients entered into trials performed a considerable time ago. Allowances have to be made therefore for this shifting evidence base, now reliant on retrospective analyses of prospectively performed clinical trials.
3. The first issue is that NHS England regards cetuximab and panitumumab as being identical in terms of efficacy and toxicity. A large head to head comparison of these 2 drugs as single agent therapy in chemotherapy-refractory colorectal cancer demonstrated identical efficacy and toxicity. In addition, there is no biological plausibility for considering that their contribution to 1st line combination chemotherapy will be any different.
4. Cetuximab has been in the CDF since 2010. When NHS England took over the CDF and it became national in 2013, it stipulated the use of 2-weekly cetuximab as there was then sufficient evidence of equivalence and widespread use of 2-weekly cetuximab rather than the weekly licensed schedule of administration of cetuximab. This stipulation of course had the bonus for patients of much greater convenience and for hospitals of significantly reducing congestion and waiting times in chemotherapy units. NHS England thus urges NICE to only consider 2-weekly schedules of cetuximab as that is the schedule used now and that is what will only be used in the future in colorectal cancer.
5. NHS England knows that the best evidence for the use of cetuximab in combination with 1st line chemotheraoy for colorectal cancer lies with an irinotecan-based combination. This evidence comes from the CRYSTAL trial and a retrospective analysis for RAS status. The improvement in median overall survival from 20 to 28 months is impressive in itself but also in a disease in which other treatment options follow for most patients and thus potentially blur the benefit in survival of earlier lines of treatment.
6. NHS England also knows that the evidence for the use of cetuximab in combination with 1st line oxaliplatin-based chemotherapy is weak. This because the retrospective RAS analysis of the OPUS trial has few patients and thus no robust conclusions can be made from this evidence alone.
7. NHS England knows that the benefit of adding panitumumab to 1st line chemotherapy lies in the PRIME trial which employed an oxaliplatin-based regimen.

This evidence base also required a retrospective analysis for RAS and resulted in an improvement in overall survival of just under 6 months, again an impressive result in the context of bowel cancer and a setting which usually witnesses several lines of chemotherapy.

8. There is no robust evidence base for the use of panitumumab in combination with 1st line irinotecan-based chemotherapy.
9. In its CDF considerations, NHS England was aware of:
    i) Oxaliplatin-based or irinotecan-based combination chemotherapy regimens offer similar efficacy but differing toxicity (see relevant NICE bowel cancer appraisals). Hence patients and clinicians can debate and choose the most appropriate regimen to use as 1st line chemotherapy
    ii) There is no difference in efficacy and toxicity between cetuximab and panitumumab
    iii) The robust evidence base for cetuximab plus 1st line chemotherapy lies with an irinotecan-based regimen
    iv) The robust evidence base for panitumumab plus 1st line chemotherapy lies with an oxaliplatin-based regimen
    v) As a consequence of i) to iv), when the CDF assessed the retention of cetuximab and panitumumab in the CDF, it recognised the impressive survival benefit of these drugs and was happy to translate the evidence base for both drugs to both oxaliplatin-based and irinotecan-based 1st line chemotherapy regimens. It thus approved the use of either cetuximab or panitumumab In combination with either chemotherapy regimen. In this way, it did not want to impose on patient choice and clinician recommendation but considered this to be a reasonable, practical and relevant interpretation of the evidence base reliant on retrospective analyses of older trials.
10. If NICE approves the use of cetuximab or panitumumab or both, NHS England urges NICE to also adopt similar considerations in order to keep NICE guidance relevant and practical, this to also include use of the 2-weekly schedule of administration of both cetuximab and panitumumab.

[redacted]

[redacted]

[redacted]

September 2016

The clinical effectiveness and cost-effectiveness of cetuximab (review of TA176) and panitumumab (partial review of TA240) for previously untreated metastatic colorectal cancer: a systematic review and economic evaluation

Addendum:

Between 3rd and 4th NICE Appraisal Committee meetings

12th January 2017

Confidential information that is commercial-in-confidence is [redacted].

