NICE Health Technology Appraisal of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer

On behalf of Merck Pharmaceuticals, I wish to give Notice of Appeal with regards to the NICE Technology Appraisal for bevacizumab and cetuximab in the treatment of metastatic colorectal cancer (mCRC). Details of the NICE defined requirements of an appeal are detailed below:

The aspect of the guidance to the NHS or appraisal process being appealed against:
The contents of sections 1 - 4 of the NICE FAD consider Erbitux as a second line treatment option. Section 4.1.7 (NICE FAD) states the need for comparative data against second line treatments (FOLFOX) and information of best supportive care (BSC). We consider comparisons versus FOLFOX as inappropriate, and that the information used by NICE of best supportive care (BSC) to be taken from a second line setting, and an overestimate biased against Erbitux. We consider Erbitux as a third line treatment option and believe that NICE have misinterpreted the position of Erbitux within the 1st, 2nd and 3rd line treatment pathway of mCRC.
The grounds for appeal:
"The institute has prepared a FAD which is perverse in the light of the evidence submitted"
The basis for the appeal:
Marketing authorisation for Erbitux was granted in 2004 and states, "Erbitux in combination with irinotecan is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer after failure of irinotecan-including cytotoxic therapy". When Erbitux marketing authorisation was granted (June 30th 2004), Technical Appraisal (TA) 33[1] was the current NICE guidance in force which recommended irinotecan as a single agent for the second line treatment of mCRC. NICE provided guidance for the use of irinotecan in combination with 5FU (FOLFIRI) in the first line setting in August 2005 (TA 93)[2]. At the time of the Merck submission of evidence for Erbitux in mCRC to NICE, irinotecan was not NICE approved as a first line treatment. Taking into account UK treatment practice and NICE guidance, the wording of the Erbitux SPC could only be construed as a third line treatment option in mCRC up until August 2005. Despite NICE TA 93 being issued in September 2005, patients in the UK still receive either 5FU (iv or oral) in 48% of cases or FOLFOX in 44% of cases. FOLFIRI is used in 9% of cases as a first line treatment option (A+A market research data)[3]. Therefore Erbitux in combination with irinotecan can still only be regarded as a third line treatment option. Merck pharmaceuticals do not intend to market Erbitux as a 2nd line option in the NHS until further clinical data and a 2nd line marketing authorisation is received. The well accepted treatment pathway would therefore remain as treatment with FOLFOX then FOLFIRI before Erbitux in combination with irinotecan would be introduced. At this point in time there is no other licensed, NICE approved or current standard treatment for patients in the third line setting. We believe comparisons made by NICE with regards to FOLFOX and the use of BSC data taken from Cunningham et al[4], Rao et al[5] and Barni et al[6] of best supportive care (BSC) are inappropriate and biased against Erbitux. In the third line setting, when Erbitux is given to a defined group of patients who, the data demonstrates, will attain the maximum benefit, we show that Erbitux is a cost effective treatment option.

Content of Appeal:

1. **Position of Erbitux within the treatment of mCRC.**
2. **NICE estimation of Best Supportive Care mean survival benefit.**
3. **The need for a third line treatment in mCRC.**
   a. **Clinician perspective.**
   b. **Patient perspective.**
4. **Proposed criteria for the use of Erbitux within the treatment pathway of mCRC.**

a. **The use of Erbitux as a third line treatment; continuation rule.**

5. **Erbitux clinical data.**
6. **Erbitux cost effectiveness data.**
7. **Erbitux budget impact.**
8. **Proposed Merck partnership with the NHS to audit the use of Erbitux, and ensure consistency with NICE guidance.**
9. **Clinical advocacy for the availability of Erbitux to the NHS and willing ness to audit.**

Key Points:

- We believe that the most appropriate position for Erbitux is as a third line treatment given the evidence presented.
- FOLFOX and FOLFIRI are the most appropriate first and second line treatment options currently available (not always in that order), and Erbitux in combination with irinotecan would be an appropriate third line option.
- Comparisons made by NICE with regards to FOLFOX and the use of BSC data taken from Cunningham et al[4], Rao et al[5] and Barni et al[6] of best supportive care (BSC) are inappropriate and biased against Erbitux.
- The rapid recruitment to the MABEL[7] study in the UK (148 patients in one year), together with the established use of Erbitux in combination with irinotecan in other European countries demonstrates the need for a third line treatment option.
- Information from oncologists and patients demonstrates that a third line treatment option is important to them.
- We propose strict eligibility and treatment continuation criteria be applied to the use of Erbitux in treating mCRC to ensure that only those patients identified as those who can benefit most actually receive the treatment.
- When the patients identified as those who can receive the most benefit receive Erbitux in combination with irinotecan, on average these patients go on to achieve a further 16.59 months of life.
- When strict criteria for the use of Erbitux in combination with irinotecan is applied, a cost per incremental Quality Adjusted Life Year (QALY) of £22,733 can be achieved.
- To ensure that the NICE criteria for the use of Erbitux is applied in the NHS, Merck Pharmaceuticals would be willing to partner with local hospitals, PCT's and Cancer Networks to audit the use of Erbitux and report findings to NICE.
- In personal communication with several NHS physicians who treat mCRC, Merck Pharmaceuticals have received confirmation that auditing the agreed use of Erbitux would be feasible and supported in the NHS if Erbitux would be available.

