

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

i) whether we consider that all of the relevant evidence has been taken into account.

Merck Pharmaceuticals do not consider that all of the relevant evidence has been taken into account. We should like to:

A. reply to certain specific points in the ACD (*in italics below*), with which we take issue.

B. draw the appraisal committee's attention to additional evidence which supports the use of cetuximab + irinotecan as a 3rd line therapy for mCRC.

A. Reply to specific points in the ACD

4.1 Clinical Effectiveness: Section 4.1.7

"The assessment group identified no studies that compared cetuximab with current standard treatments (FOLFOX or active/ best supportive care)".

We would like to highlight that we do not consider FOLFOX to be a comparator to cetuximab + irinotecan therapy. We have proposed that patients who are eligible to receive cetuximab + irinotecan therapy have already received an oxaliplatin-containing regimen in addition to an irinotecan-containing regimen. Re-challenge with FOLFOX would not therefore be a treatment option for these patients and cannot be considered a comparator treatment in this 3rd line setting.

"The participants included in the studies tended to be younger than the average age of patients receiving chemotherapy in England & Wales; a median age of 56 years was reported in two of the trials and a median age of 59 years in the other two. In all four studies, the populations tended to have good performance status (ECOG 0 to 1 or Karnofsky 80-100)".

Merck Pharmaceuticals challenged these statements in April 2006 when they appeared in the Technology Assessment Report and provided audit data from a total of 2337 UK patients with metastatic colorectal cancer receiving all lines of chemotherapy for mCRC collected in three "waves";

- May – June 2004 (n=791),
- Dec 2004 – Jan 2005 (n=796)
- October - November 2005 (n=750).

The table below summarises the mean age and ECOG performance status for those patients who specifically received 3rd line treatment for their mCRC.

3rd line patients	May – June 2004	December 2004 – January 2005	October - November 2005
n	52	69	49
Mean age (yrs)	62.3	62.8	58.7
ECOG 0 - 1 (%)	74	87	78

This clinical practice (“real life”) audit shows that the mean age of patients receiving chemotherapy in the 3rd line setting is 58.7 years - 62.8 years. In addition, between 74% and 87% of these patients have an ECOG performance status between 0 and 1.

The studies included in the submitted dossier for cetuximab + irinotecan on August 23rd 2005 reflected the epidemiological data gained from these audits:

	BOND trialⁱ	Saltz et al.,2001ⁱⁱ	Seitz et al., 2005ⁱⁱⁱ
n	329	138	24
Median age: yrs [range]	59 [26-84]	56 [26-83]	53 [31-78]
KPS/ ECOG PS [range]	87.8% (80-100)	Median 90%	Median 1 [0-2]

In summary:

- The BOND trial data matches the findings from the audits very well.
- The number of patients in the Saltz and Seitz studies are too small to exactly reflect the audit data - median ages are lower, but the ranges are similar.

We therefore believe that the population included in the clinical trials with cetuximab + irinotecan are representative of the metastatic colorectal cancer population in England and Wales who would be considered for 3rd line treatment.

All three trials showed significant efficacy of cetuximab + irinotecan in the 3rd line clinical practice setting:

- A consistent response rate of 15.2 - 22.9%
- A consistent median PFS of 2.9 - 4.1 months
- A consistent median OS of 8.4 - 8.6 months (excluding the Seitz study since the OS figure given includes 1st line of chemotherapy)
- The BOND study showed that the grade of skin rash is correlated with improved response rate and survival.

4.1 Clinical Effectiveness: Section 4.1.8

“In the RCT there was no statistically significant difference in median overall survival between the treatment groups. The median overall survival was 8.6 months in the cetuximab plus irinotecan arm and 6.9 months in the cetuximab monotherapy arm”

The Appraisal Committee have failed to acknowledge that 56 of the 111 patients in the monotherapy arm subsequently had irinotecan added back into their treatment regimen upon progression of disease. This high level of cross-over into the cetuximab + irinotecan arm, undoubtedly had a negative impact on the statistical significance in survival between the two arms.

B. Additional evidence which supports the use of cetuximab + irinotecan as a 3rd line therapy for mCRC

a) Further publications for cetuximab + irinotecan

Since Merck Pharmaceuticals submitted its dossier for cetuximab + irinotecan on August 23rd 2005, there have been several publications which further support the efficacy and safety results observed in the primary RCT (BOND) and the supporting trials (Saltz + Seitz).