Contents

1 Background to this MTA

We submitted our final report for this MTA to NICE on 7th August 2015. Cost effectiveness results were presented for two networks: the 'FOLFOX network' comparing cetuximab plus FOLFOX (CET+FOLFOX) and panitumumab plus FOLFOX (PAN+FOLFOX) to a FOLFOX only arm; and the 'FOLFIRI network' comparing cetuximab plus FOLFIRI (CET+FOLFIRI) to FOLFIRI alone. No evidence for panitumumab plus FOLFIRI was available.

Since then, we submitted Addenda on the following dates:

- 9th October 2015
- 26th October 2015
- 4th January 2016
- 18th May 2016
- 5th September 2016
- 28th November 2016

In this Addendum, we update the results we presented in our Addendum of 28th November 2016 for the most recent changes to the PAS offered for cetuximab and panitumumab and we respond to comments from Amgen (19th December 2016) and Merck Serono (undated, but we received 7th January 2017).

2 Response from Amgen (19th December 2016)

Amgen now say they believe that the liver limited subpopulation should not be considered in isolation. Instead, the overall population should be used as the basis for decision-making. We do not give an opinion on this issue, but instead believe that this is best left to the NICE committee.

Previously, the PAS price discount for panitumumab was [redacted]. Amgen now assume a larger price discount of [redacted].

The NICE committee preferred the resection rates that we used, and which are taken directly from the RCTs that underpin this HTA (Section 4.17 October FAD). Nonetheless, in Tables 1 and 2, Amgen now present ICERs given different resection rates for panitumumab+FOLFOX and FOLFOX. Although we do not endorse the use of these rates, we nonetheless find the corresponding ICERs in these Tables to be correct.

With the revised PAS for panitumumab, Amgen now find an ICER for panitumumab+FOLFOX vs. FOLFOX of [redacted] per QALY. We agree with this value (Table 2, p10 of this report).

3 Response from Merck Serono (January 2017)

Previously, the PAS price discount for cetuximab was [redacted]. Merck Serono now assume a larger price discount of [redacted].

Merck Serono correctly say that we presented results separately for the All Patients group and Liver Limited subgroup. They believe that we should have presented results for the All Patients group only, as they consider this to be the only relevant group.

However, in this Addendum, we continue to present results for both the All Patients and Liver Mets subgroups. As discussed above, we leave it to the NICE committee to choose the results they consider relevant.

Merck Serono say the NICE Committee have indicated a willingness to consider the cost of fortnightly dosing of cetuximab. As we have previously stated, we are sympathetic to this assumption.

In Table 1 of their response, Merck Serono provide ICERs for cetuximab+FOLFIRI vs. FOLFIRI given a range of proportions of patients receiving cetuximab weekly and fortnightly. All figures assume a full distribution of patient body surface areas when costing cetuximab acquisition. We agree that these values are factually correct.

Next, they present market research, in which they estimate the proportion of patients that currently receive cetuximab fortnightly vs. weekly in the NHS. They say they surveyed a geographical spread oncologists in England and Wales who prescribe cetuximab for 1st line RAS-wt mCRC patients, and the mean proportion of patients receiving cetuximab fortnightly was 80% and weekly 20%.

With this split, they estimate an ICER of [redacted] per QALY. We agree.

4 Bases for cost-effectiveness analyses

In the current Addendum, we repeat the analyses we performed for our Addendum of 28th November 2016. The only difference is that we have now changed the PAS price discounts for cetuximab and panitumumab as explained in Section 4.1, p7.