1. Position of Erbitux within the treatment pathway of mCRC

The Erbitux SPC states:

"Erbitux in combination with irinotecan is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer after failure of irinotecan-including cytotoxic therapy."

Merck pharmaceuticals consider Erbitux as a third line treatment option. We realise that this may conflict with the wording of the Erbitux SPC, in that irinotecan (FOLFIRI) may now be considered as a first line treatment, however we believe that the positioning as stated by NICE, for the second or subsequent treatment of mCRC, is too broad and not consistent given the publication of Technical Appraisal 93. Market research of actual usage of irinotecan does not support the belief that FOLFIRI is now an accepted 1st line treatment option in the UK with just 9% of mCRC patients receiving this treatment[3].

Table 1 below presents the current commonly used treatment options for mCRC in the UK. This is augmented by A+A market research data to provide evidence of the relative usage of each treatment. Where a treatment is not licensed or NICE approved, this has been indicated as such.

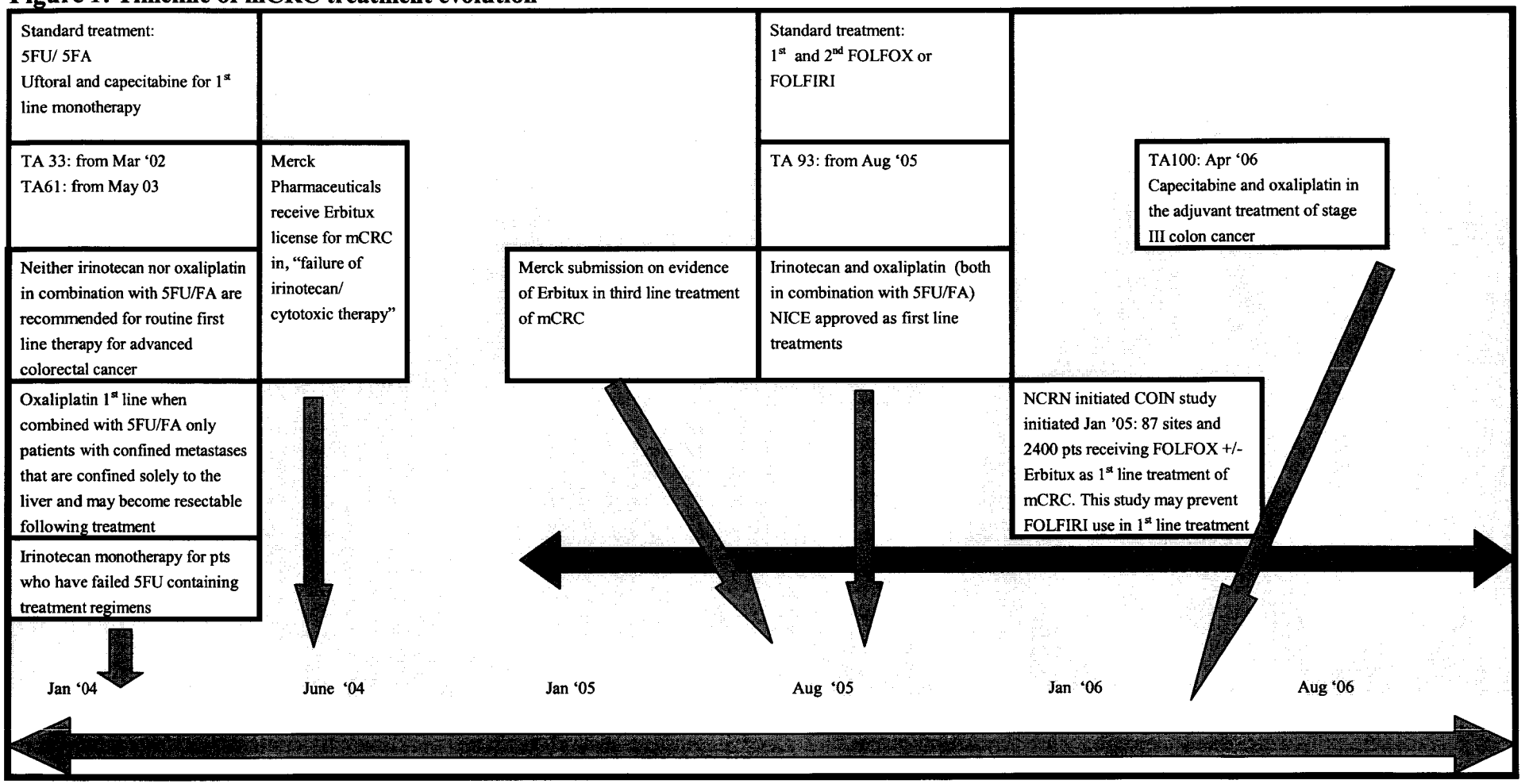
Table 1: Currently used Treatment options for mCRC in the UK (November '05)