The key population data from these trials are summarised in the tables below:

	Vincenzi et al., 2006^{iv}	Gebbia et al., 2006^v
n	55	60
Median age (yrs) [range]	63 [27-79]	62 [37-81]
ECOG PS	0-2	1-2
Previous Treatment	<ul style="list-style-type: none"> • 58.2% with adjuvant 5FU/LV chemotherapy • 1st line: <ul style="list-style-type: none"> ○ XELOX 69% ○ FOLFOX 31%, • 2nd line: <ul style="list-style-type: none"> ○ FOLFIRI 100% 	<ul style="list-style-type: none"> • 98% Surgery • 90% adjuvant chemotherapy • 1st and 2nd line: <ul style="list-style-type: none"> ○ all with oxaliplatin and irinotecan • Number of lines of previous chemotherapy: <ul style="list-style-type: none"> ○ 65% 2 lines; ○ 35% ≥3 lines;

In summary,

- While the numbers of patients are small, the population data reflect the audit data very well in terms of age and performance status
- These patients were heavily pre-treated.

Importantly, these two trials confirmed the efficacy of cetuximab + irinotecan in the 3rd line setting:

Study	Vincenzi et al., 2006^{iv}	Gebbia et al., 2006^v
ORR % [95% CI]	25.4% [21.7-39.6%]	20% [11-32%]
PFS (months) [95% CI]	4.7 [2.5 - 7.1]	3.1 [1.2 - 9]
OS (months) [95% CI]	9.8 [3.9 - 10.1]	6 [2 - 13]

In addition, the study by Vincenzi confirmed the correlation between acne-like rash and tumour response reported by Cunningham in the BOND study.

Furthermore, Merck Pharmaceuticals has conducted the following international study (MABEL^{vi}) which included 148 patients from 24 centres in the UK.

Study	MABEL
n	1147
Median age [95% CI]	62 yrs [25-84yrs]
Previous treatment lines	
1 line	17%
2 lines	37%
3 or more lines	46%
KPS	Majority 80-100%
ORR [95% CI]	20% [18-23%]
PFS	
12 weeks	61%
24 weeks	34%
36 weeks	17%
48 weeks	6%
OS (months) [95% CI]	9.2 [8.7-9.9]

Therefore the MABEL trial confirms previously reported efficacy parameters for the combination of cetuximab + irinotecan in a clinical practice setting:

- A consistent response rate of 15.2 - 25.4% across all trials
- A consistent median PFS of 2.9 - 4.7 months
- A consistent median OS of 6 - 9.8 months

Further, cetuximab monotherapy has been shown to be active (this is a licensed indication in the USA). It is important to consider the absolute survival in a group of patients being treated largely in the third and fourth-line setting for metastatic colorectal cancer who were progressing at the time of study entry – a group with a very limited life expectancy.

Based on these clinical efficacy data, cetuximab has been granted reimbursement status in the European countries listed in the section below.

b) Positive endorsement of cetuximab + irinotecan as a 3rd line treatment for mCRC from other Health Technology Appraisal Bodies

AWMSG

Following deliberation at the All Wales Medicines Strategy Group meeting on 2nd March 2006, a recommendation was made to the Minister for Health and Social Services in Wales that *“cetuximab, in combination with irinotecan, should be endorsed for use within NHS Wales (with specific restrictions) for the treatment of EGFR-expressing metastatic colorectal cancer after failure of irinotecan-including cytotoxic therapy. Treatment must only be initiated and administered under the supervision of a physician experienced in the use of chemotherapeutic agents^{vii}.”*

On June 14th 2006, the Minister for Health and Social Services in Wales endorsed this decision.

This recommendation and details of the restrictions applied can be found in Reference ^{vii} attached. In brief, patients eligible for treatment must meet the following criteria:

- Irinotecan-refractory disease (i.e. progression of disease within 12 weeks of stopping an irinotecan-containing schedule)
- received and discontinued a prior oxaliplatin-containing schedule
- EGFR-expressing disease
- a performance status of 0 or 1 and not have any contraindications to receiving further irinotecan therapy

Monitoring requirements ensure that non-responding patients do not continue treatment beyond 6 weeks. Further monitoring will be at 6-8 week intervals. Patients will be registered with the Welsh Medicines Partnership within 28 days of starting treatment and outcomes will be audited.