As we reported in our Addendum of 28th November 2016, after the 3rd NICE committee meeting on 7th September 2016, NICE asked us, the Assessment Group, to estimate cost-effectiveness separately on each of the following 8 = 2 x 1 x 2 x 2 bases for the All Patients group:

- With and without adjustment for OS for subsequent treatments (2 bases).
- No treatment stopping rule (1 basis), for the reason given in Section 4.4 below.
- Estimating the acquisition cost of cetuximab either based on mean patient body surface area or on the full distribution of patient body surface areas across patients. Similarly for panitumumab, based on patient weights (2 bases).
- Cetuximab given either weekly or fortnightly (2 bases)

They also asked us to estimate cost-effectiveness separately on each of the following 24 = 2 x 3 x 2 x 2 bases for the Liver mets group:

- With and without adjustment for OS for subsequent treatments (2 bases).
- Treatment stopping rules (3 bases):
    - No treatment stopping modelled.
    - 16 week treatment stopping rule with no change in PFS or OS.
    - 16 week treatment stopping rule with adjusted PFS and OS.
- Estimating the acquisition cost of cetuximab either based on mean patient body surface area or on the full distribution of patient body surface areas across patients. Similarly for panitumumab, based on patient weights (2 bases).
- Cetuximab given either weekly or fortnightly (2 bases)

In our Addendum of 18th May 2016, we presented results on the following 20 = 2 x 2 x 5 bases, always assuming that cetuximab is administered weekly:

- All patients and Liver mets subgroup (2 bases).
- With and without adjustment for OS for subsequent treatments (2 bases).

- Treatment stopping rules (5 bases):
    1. No treatment stopping modelled
    2. 8 week treatment stopping rule with no change in PFS or OS
    3. 8 week treatment stopping rule with adjusted PFS and OS
    4. 16 week treatment stopping rule with no change in PFS or OS
    5. 16 week treatment stopping rule with adjusted PFS and OS.

The difference is that we now:

- Also model cetuximab given fortnightly,
- Also assume full distributions across patients for patient body surface areas and weights.
- Model the treatment stopping rule at 16 weeks only, not 8 or 16 weeks, for the reason given in Section 4.4 below.

4.1 Prices of cetuximab and panitumumab

In our Addendum of 28th November 2016, we assumed the following PAS prices:

- Cetuximab: reduction of [redacted] on the list price. Previously, the reduction was 35.6%.
- Panitumumab: reduction of [redacted] on the list price.

Now we assume the following PAS prices:

- Cetuximab: reduction of [redacted] on the list price.
- Panitumumab: reduction of [redacted] on the list price.

4.2 PFS or OS method

This section is a repeat of that given in our Addendum of 28th November 2016.

In the PenTAG model, OS is estimated either by the:

- "OS method", in which OS is estimated directly from that observed in the 1st-line trials of CET and PAN, or
- "PFS method", in which OS is estimated as the cumulative time on 1st-line PFS, 2nd-line PFS and 3rd-line BSC.

NICE have previously requested additional analyses using the OS method only. Therefore, this method is used in all our analyses in this Addendum.

4.3 Body surface areas and weights

This section is a repeat of that given in our Addendum of 28th November 2016.

Theoretically, it is preferred to assume the full distribution of body surface areas and weights across all patients in order to estimate the doses of cetuximab and panitumumab. However, we chose to assume all patients at the same mean body surface area and weight because we found that in the previous 2012 NICE assessment of cetuximab and panitumumab for 3rd-line mCRC, TA242, that cost-effectiveness was insensitive according to whether the means or full distributions were modelled (p161 of our assessment report https://www.nice.org.uk/guidance/ta242/documents/colorectal-cancer-metastatic-2nd-line-cetuximab-bevacizumab-and-panitumumab-review-assessment-report3).

NICE have now asked us to considered scenarios in which the full distributions of body surface areas and weights across patients are modelled. As explained in our original report for this MTA, we originally estimated the mean body surface area from a database of people receiving palliative chemotherapy for CRC (Appendix S3 of Sacco and colleagues (2010)), with 66% males, 34% females, a gender mix reflective of the RCTs for mCRC.