Stage of treatment	Irinotecan containing:	Oxaliplatin containing	5FU, Capecitabine UFT oral containing
1st line	• FOLFIRI • CAPIRI* † • Irinotecan monotherapy	• FOLFOX • CAPOX* †	• 5 FU /FA • Capecitabine • Uftoral
1st line percentage	9%	43.9%	47.6%
2nd line	• FOLFIRI • CAPIRI* † • Irinotecan monotherapy	• FOLFOX • CAPOX* †	• 5 FU/ FA † • Capecitabine † • Uftoral**
2nd line percentage	55%	25%	18%
3rd line	No current standard, no licensed treatments, no NICE approved treatments		
3rd line potential treatments	• FOLFIRI † • CAPIRI* † • Irinotecan monotherapy † • Irinotecan in comb with Erbitux ‡	• FOLFOX † • CAPOX* †	• 5 FU/ FA † • Capecitabine † • Uftoral †
3rd line percentage	49%	37%	4%
Other treatments used in the third line setting ***	• Mitomycin C + 5FU † • Clinical trial • BSC		

* The acronymns CAPOX and CAPIRI consist of the replacement of 5FU with capacitabine.
† Not licensed and approved by NICE for treatment.
‡ Not approved by NICE for treatment.

Merck pharmaceuticals submitted evidence for Erbitux to NICE for the third line treatment of mCRC in August 2005. This submission was prior to NICE publication of Technology Assessment 93 on the use of irinotecan and oxaliplatin in the first line setting. Figure 1 below presents a timeline of how treatment has evolved up to the present day.

Figure 1: Timeline of mCRC treatment evolution



Given this information, Merck Pharmaceuticals reaffirm that the most appropriate position for Erbitux is as a third line treatment option, regardless of changes in position of irinotecan from 2nd to 1st line. We believe that FOLFOX is a first or second line treatment for mCRC, and not an appropriate comparator for patients proposed to receive Erbitux in combination with irinotecan in the third line setting.

Merck Pharmaceuticals confirm that Erbitux will only be marketed for the treatment of patients in a third line setting. Please find enclosed a further letter from Mr David Garmon Jones (Managing Director, Merck Pharmaceuticals UK) confirming that the marketing of Erbitux will strictly follow specified criteria as agreed by NICE.

2. NICE estimation of Best Supportive Care

The BOND study represents a treatment environment very typical to that of a non-trial third line treatment environment. This is typified by the previous treatments received by the patients in BOND. The previous treatments received by those patients treated with Erbitux in combination with irinotecan are presented below in Table 2.

Table 2: BOND previous treatments received prior to trial initiation

Number of chemotherapy lines for metastatic disease	
1	18.8%
2	36.2%
≥3	45.0%

Bond is a phase II randomised clinical trial, which provided sufficient information to achieve marketing authorisation in mCRC. However, it is accepted that the ideal clinical data to present to NICE would be of Erbitux in combination with irinotecan against best supportive care (BSC). In the absence of this information, assumptions must be made to put into context the clinical relevance of the data presented in BOND. Given that there is no other licensed treatment for the third line treatment of mCRC, there is no obvious clinical data against which a comparison against Erbitux in combination with irinotecan can be made.

In its original submission in August 2005, Merck Pharmaceuticals calculated an overall survival for BSC in the 3rd line setting of 5.6 months. This figure was derived through two sources:

- The BOND study assessed Erbitux in combination with irinotecan vs. Erbitux monotherapy.
- Cunningham et al[4], a study between active cytotoxic chemotherapy and ASC/BSC in the second-line setting.

To adjust the Erbitux monotherapy arm in the BOND study to be more representative of BSC, the BSC data from Cunningham et al was used to derive a survival hazard ratio of 1.71 which was then applied to Erbitux monotherapy data. The Erbitux monotherapy data was therefore adjusted from 9.64 months mean survival, to 5.64 months mean survival.

This assumption has been validated by data recently presented data by Peeters et al[8]. A phase III randomised clinical trial compared panitumumab, as a single agent to BSC in the third line setting. Data presented suggested a best supportive care median overall survival of 5.5 months.

NICE assumed that BSC provided a mean survival of 7.2 – 9.24 months (0.6 – 0.77 life years), which we believe is an overestimation within the third line setting and more representative of the 2nd line setting.

NICE assessed studies by Cunningham et al [4Error! Bookmark not defined.], Rao etal [5], and Barni etal [6] to derive average survival of BSC. The patient characteristics of patients entering these studies are compared to the BOND study and are presented below in Table 3.

Table 3 Health outcomes in the active/best supportive care trials used by NICE

	BOND (Erbitux + irinotecan arm) [15]	Barni et al [6]	Rao [5]	Cunningham [4]
Patient numbers	111	50	133	90*
Age, years	58	59	62	62
Performance Status	KPS>60	Median 80	ECOG 0-2	WHO 0-2 0: 31% 1: 46% 2: 23%
1 line of chemotherapy	18.8%	100%	4.5%	58%**
2 ≥lines of chemotherapy	36.2%	0%	52%	26%
3 ≥lines of chemotherapy	45.0%	0%	44%	Not reported
Median Overall Survival for best supportive care (months)	NA	6.5	6.1	6.5

* Patients (Cunningham 1998) had received no more than 2-lines of prior 5FU.
** 63% of patients had documented progression on 5FU

This table demonstrates clearly that there are differences in the baseline patient characteristics from the the BOND study to those used by NICE to derive an estimate of BSC. This is demonstrated most clearly in the previous treatment received. When we consider the Erbitux in combination with irinotecan arm of the BOND study, 36.2% of patients had received greater than two previous lines of chemotherapy and 45% greater than 3 lines. This is in contrast to Barni et al (0% and 0% for more than two or three previous lines respectively), Cunningham (26% received more than two previous lines) and Rao etal (52% and 44% received more than two or three previous lines respectively).