Merck Pharmaceuticals are in agreement with this recommendation and support these restrictions.

Belgium

The “Moniteur Belge” dated 20th June 2006 (No 196) listed cetuximab + irinotecan for patients who have failed irinotecan-containing therapy as a reimbursed medication^{viii}. The reimbursement will come into effect on July 1st 2006.

The conditions associated with this reimbursement are similar to those endorsed by the AWMSG on June 14th 2006.

This recommendation and details of the restrictions applied are attached in the original language together with a précis English translation ^{ix}.

c) Other European countries that reimburse the use of cetuximab + irinotecan for mCRC patients

The table below shows the reimbursement status for cetuximab + irinotecan for mCRC patients in 20 European countries.

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ii) whether we consider the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate.

Merck Pharmaceuticals would like to draw the attention of the Appraisal Committee to the following points:

a) The proposed positioning of cetuximab + irinotecan in the treatment of mCRC following irinotecan failure.

We believe that the positioning proposed by NICE is too broad. The evidence upon which the licence for cetuximab is based clearly positions cetuximab + irinotecan as a 3rd line treatment in the UK setting. The proposed wording by NICE – “use of cetuximab + irinotecan for the second-line or subsequent treatment of mCRC” is misleading.

We would propose that NICE refrain from making a recommendation of the use cetuximab + irinotecan in the 2nd line setting until the evidence from the EPIC study are available *Commercial in confidence information removed*

We would propose that NICE carefully evaluate the “restrictions for use” detailed in the AWMSG document and consider whether approval for use in the UK could be based on such parameters.

b) Comments on the models used by NICE in its decision making process

We agree with NICE that the level of uncertainty in the “indirect analysis” economic model means it should not be used to aid decision making and would request that all reference to this model, and the results it produced, are removed from the assessment report to avoid confusion.

However, we dispute the manner in which evidence from the “threshold analysis” was used, especially the conclusion from the threshold analysis; “it was not possible (for cetuximab) to achieve a cost per QALY of less than £30,000” (ACD Section 4.2.12). Such a conclusion implies that the only parameter of interest to NICE is the survival of patients in ASC/BSC. The results of the “threshold analysis” assume that the costs of ASC/BSC are assumed constant, as are the utility values.

We believe there are two conditions in which cetuximab + irinotecan is a cost effective treatment option (ie: incremental cost per QALY < £30,000) and compatible with the best use of NHS resources:

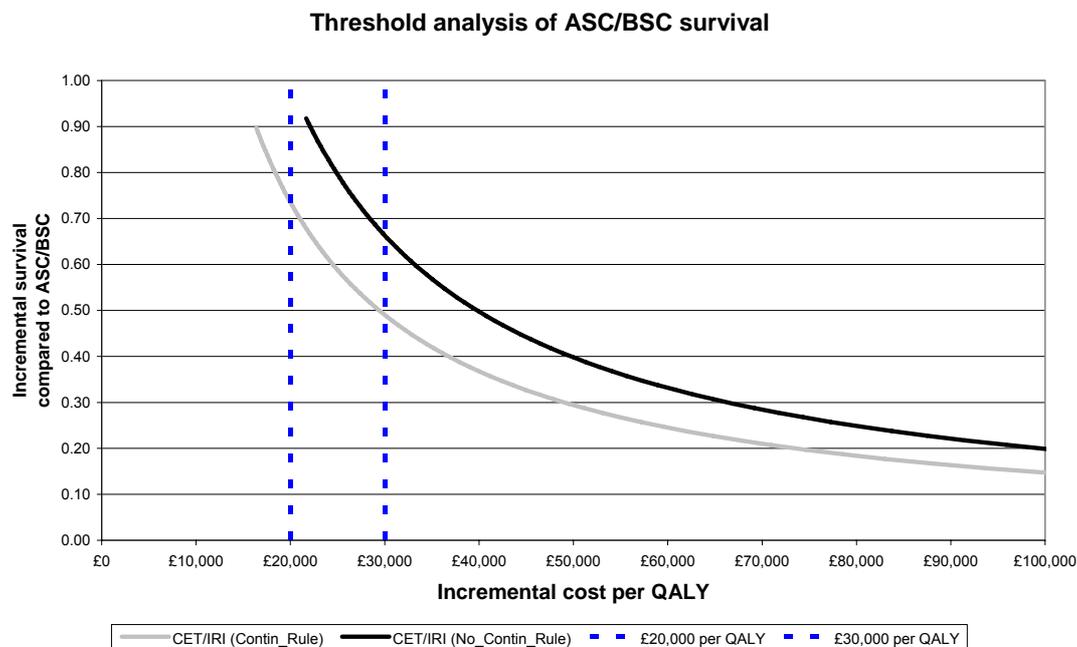
- when a utility value of 0.95 is utilised; and,
- when the survival benefit of ASC/BSC is less than 4.5 months.