In the current MTA, Merck Serono assumed a mean body surface area of 1.79m^2. In TA242, they also made this assumption. They further cited the source of this data also as Sacco and colleagues (2010). However, in TA242, we criticised this value as it refers to people with a range of cancers (p161 of our report). To be more precise, we chosen the mean of 1.85m^2, as it refers to people receiving palliative chemotherapy for colon cancer with 66% males, 34% females.

To estimate the dose of panitumumab, we also took the mean weight of 74.9kg from data from the study Sacco and colleagues (2010). The publication does not give weights. As stated in our report for TA242, on request, Dr Sacco kindly provided us with the weights data which were used to calculate the published body surface areas.

4.4 Treatment stopping rules

This section is a repeat of that given in our Addendum of 28th November 2016.

NICE previously asked us to consider scenario analyses in which treatment stopping rules are applied. In some analyses, we assumed no impact on PFS and OS of stopping rules. In other analyses, we assumed equal rates of progression and mortality between treatments after treatment stops.

We understand that there is a good clinical reason for a stopping rule to be applied at 16 weeks for the liver metastases subgroup, because this is the time at which patients are assessed for suitability for resection, and a reasonable proportion of these patients are then found suitable for resection.

However, we question the usefulness of our previous analyses of stopping rules for All patients combined, because the great majority of these patients would not be suitable for resection at 16 weeks, and we understand that clinicians would consider it inappropriate to withdraw cetuximab or panitumumab treatment at 16 weeks for these patients. For instance, we understand that this is also the view shared by Amgen and Merck Serono and Dr Saifee Mullamitha, Consultant Medical Oncologist and Dr Vanessa Potter, Consultant Medical Oncologist, who have previously given written statements. After discussions, NICE agreed that we should not present stopping rule scenarios for All patients combined.

Next, for the liver mets subgroup, we now present the 16 week stopping rule only, not the 8 week rule. This is because we recall that at the 3rd committee meeting it was agreed that this scenario would not be considered useful by clinicians.

4.5 Other parameters

This section is as we reported in our Addendum of 28th November 2016.

Other parameters are as in our original report or previous addenda:

- In our base case, we have always assumed the resection rates given in Section 6.1.4.1 of our original report.
- Assume all treatment durations from the RCTs, as provided by Merck Serono and Amgen.
- FOLFOX6, not FOLFOX4.
- eMiT (discounted) prices for FOLFOX rather than BNF prices.

5 Cost-effectiveness results

We stress that all ICERs in this section corresponding to OS adjusted for subsequent treatments should be treated with caution.

Further, these ICERs are not given for CET+FOLFOX because Merck Serono did not perform this analysis on the data from OPUS.

5.1 All patients results

As expected, in all cases, ICERs fall when adjustments are made for imbalances in subsequent treatments between treatment arms, see tables below.

Also as expected, all ICERs fall substantially assuming cetuximab is administered fortnightly as compared to weekly. This is because the mean per patient cost of acquisition and administration of cetuximab is much reduced, whilst the effectiveness of cetuximab is assumed unaltered.

In all cases, cost-effectiveness is insensitive to whether we assume all patients are the same mean body surface area (to estimate the dose of cetuximab) or weight (to estimate the dose of panitumumab) compared to assuming the full distribution across patients of body surface areas and weights.

Table 1. ICERs (£/QALY) for CET+FOLFOX vs. FOLFOX: All patients

Cetuximab administered	Patient body surface areas	OS not adjusted for subsequent treatments	OS adjusted for subsequent treatments
Weekly	**Mean**	[redacted]	n/a
Weekly	**Distribution**	[redacted]	n/a
Fortnightly	**Mean**	[redacted]	n/a
Fortnightly	**Distribution**	[redacted]	n/a

Table 2. ICERs (£/QALY) for PAN+FOLFOX vs. FOLFOX: All patients

Patient weights	OS not adjusted for subsequent treatments	OS adjusted for subsequent treatments
Mean	[redacted]	[redacted]

Patient weights	OS not adjusted for subsequent treatments	OS adjusted for subsequent treatments
Distribution	[redacted]	[redacted]