In the independent assessment group modelling, no adjustment was made to the survival benefit of BSC estimates to reflect a third line setting, and the different levels of previous treatment received.

Evidence that the methods used by the independent assessment group are flawed lies in results which are inconsistent with randomised controlled data. Within the independent assessment group model, overall survival was estimated for the cetuximab/irinotecan, cetuximab monotherapy and ASC/BSC treatment groups presented below in Table 4.

Table 4 Life years gained results from independent assessment group cetuximab model

Treatment group	**Life years gained**	**Reference**
cetuximab/irinotecan – no stopping rule (ScHARR AUC method)	0.79	ScHARR cetuximab model
cetuximab monotherapy (ScHARR AUC method)	0.73	ScHARR cetuximab model
ASC/BSC (Barni et al.)	0.77	ScHARR cetuximab model

These estimates suggest that BSC survival would be *superior* to cetuximab monotherapy (0.767 life years gained vs. 0.727 life years gained). This implies that cetuximab monotherapy is, objectively, harmful to patients – a result which is clearly contradictory to all available evidence

It is the opinion of Merck Pharmaceuticals that only the Rao et al study is representative of the third line setting in the UK (i.e. previous treatment with two lines of chemotherapy) quoting a BSC of 6.1 months. Without adjustment to BSC survival benefits, we believe that Barni et al and Cunningham are not appropriate for comparison as they present a BSC estimate more reflective of the second line setting.

It is difficult to argue that survival of 5.6 months is an unrealistic assumption given the available information. It is the opinion of Merck Pharmaceuticals that the average survival benefits of BSC is 5.6 months, and at best, 6.1 months as presented by Rao et al.

3. The need for a third line treatment in mCRC

a. Clinician perspective

The need for a third line treatment in mCRC is demonstrated from continued prescription of Erbitux both in the UK, in private health care and other European countries.

Figure 2 below presents market research data of the number of patients treated with Erbitux in the private setting (January 2005 to June 2006).

Figure 2: [redacted]

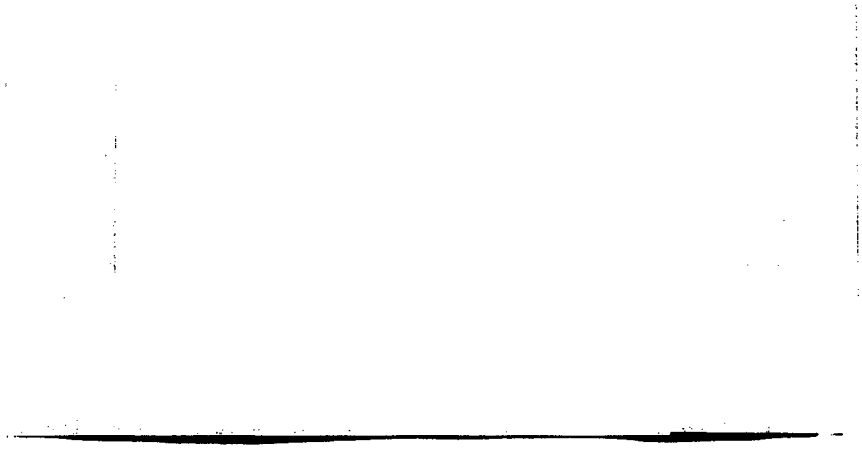
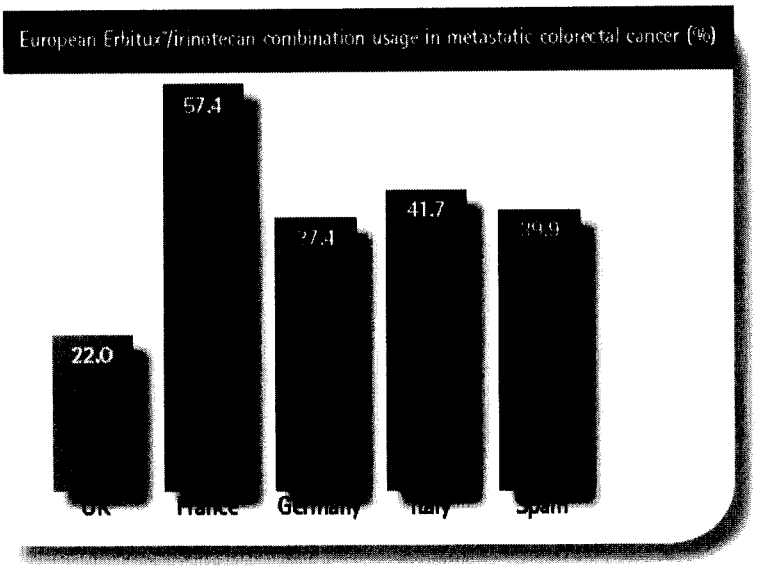


Figure 3 below presents market research data from five major European countries. This information shows how in European countries other than the UK, the introduction Erbitux in combination with irinotecan as a third line treatment option has fulfilled a need for patients with mCRC.

