# CETUXIMAB FOR THE FIRST LINE TREATMENT OF METASTATIC COLORECTAL CANCER

## REPORT BY THE DECISION SUPPORT UNIT

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20th March 2009

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**ACKNOWLEDGEMENTS**

The DSU thanks Graeme Poston and Paul Tappenden for their comments on the appropriate cost of liver resection surgery.

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## ABBREVIATIONS AND DEFINITIONS

| | |
|---|---|
| AC | Appraisal Committee |
| ACD | Appraisal Consultation Document |
| BSA | Body Surface Area |
| CEA | Cost Effectiveness Analysis |
| CTX | Cetuximab |
| DSU | NICE Decision Support Unit |
| ERG | Evidence Review Group |
| FAD | Final Appraisal Determination |
| FOLFIRI | 5-fluorouracil/folinic acid/irinotecan therapy |
| FOLFOX/FOLFOX-4 | 5-fluorouracil/folinic acid/oxaliplatin |
| HRG | Healthcare Resource Group |
| HTA | Health Technology Assessment |
| ICER | Incremental Cost Effectiveness Ratio |
| mCRC | Metastatic Colorectal Cancer |
| Merck | Merck-Serono |
| NICE | National Institute for Health and Clinical Excellence |
| PF | Progression Free |
| PFS | Progression Free Survival |
| PSA | Probabilistic Sensitivity Analysis |
| QALY | Quality Adjusted Life Year |
| STA | Single Technology Appraisal |

# 1 INTRODUCTION

## *1.1 Background*

The appraisal committee requested at its meeting held on January 6th 2009 that Merck provide additional economic analyses for the use of cetuximab as first line treatment of metastatic colorectal cancer. The committee also asked for clarification on how the costs of liver resection surgery are derived in the economic model.

Specifically, the committee requested calculation of the incremental cost effectiveness ratio (ICER) for cetuximab in combination with FOLFOX compared with FOLFOX alone, and cetuximab in combination with FOLFIRI compared to FOLFOX alone, incorporating the following:

- Stopping treatment with cetuximab at 16 weeks (the point at which people are assessed for curative liver resection) for all patients in the analysis, including both those for whom the liver resection is not successful and those assessed as not suitable for liver resection surgery.
- Alternative relative differences in the rates of resection between the two treatment groups, using liver resection rates of 30%, 35% and 43% for the cetuximab plus FOLFOX group and the cetuximab plus FOLFIRI group, and 22% for the FOLFOX alone group.

The manufacturer was asked to provide the effect of each of these factors individually and cumulatively on cost effectiveness incorporating a lifetime horizon, a 5% failure rate for liver resection in both treatment groups and including the application of the proposed patient access scheme rebate of 16% where appropriate.

In addition the manufacturer was asked to clarify the identification of the codes used to calculate the costs of liver resection surgery used in the economic analysis. Specifically they were requested to provide evidence on the HRG codes used to code resection of liver metastases in people with metastatic colorectal cancer. The manufacturer was asked to demonstrate the effect on the cost effectiveness of using

alternative codes to calculate the costs of liver resection surgery for people with metastatic colorectal cancer, and to perform sensitivity analysis around this parameter. The analysis should be undertaken in combination with the other factors detailed above.

## *1.2 Establishing the basecase model*

As highlighted in the ERG briefing note provided for the 3rd appraisal committee on 16th Dec 2008, the model submitted by the manufacturer did not produce the same results as given in their ACD response document (16th October 2008). The model and the results were checked by NICE and the DSU, and it was observed that the model had to have the cetuximab list price corrected (£1.365 base case cost of cetuximab 1mg) for it to produce the deterministic results reported in the ACD response by Merck. With this correction, the ICER that is the starting point for all DSU analyses is £28,024 per QALY gained for cetuximab plus FOLFIRI compared to FOLFIRI, and £33,780 per QALY gained for cetuximab plus FOLFOX compared to FOLFOX (best-case scenario – 43% resection rate). The DSU has not performed a validation of the model.

# 2 MANUFACTURERS REVISED MODEL

## *2.1 Changes to the basecase model*

Merck were asked that all changes and scenarios run through their model included a number of key assumptions. These were that the model assumes a 5% failure rate of liver resection surgery, a lifetime horizon, and that 16% rebate scheme as proposed in Merck's Patient Access Scheme is implemented. Each of these requested changes will be discussed in the following subsections.