Table 3. ICERs (£/QALY) for CET+FOLFIRI vs. FOLFIRI: All patients

Cetuximab administered	Patient body surface areas	OS not adjusted for subsequent treatments	OS adjusted for subsequent treatments
Weekly	Mean	[redacted]	[redacted]
Weekly	Distribution	[redacted]	[redacted]
Fortnightly	Mean	[redacted]	[redacted]
Fortnightly	Distribution	[redacted]	[redacted]

5.2 Liver mets results

ICERs for the liver mets subgroup are given in the tables below.

Again, in all cases, ICERs versus the chemotherapy only arms (FOLFOX or FOLFIRI) decrease with the 16 week stopping rule with PFS and OS unadjusted. This is due to the substantial reductions in the costs of drug acquisition and administration for cetuximab and panitumumab.

As expected, for CET+FOLFIRI, ICERs versus FOLFIRI are far higher when PFS and OS are adjusted given stopping rules compared to no adjustment to PFS and OS. This is because we estimate a clear benefit for OS for unresected patients: CET+FOLFIRI vs. FOLFIRI: 37 vs 29 months. The reverse is found for CET+FOLFOX because life expectancy for unresected patients is actually predicted to be slightly higher for the FOLFOX arm than CET+FOLFOX. ICERs for PAN+FOLFOX vs. FOLFOX increase only slightly when PFS and OS are adjusted given stopping rules compared to no adjustment to PFS and OS for the following reason. We estimate only a slight benefit of PAN+FOLFOX over FOLFOX for the liver mets group for resected and non-resected patients: estimated mean OS 43 vs. 39 months. When the resected patients are removed, we estimate only a very small benefit of PAN+FOLFOX: 38 vs 35 months.

As expected, the ICERs for CET+FOLFIRI vs. FOLFIRI decrease slightly when adjustment is made for imbalances in subsequent treatments between treatment arms because the adjustment is predicted to increase slightly the difference in life expectancy between treatment arms. However, the ICERs for PAN+FOLFOX vs. FOLFOX increase because after adjustment for imbalances, we expect a smaller benefit of PAN+FOLFOX compared to FOLFOX.

Table 4. ICERs (£/QALY) for CET+FOLFOX vs. FOLFOX: Liver mets

Cetuximab administered	Stopping rule	Patient body surface areas	OS not adjusted for subsequent treatments	OS adjusted for subsequent treatments
Weekly	None	Mean	[redacted]	n/a
	None	Distribution	[redacted]	n/a
	16 weeks PFS & OS unchanged	Mean	[redacted]	n/a
	16 weeks PFS & OS unchanged	Distribution	[redacted]	n/a
	16 weeks PFS & OS changed	Mean	[redacted]	n/a
	16 weeks PFS & OS changed	Distribution	[redacted]	n/a
Fortnightly	None	Mean	[redacted]	n/a
	None	Distribution	[redacted]	n/a
	16 weeks PFS & OS unchanged	Mean	[redacted]	n/a
	16 weeks PFS & OS unchanged	Distribution	[redacted]	n/a
	16 weeks PFS & OS changed	Mean	[redacted]	n/a
	16 weeks PFS & OS changed	Distribution	[redacted]	n/a

Table 5. ICERs (£/QALY) for PAN+FOLFOX vs. FOLFOX: Liver mets

Stopping rule	Patient weights	OS not adjusted for subsequent treatments	OS adjusted for subsequent treatments
None	Mean	[redacted]	[redacted]
None	Distribution	[redacted]	[redacted]

Stopping rule	Patient weights	OS not adjusted for subsequent treatments	OS adjusted for subsequent treatments
16 weeks PFS & OS unchanged	Mean	[redacted]	[redacted]
16 weeks PFS & OS unchanged	Distribution	[redacted]	[redacted]
16 weeks PFS & OS changed	Mean	[redacted]	[redacted]
16 weeks PFS & OS changed	Distribution	[redacted]	[redacted]