Figure 3: UK vs EU % of 3rd line NHS patients receiving Erbitux in combination with irinotecan (November '05) in the third line setting



NB: Much of this UK usage was accounted for by the MABEL study which has now completed recruitment

This data clearly demonstrates how a clinical need for a third line treatment of patients with mCRC has been fulfilled through the use of Erbitux in other European countries.

3. The need for a third line treatment in mCRC
b. Patient perspective

The value and need for a third line treatment is also demonstrated from the patient perspective. To understand the concerns of actual patients, and how patients balanced competing issues of goals of treatment and toxicity in cancer, Matsuyama et al, [10] completed a literature search from 1980 to present and assessed why patients choose chemotherapy treatment options towards the end of their life. This research incorporated three key papers from the UK; Slevin[11], Davies et al[12 13], and Balmer et al[14]. Matsuyama reported the following findings:

- *Many patients would choose chemotherapy for a small benefit in health outcomes, and for a smaller benefit than perceived by their health care providers for their own treatment.*
- *Adverse effects are less a concern for patients than for their well health care providers.*
- *Patients from the United Kingdom were far more willing to undergo hypothetical toxic cancer treatment than were their doctors and nurses, and choices were consistent after chemotherapy.*
- *Patients value even small benefits greatly, and believe that toxicity is less important than small gains or even the hope of small gains. Oncologists may be the most cognizant of how hopeful people are for small benefits.*

This research is reinforced by the numerous patient testimonials submitted to NICE by Bowel Cancer UK and demonstrates the importance of patient choice, which we understand to be a high priority for the Government.

4. Proposed criteria for the use of Erbitux within the treatment of mCRC

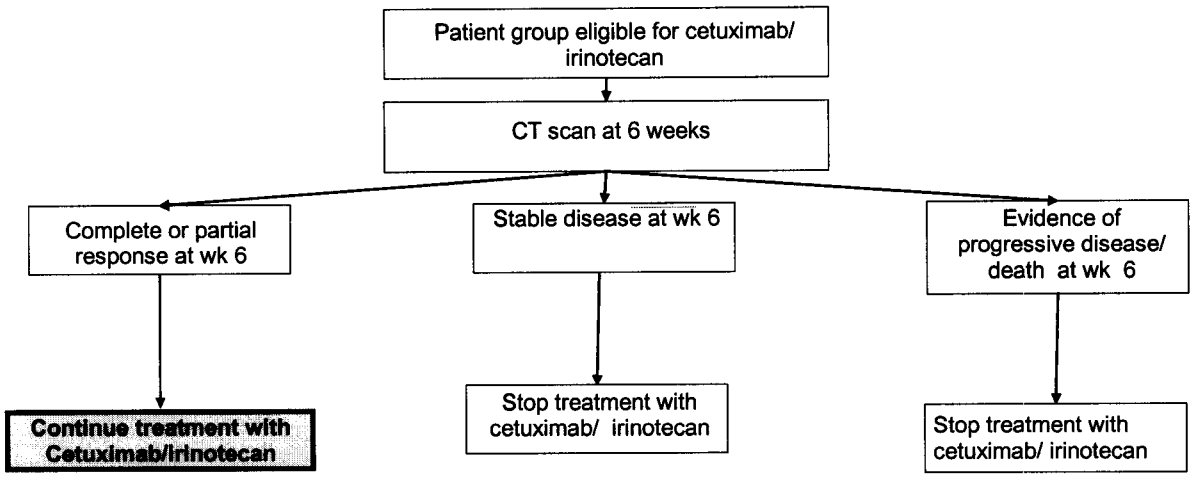
a. The use of Erbitux as a third line treatment option; continuation rule

We would propose that Erbitux is only prescribed as a third line treatment option using the following criteria, (similar to that specified by the AWMSG as detailed below):

- Cetuximab may be considered for use, in combination with irinotecan, in suitable patients (those with epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer) with previously treated metastatic colorectal cancer who are irinotecan refractory; that is patients who progress on irinotecan therapy or have clinical progression within 12 weeks of stopping the irinotecan-containing schedule
- Patients must also have had prior therapy with oxaliplatin (either as adjuvant or metastatic disease treatment) and discontinued oxaliplatin due to progression of disease or cumulative toxicity, *as well as an irinotecan-containing schedule*
- Cetuximab in combination with irinotecan is endorsed only for patients whose tumours are EGFR expressing disease.
- Patients to be considered for cetuximab treatment must be fit for chemotherapy (and therefore must have WHO performance status 0 or 1), and be able to receive irinotecan chemotherapy (see irinotecan summary of Product Characteristics (SPC) for full list of contraindications and special warnings and precautions). There must be no contraindication for irinotecan therapy at the time of start of cetuximab plus irinotecan therapy
- Patients benefiting from cetuximab plus irinotecan combination who discontinue therapy without progressive disease may restart combination cetuximab plus irinotecan on subsequent evidence of progressive disease
- Detailed guidance on the contraindications, special warnings and precautions for use, dosage, supportive medication, side effects and dose modifications for cetuximab can be found in the SPC, for cetuximab (Erbitux ®), which should be consulted at all times
- There is insufficient support for the use of single agent cetuximab following progression on irinotecan-based chemotherapy. The potential benefits are relatively small and therefore the use of cetuximab monotherapy is not supported
- Cetuximab is not presently licensed for use as a first-line agent and its use is not supported in this setting in the NHS

In addition we propose that a continuation rule be applied to ensure that the patients that demonstrate the most benefit are the ones that receive Erbitux. The proposed continuation rule is presented in Figure 4 below.