The NICE presented “threshold analysis” (ACD section 4.2.11) uses utility values of 0.8 and 0.6 for progression free and progressive disease,

respectively. To assess the impact of such a “threshold analysis”, we modified the Merck cost effectiveness model to replicate NICE analyses and results. We found that if a utility value of 0.95 is used (Petrou and Campbell 1997) it is possible for cetuximab (with or without the continuation rule) to have a cost per QALY of less than £30,000 (see Figure 1).

Figure 1 also shows that when using a utility value of 0.95 in a “threshold analysis”, the survival advantage required over ASC/BSC for cetuximab + irinotecan could be as low as 0.4 years to be cost-effective. Therefore, cetuximab + irinotecan can achieve cost-effectiveness if survival with ASC/BSC is less than 4.5 months (not 2 months as per the ACD; Section 4.3.12). It is difficult to argue that survival of 4.5 months or less is an unrealistic assumption in the same way NICE have assumed that survival of 2 months or less is unrealistic (ACD; Section 4.3.12). Consequently, there is a reasonable likelihood that cetuximab + irinotecan has a cost per QALY of less than £30,000.

Figure 1: Threshold analysis of the Merck cost-effectiveness analysis when a utility value of 0.95 is used



Given the level of uncertainty both in the model used by Merck Pharmaceuticals and the “indirect analysis” provided by the assessment group, NICE appear to rely on a “threshold analysis” to determine whether or not it is possible for cetuximab to be cost-effective; *“The Committee therefore considered the threshold analysis completed by the assessment group”* (ACD Section 4.3.12). However, our assessment of a “threshold analysis” suggests that results are based on a single variable (i.e. survival in ASC/BSC). When other variables are taken into account (e.g. utilities) there is a distinct possibility that cetuximab + irinotecan has an incremental cost per QALY of less than £30,000 and therefore is compatible with the best use of NHS resources.

It is appreciated that there exists a reasonable amount of uncertainty in this decision and so NICE have attempted to minimise the level of uncertainty by using the “threshold analysis”. However, in doing so it is assumed that some uncertain parameters (eg: utility values) are certain. These assumptions have been biased against cetuximab. When these assumptions are relaxed, as in the threshold analysis presented here, it is found that there is a possibility that cetuximab is a cost-effective intervention.

c) Cost implications of non-implementation of cetuximab + irinotecan therapy

A pertinent point was made by Dr Levine on behalf of The Association of Coloproctologists in their submission to NICE; that the cost of non-implementation of cetuximab + irinotecan therapy should not be underestimated. He highlights that a minimum of 2 - 3 hours is taken up by clinicians and a wide variety of other hospital staff in explaining to a fit patient why a licensed drug cannot be used to treat their cancer because of financial reasons, which could be argued is not a good use of NHS resources. Further, the costs of such non-implementation are not taken into account in the analysis of cost effectiveness conducted by NICE.

iii) whether we consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS

Merck Pharmaceuticals do not consider that the provisional recommendations are sound and constitute a suitable basis for the preparation of guidance to the NHS for the following reasons:

Positioning of cetuximab in the treatment pathway

NICE's positioning of cetuximab + irinotecan in the treatment of mCRC is too broad. We would not advocate its use as a 2nd line treatment based on current evidence but would support its use as a 3rd line agent with restrictions applied as detailed in the AWMSG decision.