### 2.1.1 5% failure rate of liver resection surgery

The manufacturers were asked that the model included a 5% failure rate of liver resection surgery. This has been correctly implemented in both arms of the model, with patients who undergo surgery having a 5% probability of their resection surgery failing, and seeing them progress to the "PF 1st line unsuccessful curative-intent resection" state. In the manufacturer's basecase results, the probability of the failure of liver resection surgery is 5% in both arms. Table 1 summarises the basecase model with the 5% failure rate, as well a 27.8% failure rate in both arms.

**Table 1 - 5% failure rate of liver resection surgery**

| ***Model*** | ***Comparator*** | ***Cost*** | ***QALY*** | ***ICER (cost/QALY)*** |
|---|---|---|---|---|
| **Basecase model (5% failure rate for both arms)** | FOLFOX | £22,366 | 1.35 | |
| | Cetuximab+FOLFOX | £40,096 | 1.87 | £33,780 |
| | FOLFIRI | £26,121 | 1.39 | |
| | Cetuximab+FOLFIRI | £44,474 | 2.05 | £28,024 |
| Basecase model (27.8% failure rate for both arms) | FOLFOX | £22,303 | 1.26 | |
| | Cetuximab+FOLFOX | £41,034 | 1.70 | £41,938 |
| | FOLFIRI | £26,067 | 1.36 | |
| | Cetuximab+FOLFIRI | £45,263 | 1.89 | £36,117 |

### 2.1.2 Lifetime Horizon

In the original basecase model, Merck have assumed a lifetime horizon in their model by running it through 520 weekly cycles (c.10 years with a mean starting age of 60 years). Running the model through 520 cycles allows 95.1% of patients to progress to the dead state in the CTX+FOLFOX arm.

The updated models from Merck have assumed a lifetime horizon in their model by running the model for 1200 cycles (c.23 years with a mean starting age of 60 years). This also contains a rule that stops the model once the average age of the population is 80, so therefore the model runs for 20 years (80-60 years at start). At this point, 98.3% of patients have died in the CTX+FOLFOX arm of the revised model. The model can be run for up to 2000 cycles (c.38 years), and the 80 year old limit can be disabled. The original model and the revised "Treat Until Progression" model were run by the DSU for the FOLFOX comparison with both 1200 and 2000 cycles and with the 80 year age limit both activated and deactivated. The results are summarised in Table 2.

**Table 2 - Time Horizon – DSU Model Runs**

| | ***Cycles*** | ***Age Limit*** | ***Comparators*** | ***Cost*** | ***QALY*** | ***ICER (cost/QALY)*** |
|---|---|---|---|---|---|---|
| Basecase Model | 520 | n/a | FOLFOX<br>Cetuximab+FOLFOX | £22,366<br>£40,096 | 1.35<br>1.87 | £33,780 (basecase ICER) |
| | 1200 | 80 | FOLFOX<br>Cetuximab+FOLFOX | £22,367<br>£40,097 | 1.41<br>2.01 | £29,891 |
| | 1200 | None | FOLFOX<br>Cetuximab+FOLFOX | £22,367<br>£40,097 | 1.42<br>2.03 | £29,396 |
| | 2000 | 80 | FOLFOX<br>Cetuximab+FOLFOX | £22,367<br>£40,097 | 1.41<br>2.01 | £29,891 |
| | 2000 | None | FOLFOX<br>Cetuximab+FOLFOX | £22,367<br>£40,097 | 1.44<br>2.05 | £28,766 |
| Merck Updated | 1200 | 80 | FOLFOX<br>Cetuximab+FOLFOX | £23,729<br>£36,219 | 1.41<br>2.01 | £21,056 (revised |

| | | | | | | |
|---|---|---|---|---|---|---|
| model (16 week stopping rule) | | | | | | basecase ICER) |
| | 1200 | None | FOLFOX<br>Cetuximab +FOLFOX | £23,729<br>£36,219 | 1.42<br>2.03 | £20,708 |
| | 2000 | 80 | FOLFOX<br>Cetuximab +FOLFOX | £23,729<br>£36,219 | 1.41<br>2.01 | £21,056 |
| | 2000 | None | FOLFOX<br>Cetuximab +FOLFOX | £23,729<br>£36,219 | 1.44<br>2.05 | £20,264 |