Figure 4: Schematic of proposed continuation rule



Please note that this is a modified version of the continuation rule submitted in August 2005. This continuation rule is much more restrictive.

In summary, the proposed continuation rule operates as follows:

- Patients appropriate for Erbitux in combination with irinotecan initiate treatment.
- All patients undergo a CT scan at 6 weeks.
- If the CT scan demonstrates a complete or partial response to the treatment, the patient continues to receive Erbitux/ irinotecan for as long as it remains clinically appropriate.
- If the CT scan demonstrates either stable or progressive disease at this time point, the patient would be discontinued from cetuximab/irinotecan treatment.

5. Erbitux clinical data when using aforementioned continuation rule

Information from the BOND[15] study demonstrated that 27 of 218 (12%) patients exhibit either complete or partial response at the 6 week assessment. These patients, on average, then go on to achieve a further 16.59 months of life. Table 5 below presents the number of patients who achieve partial or complete response at a 6 week assessment, and the relative life expectancy of patients with different levels of response.

Table 5: Patient characteristics of patients with differential response

Patient group	N	Proportion of total patient group (%)	Life-expectancy in BOND dataset (with imputations for censored data)
Patients with partial response at 6-week scan	27	12.4%	16.59 months
Patients with progressive disease at 6 weeks	68	31.2%	5.90 months
Patients with stable disease at 6 weeks and grade 2 or above acne-like rash	47	21.6%	15.27 months
Patients with stable disease at 6 weeks but not grade 2 or above acne-like rash	47	21.6%	14.01 months
Patients deceased prior to 6 weeks	9	4.1%	0.81 months
Patients who are not assessed for continuation rule due to lack of complete data	20	9.2%	8.38 months
Total	**218**	**100.0%**	**11.01 months**

6. Erbitux Economic data

When applying strict criteria to the use of Erbitux in combination with irinotecan it is the opinion of Merck Pharmaceuticals that this is an effective and cost effective treatment option for the third line treatment of mCRC.

It is clear from NICE published documentation that there are particular issues in modelling the cost effectiveness of Erbitux in the third line setting. To overcome such issues, Merck Pharmaceuticals have completed further analyses and adapted our economic model to meet NICE's concerns. Issues raised by NICE are:

- Estimates of utility applied
- Estimates of best supportive care applied (BSC)
- The method used by Merck Pharmaceuticals to extrapolate censored data

With regards to the first two issues addressed by NICE, it is the opinion of Merck Pharmaceuticals that there is still significant uncertainty and potential variation of the utility and BSC values to be used.

Please find presented below a series of analyses and incremental cost per Quality Adjusted Life Year (QALY) calculations when using different modelling variations, and estimates of utility and BSC. The primary modelling variation to the Merck Pharmaceuticals economic model is a modification of the extrapolation technique to answer criticisms as presented by NICE. When a model has been used which utilises the original extrapolation method it will be referred to as 'Model A' and alternative extrapolation as 'Model B'. Table 6 below presents these results. All results presented utilise the strict criteria for the use of Erbitux as detailed in section 4 of this appeal.

Table 6: Cost per QALY of Erbitux in combination with irinotecan

Model used	Utility Estimate	BSC estimate OS (months)	Incremental cost	Cost per LYG	Cost per QALY	Threshold value of BSC (months) when Cost QALY is £30K
Model A	0.95	5.64	£8,739.71	£21,941	£23,096	6.76
Model A	0.73	5.64	£8,739.71	£21,941	£30,056	5.66
Model B	0.95 stable & 0.6 prog disease	5.64	£6,886	£23,157	£28,115	5.98
Model B	0.8 stable & 0.6 prog disease	5.64	£6,886	£23,157	£31,818	5.31