Incomplete evidence base

The evidence base to support the use of cetuximab + irinotecan in the licensed setting has expanded since the original dossier was submitted. This new evidence consistently supports the efficacy of cetuximab + irinotecan as a 3rd line treatment option in patients who have exhausted other chemotherapy options

Uncertainty surrounding the use of the "threshold model"

There is reasonable uncertainty in assessing the cost-effectiveness of cetuximab. We appreciate that this response does not eliminate this uncertainty, however, it is argued that with a relatively small budget impact (approximately £3.6m for 410 patients rising to £10m for 1125 patients) NICE should feel comfortable making a decision even with this uncertainty when the potential benefits of cetuximab are so highly valued as evidenced by the submissions made by the Patient Groups, expert clinicians and clinician groups to NICE. Furthermore we have shown that there exists a reasonable likelihood that the cost per QALY for cetuximab + irinotecan is less than £30,000.

NICE's opinion of what constitutes "Cost-effectiveness"

NICE appear to have made their recommendation because they do not believe that cetuximab has a cost per QALY of less than £30,000. This belief has two fundamental flaws:

- i) It is a belief based on an interpretation of the "threshold analysis" that has no evidence base – *"This (a cost per QALY of less than £30,000) could only be achieved if survival with ASC/BSC is less than 2 months, which was agreed to be an unrealistic assumption"* ACD Section 4.3.12
- ii) It is a belief built upon a "threshold analysis" which considers only one variable (survival in ASC/BSC) and therefore regards as certain all other variables in the assessment of cost-effectiveness (eg: utility values).

The model proposed by Merck Pharmaceuticals takes more variables into account and is therefore not subject to the high risk of being inaccurate associated with dependency on one particular variable.

We therefore consider that the guidance with respect to cost-effectiveness is based upon an interpretation which lacks any evidence base, i.e. that of a flawed “threshold analysis” and does not, therefore, constitute a suitable basis for the preparation of guidance to the NHS.

Timelines for re-review

We would strongly oppose the recommendation that this TA is considered for review in May 2009. The evidence base and further indications for cetuximab and bevacizumab are rapidly expanding but at a different pace.

We should like to propose that the two technologies are not appraised together in the future, but are subject to individual STAs (as in the case of paclitaxel and docetaxel for early breast cancer). Merck Pharmaceuticals are able to provide NICE with anticipated 2nd and 1st line indication dates in order to plan the timing of these STA's.

ⁱ Cunningham D, Humblet Y, Siena S et al.
Cetuximab Monotherapy and Cetuximab plus Irinotecan in Irinotecan-Refractory Metastatic Colorectal Cancer (MCRC).
N Engl J Med 2004;351:337-45.

ⁱⁱ Saltz L, Rubin M, Hochster H, et al.
Cetuximab (IMC-C225) plus irinotecan (CPT-11) is active in CPT-11 refractory colorectal cancer (CRC) that expresses epidermal growth factor receptor (EGFR).
Proc Am Soc Clin Oncol 2001;20. Abstract 7. Updated information presented at the meeting and subsequent reanalysis of data available as data on file and Erbitux SPC

ⁱⁱⁱ [Seitz JF, Dahan L, Richard K et al](#)
Impact of Cetuximab - Irinotecan salvage combination on overall survival (OS) in refractory metastatic colorectal cancer (mCRC).
Proc Am Soc Clin Oncol 2005:Abstract 3737

^{iv} Vincenzi B, Santini D, Rabitti C et al.
Cetuximab and irinotecan as third-line therapy in advanced colorectal cancer patients: a single centre phase II trial.
Br J Cancer. 2006 Mar 27;94(6):792-7.

^v [Gebbia V, Del Prete S, Borsellino N et al.](#)
Efficacy and safety of Cetuximab/Irinotecan in Chemotherapy-refractory metastatic colorectal Adenocarcinomas: A clinical practice setting, multicenter experience.
Clinical Colorectal Cancer. 2006; 5(6): 422-428.

^{vi} Wilke H, Glynne-Jones R, Thaler J et al.
MABEL - a large multinational study of cetuximab plus irinotecan in metastatic colorectal cancer progressing on irinotecan.
Proc Am Soc Clin Oncol 2006. Abstract 3549. Updated information presented at the meeting.

^{vii} AWMSG Final ratification June 14th 2006

^{viii} Moniteur Belge, June 20th 2006

^{ix} Moniteur Belge, June 20th 2006 – English translation