The results show that running the basecase model for 1200 cycles instead of 520 will see a substantial increase in the amount of QALYs accumulated, and cause the ICER to fall from £33,780 to £29,891 (no age limit). The results also show that the length that the revised model runs in bound by the age limit at 80 years, and not by having the cycle limit set at 1200 or 2000. Removing the age limit and letting the model run for 23 years (1200 cycles) sees 98.78% of patients have died in the CTX+FOLFOX arm. Letting the model run for 38 years (2000 cycles) sees that 99.91% of the population have died in the CTX+FOLFOX arm. Allowing the revised model to run for the full 38 years sees almost all of the population progressing to the dead state, and the ICER has captured all the resulting QALY gains, causing the ICER to fall from £21,056 to £20,264. Therefore extending the time horizon of the model beyond 23 years makes very little difference to the estimated results.

### 2.1.3 Proposed Patient Access Scheme (PAS)

The manufacturer proposed a Patient Access Scheme (PAS) in their response to the NICE ACD. The manufacturer has implemented this scheme by taking the original list price of 1mg cetuximab (£1.365) and reducing this by 16% (£1.147).

**Table 3 - ICERs with PAS scheme applied**

| ***Model*** | ***Comparator*** | ***Cost*** | ***QALY*** | ***ICER (cost/QALY)*** |
|---|---|---|---|---|
| Basecase model (original price £1.365) | FOLFOX<br>Cetuximab+FOLFOX | £22,366<br>£40,096 | 1.35<br>1.87 | £33,780 |
| Basecase model (new | FOLFOX | £22,366 | 1.35 | |

| | | | | |
|---|---|---|---|---|
| 16% reduction in price of cetuximab £1.147) | Cetuximab+FOLFOX | £37,763 | 1.87 | £29,335 |
| Revised 16 week stopping rule model (original price £1.365) | FOLFOX<br>Cetuximab+FOLFOX | £23,729<br>£37,733 | 1.41<br>2.01 | £23,608 |
| Revised 16 week stopping rule model (new 16% reduction in price of cetuximab £1.147) | FOLFOX<br>Cetuximab+FOLFOX | £23,729<br>£36,219 | 1.41<br>2.01 | £21,056 |

Table 3 shows that the price reduction of 16%, when applied to the basecase model, sees the ICER drop from £33,780 to £29,335 for the Cetuximab+FOLFOX vs FOLFOX comparison. When applied to the revised model with the 16 week stopping rule, the ICER drops from £23,608 to £21,056.

## *2.2 HRG Codes*

### 2.2.1 Original Estimate

The manufacturer has revised their estimate of the cost of liver resection surgery. Originally their estimate was a value of £2,271. This value was derived from a weighted average of 2005 HRG codes G02, G03, G04 and G05, weighted by the HES data for the number of Finished Consultant Episodes (FCEs). The values are show in Table 4.

**Table 4 - Manufacturers original estimate of the cost of liver resection surgery**

| ***HRG Code*** | ***Health Care Resource Group*** | ***No. of FCE s*** | ***National Average Unit Cost*** |
|---|---|---|---|
| G02 | Liver – Complex Procedures | 1183 | £7,222 |
| G03 | Liver – Very Major Procedures | 1366 | £3,280 |
| G04 | Liver – Major Procedures >69 or w cc | 1695 | £1,810 |
| G05 | Liver – Major Procedures <70 w/o cc | 5015 | £984 |

| | | | |
|---|---|---|---|
| | **Weighted average, per operation** | | **£2,271** |

In the original estimate, it is clear that with 5015 FCEs, the G05 HRG has a significant impact on the weighted average cost. THE HES HRG* data reports that the majority of these G05 procedures are day case stays (58%), with mean length stay at 3 days (median = 1 day). Also, the majority of patients receiving this procedure are in the 15-59 age group (78%). With the model beginning at age 60, and the evidence shown to the appraisal committee (ACM2 – Presentation) suggesting an average age at diagnosis of 70, it seems inappropriate to include this HRG code in the estimating of the cost of liver resection surgery. The manufacturer has omitted this HRG from the revised estimate. Using the manufacturer's original estimate, if the G05 HRG is removed the weighted average cost of liver resection surgery rises to £3,792.