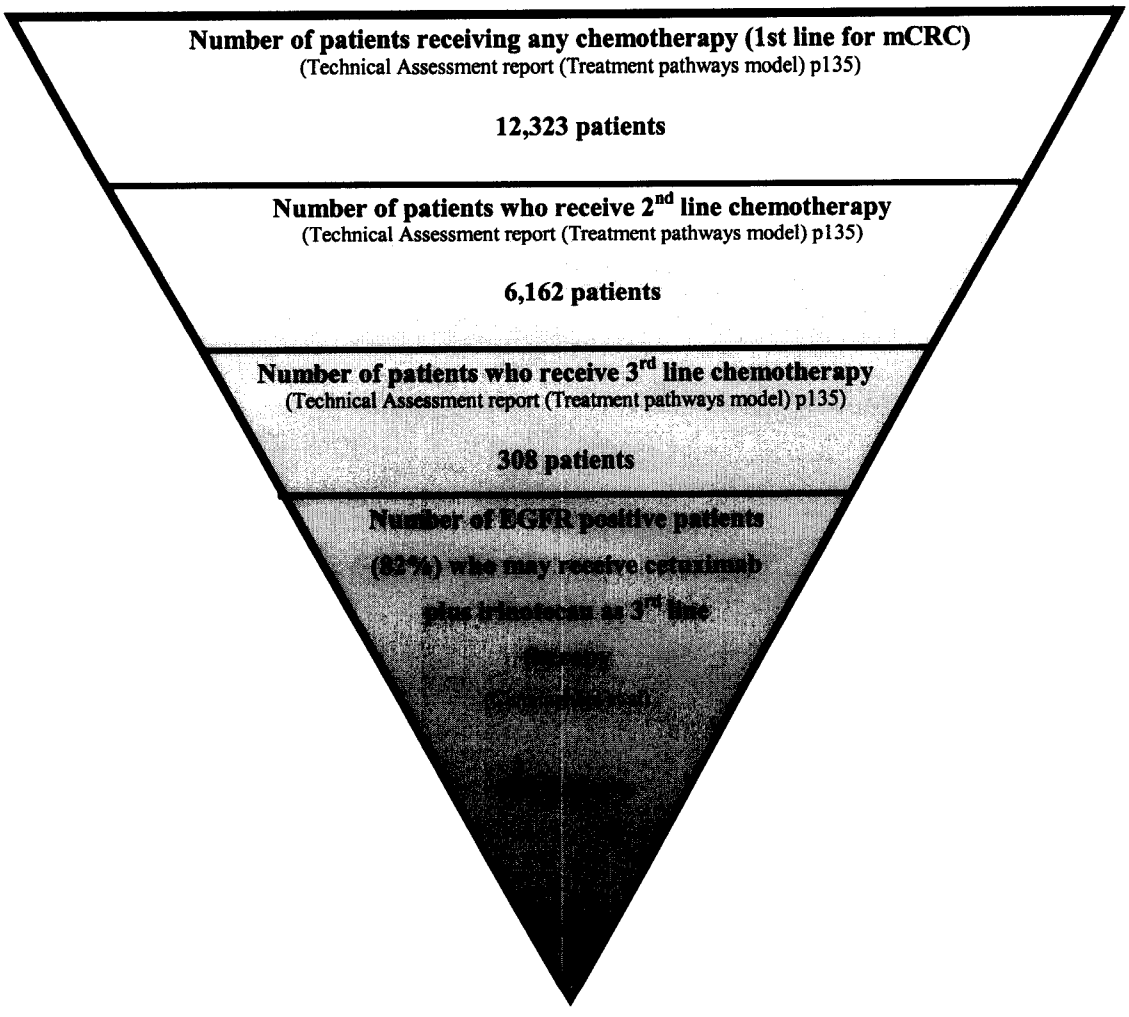
Table 6 presents incremental cost per QALY estimates ranging from £23,096 to £31,818. At best, with Model A, a cost per QALY of £23,096 can be attained when we assume a utility estimate of 0.95 and a BSC estimate of 5.64 months. Given the strict eligibility and continuation rule applied to the use of Erbitux (which continues treatment in patients identified as those who can receive the most benefit), such a utility estimate is not entirely unrealistic. When the utility assumption is lowered to an estimate of 0.73 (as defined from the MABEL study[7]), an incremental cost per QALY of £30,056 can be presented.

Model B uses stricter assumptions and a modified extrapolation technique to answer criticisms as presented by NICE. When we assume a utility value of 0.95 for stable disease and 0.6 for progressive disease, a cost per QALY of £30,000 can be attained when we assume an average BSC survival of 5.98 months. Again, when the utility rate is lowered to 0.8 for stable disease and 0.6 for progressive disease an incremental cost per QALY of £30,000 can be attained when we assume an average BSC survival of 5.31 months.

7. Erbitux budget impact

Figure 5 below presents a schematic of the number of patients treated in the first, second and third line settings for mCRC, and those eligible for Erbitux treatment in the third line setting. Patient numbers presented are taken from the technical assessment report[16] and Cunningham et al[15] to give consistency and clarity to the results as previously presented.

Figure 5: Estimated number of patients eligible for treatment



As described in Figure 5, the eligible population of patients for the third line treatment of mCRC is 253 patients. For the sake of simplicity, budget impact calculations will assume a 100% take up of Erbitux in combination with irinotecan in the third line setting. Estimates per patient based upon the strict eligibility criteria as defined in section 3 of this document are presented below in Table 6:

The total number of vials of Erbitux used in the 218 patients in the combination arm of the BOND Study was 18,849, which is equivalent to an average of 86.46 per patient. The number of vials that would have been used had the continuation rule applied has also been calculated as a total of 9,331 vials which is equivalent to an average of 42.80 per patient (data on file).