Table 6. ICERs (£/QALY) for CET+FOLFIRI vs. FOLFIRI: Liver mets

Cetuximab administered	Stopping rule	Patient body surface areas	OS not adjusted for subsequent treatments	OS adjusted for subsequent treatments
	None	Mean	[redacted]	[redacted]
	None	Distribution	[redacted]	[redacted]
Weekly	16 weeks PFS & OS unchanged	Mean	[redacted]	[redacted]
	16 weeks PFS & OS unchanged	Distribution	[redacted]	[redacted]
	16 weeks PFS & OS changed	Mean	[redacted]	[redacted]
	16 weeks PFS & OS changed	Distribution	[redacted]	[redacted]
	None	Mean	[redacted]	[redacted]
	None	Distribution	[redacted]	[redacted]
Fortnightly	16 weeks PFS & OS unchanged	Mean	[redacted]	[redacted]
	16 weeks PFS & OS unchanged	Distribution	[redacted]	[redacted]
	16 weeks PFS & OS changed	Mean	[redacted]	[redacted]
	16 weeks PFS & OS changed	Distribution	[redacted]	[redacted]

5.3 Uncertainty in cost-effectiveness

Given that the deterministic cost-effectiveness results vary considerably, there is clearly substantial structural uncertainty. We did not perform probabilistic sensitivity analyses because parameter uncertainty represents only a portion of total uncertainty. We consider that PSAs would not help the NICE committee in its decision making processes.

However, we can say qualitatively that parameter uncertainty is greatest for CET+FOLFOX vs. FOLFOX because OPUS was a relatively small trial, and parameter uncertainty is much greater for the liver mets subgroup compared to all patients, as it represents only about 25% of all patients.

5.4 End of Life criteria

We maintain that our discussion of End of Life in our Addendum of 18th May 2016 remains valid because none of the analyses new to this Addendum concern life expectancy. Instead, they concern only drug acquisition costs.

5.4.1 All patients

The most recent NICE committee found that the EoL criteria are satisfied in the All patients group (Section 4.25 FAD of October 2016).

However, in our Addendum of 18th May 2016, we claimed that we found the EoL criteria for life expectancy of the comparator < 2 years and incremental life expectancy of treatment > 3 months is satisfied only for CET+FOLFIRI vs. FOLFIRI for all scenarios in which OS is adjusted for subsequent treatments. It is not satisfied for CET+FOLFOX vs. FOLFOX or PAN+FOLFOX vs FOLFOX. In Table 7 below, we reproduce the figures that remain relevant.

Therefore, we disagree with Section 4.25 of the suspended NICE FAD of October 2016.

Table 7. Life expectancy (years) by treatment: All patients

	OS not adjusted for subsequent treatments		OS adjusted for subsequent treatments	
	Life expectancy FOLFOX or FOLFIRI	**Incr. life expectancy**	**Life expectancy FOLFOX**	**Incr. life expectancy**
CET+FOLFOX vs. FOLFOX	2.35	0.17	n/a	n/a
PAN+FOLFOX vs. FOLFOX	2.35	0.50	2.18	0.67
CET+FOLFIRI vs. FOLFIRI	2.10	0.80	1.82	1.08

Key: black shading indicates that the criterion is not satisfied, white shading that the criterion is satisfied. n/a represents scenarios for which the information is unavailable

5.4.2 Liver mets subgroup

The most recent NICE committee found that the EoL criteria are not satisfied in the Liver Mets subgroup (Section 4.28 FAD of October 2016).

We agree, and as explained in our Addendum of 18th May 2016, we found that the EoL criterion for life expectancy of the comparator < 2 years was not satisfied in any scenario.

6 References

Sacco JJ, Botten J, Macbeth F, Bagust A, Clark P. The average body surface area of adult cancer patients in the UK: a multicentre retrospective study. PloS one. 2010;5(1):e8933. http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0008933