Table 7: Overall costs per patient (applying the restrictive 6 weeks continuation rule)

Resource-consuming item	Cost
Cetuximab	£5,842.58
Irinotecan	£1,808.65
Other chemotherapy	£0.00
Drug administration	£2,074.79
Other resources (best supportive care)	£2,381.79
Total	£12,107.79

The total cost presented in Table 7 is calculated as follows:

- The acquisition cost of Erbitux is £136.50 per 100 mg vial (BNF 50).
- In the budget impact calculation, each patient dose is rounded up to the nearest whole vial and the full cost absorbed.
- The dosage regimen of Erbitux is an initial loading dose of 400mg/m^2 in week one followed by subsequent doses of 250mg/m^2 for up to 16 weeks.
- Assuming a body surface area range of 1.6m2 to 1.8m2, the drug cost per whole course of therapy is: **£5,842.58**
  - 30 (12%) patients achieve complete or partial response to treatment at the six week assessment and continue treatment for an average 28.49 weeks:
    - Responder patient cost: **£35,974.12**
    - 12% of population responder cost: **£1,292,174**
  - 222 (88%) patients who do not achieve complete or partial response to treatment at the six week assessment and discontinue treatment:
    - Non responder patient cost: **£8,735.41**
    - 88% of population "non-responder" population cost: **£1,944,852**
  - Average cost of all patients who initiate Erbitux in combination with irinotecan treatment cost:
    - Average cost per patient who initiates treatment: **£12.107,79**
    - Total cost for 253 patients **£3,063,220.2**

Please note that these numbers are subject to rounding errors, and may not be additive.

8. Proposed Merck partnership with the NHS to audit the use of Erbitux, and ensure consistency with NICE guidance

To ensure that the NICE criteria for the use of Erbitux is applied in the NHS, Merck Pharmaceuticals would be willing to partner with local hospitals to audit the use of Erbitux and provide findings to NICE.

This would be implemented through the provision of an audit questionnaire provided to the local NHS. This tool would include criteria for the use of Erbitux as specified by NICE, and implemented with the local hospital upon formulary access. This would require commitment from Merck Pharmaceuticals for the following:

- provide a data capture tool
- resource to collate data
- report data to NICE (including results and hard copies of audit materials)

This would also require commitment from health care representatives for the following:

- to follow NICE specified criteria in the administration and follow up when treating with Erbitux
- to complete the required data collection tool for each new patient treated with Erbitux
- to send the completed data collection tool to Merck Pharmaceuticals for collation of data

9. Clinical advocacy for the availability of Erbitux to the NHS and willingness to audit

To gain further guidance with regards to the proposed strict criteria and willingness to audit the use of Erbitux in the third line treatment of mCRC, Merck Pharmaceuticals consulted a number of Oncologists.

In personal communication with several oncologists who treat mCRC patients in the NHS, Merck Pharmaceuticals has received confirmation that the strict criteria proposed for the use of Erbitux and that auditing the correct use of Erbitux, would be feasible and supported in the NHS if Erbitux would be an available treatment option for them.

The following doctors would agree to follow the strict criteria of patient eligibility and treatment continuation outlined and undergo an audit of their NHS use of Erbitux in combination with irinotecan in mCRC patients. This can be found on the following page:

Table of names has been removed to comply with the Data Protection Act.

---

1 Technology Appraisal 33. National Institute for Health and Clinical Excellence. Guidance on the use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer. March 2002

2 Technology Appraisal 93. National Institute for Health and Clinical Excellence. Guidance on the use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer. August 2008

3 Data on file - A+A Healthcare market research audit Merck KgaA

4 Cunningham et al. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. *Lancet*, 1998; 352:1413-18

5 Rao etal et al. Phase III Double-Blind Placebo-Controlled Study of Farnesyl Transferase Inhibitor R115777 in Patients With Refractory Advanced Colorectal Cancer. Journal of Clinical Oncology 2004; 22:3950-3957

6 Barni et al. A randomised study of low-dose subcutaneous interleukin-2 plus melatonin versus supportive care alone in metastatic colorectal cancer patients progressing under 5-fluorouracil and folates. *Oncology*, 1995; 52 243-245

7 Wilke H et al. MABEL – a large multinational study of cetuximab plus irinotecan in metastatic colorectal cancer progressing on irinotecan. ASCO 2006. Abstract 3549.

8 Peeters et al. Plenary Presentation at the 97th Annual meeting of the AACR, Washington DC, USA. 3rd April 2006. Abstract CP1.

9 [redacted]

10 Matsuyama R, Reddy S, Smith TJ. J Clin Oncol. 2006 Jul 20;24(21):3490-6. Why do patients choose chemotherapy near the end of life? A review of the perspective of those facing death from cancer.

11 Slevin ML, Stubbs L, Plant HJ, et al: Attitudes to chemotherapy: Comparing views of patients with cancer with those of doctors, nurses, and general public. BMJ 300:1458-1460, 1990.

12 Davies E, Clarke C, Hopkins A: Malignant cerebral glioma: Part I. Survival, disability, and morbidity after radiotherapy. BMJ 313:1507-1512, 1996.

13 Davies E, Clarke C, Hopkins A: Malignant cerebral glioma: Part II. Perspectives of patients and relatives on the value of radiotherapy. BMJ 313: 1512-1516, 1996.

14 Balmer CE, Thomas P, Osborne RJ: Who wants second-line, palliative chemotherapy? Psychooncology 10:410-418, 2001

15 Cunningham D *et al.* 2003.Cetuximab (C225) alone or in combination with irinotecan (CPT-11) in patients with epidermal growth factor receptor (EGFR)-positive, irinotecan-refractory metastatic colorectal cancer (MCRC). *Proceedings of the American Society of Clinical Oncology* 22: 252. Abstract 1012 (Updated information presented by Cunningham at meeting).

16 National Instituite for Health and Clinical Excellence. Bevacizumab and cetuximab for the treatment of metastatic colorectal Cancer. Assessment Report produced by ScHARR (p135)