The NICE Methods Guide[1] highlights National HRG data as being a valuable source of information, however recognises that they may not be appropriate *"…in all circumstances (for example, when the definition of the HRG is broad or the mean cost probably does not reflect resource use in relation to the technology under appraisal). In such case, other sources of evidence, such as micro-costing studies, may be more appropriate."*

A cost-effectiveness analysis of hepatic resection for colorectal liver metastases was published in 2000[2] by Beard et al. The study recorded the actual costs for performing 100 resections at a UK hospital, and estimates the total cost of liver resection surgery for colorectal liver metastases as £6,742 (year:1999). This cost included pre and post-surgery appointments and care-allocations. Whilst this estimate is obviously dated, and likely to have changed, it provides an indication that the cost is likely to be significantly higher than £2,271. The analysis reported that the mean hospital stay required for liver resection surgery was 10.3. Based on length of stay alone, if it is assumed that patients require a similar amount of time in hospital then the 2007 HRG code GA05A (Hepatobiliary Procedures category 5 with CC) may be an accurate estimate of the cost of a liver resection, with a mean length of stay in hospital at 10.34. The national average unit cost for this HRG is £6,024 (2007 HRG).

* http://www.hesonline.org.uk/Ease/servlet/ContentServer?siteID=1937&categoryID=206

### 2.2.2 Revised estimate

The revised estimate provided by the manufacturer is £8,929. This has been estimated by reviewing the OPCS 4.2 codes for these HRGs and concluding that G02 and G03 are the correct HRG codes for liver resection surgery. The manufacturer identifies the proportion of patients that require specific components of surgery, taken from the Adam et al paper, and then uses this to produce a weighted average estimate. Table 5 below explains the manufacturer's methods.

**Table 5 - Manufacturers revised estimate of the cost of liver resection surgery**

| | ***Technique*** | ***Proportion of patients from Adam et al*** | ***HRG code assigned*** | ***Cost of HRG code (2005)*** |
|---|---|---|---|---|
| 1. | Single procedure for liver resection | 100% | G02 | £7,222 |
| 2. | Portal vein embolisation (PVE) prior to resection | 10% | G03 | £3,280 |
| 3. | Radio frequency ablation as part of the procedure | 10% | G03 | £3,280 |
| 4. | Two stage resection including PVE for all | 10% | G02+G03 | £7,222+£3,280 = £10,502 |

Weighted average = G02 + (0.1xG03) + (0.1xG03) + (0.1x(G02+G03)) = **£8,929**

The manufacturer provides two costs for sensitivity analysis, £10,502 (assume all liver surgery requires some additional treatment: G02+G03). £17,724 (assume all patients require a two stage operation with PVE (G02x2 + G03).

Therefore the manufacturer's revised estimate of a cost of liver resection surgery appears to be more robust in its methods, and appears to be a much closer reflection of the actual cost of surgery. The manufacturer provided results using a range of values for the cost of liver resection (£2,271(original), £7,222, £8,929(revised), £10,502, £17,724). These results have been checked and verified by the DSU (See Figure 1

and Figure 2). The DSU has run the model to include its estimates of £3,792 and £6,024 alongside the manufacturer's results. Table 6 summarises the impact on the ICER when applying the revised estimates of the cost of liver resection on the manufacturers original model. Table 7 and Table 8 apply the revised estimates of the cost of liver resection to the updated Merck models (Treat Until Progression and 16 week stopping rule). The updating of the cost from £2,271 to £8,929 sees the ICER of the basecase model rise from £33,780 to £36,489. Applying the revised cost estimate on the updated models sees ICER range (depending on the rate of liver resection) from £21k to £33k in the stopping rule model, and £28k to £48k in the Treat Until Progression model.

**Table 6 - ICERs with revised cost of liver resection**

| ***Model*** | ***Comparator*** | ***Cost*** | ***QALY*** | ***ICER (cost/QALY)*** |
|---|---|---|---|---|
| Basecase model (liver resection surgery cost £2,271) | FOLFOX<br>Cetuximab+FOLFOX | £22,366<br>£40,096 | 1.35<br>1.87 | £33,780 |
| £3,792 (DSU revised basecase) | FOLFOX<br>Cetuximab+FOLFOX | £22,678<br>£40,732 | 1.35<br>1.87 | £34,399 |
| £6,024 (Beard et al estimate) | FOLFOX<br>Cetuximab+FOLFOX | £23,134<br>£41,666 | 1.35<br>1.87 | £35,307 |
| £7,222 | FOLFOX<br>Cetuximab+FOLFOX | £23,380<br>£42,166 | 1.35<br>1.87 | £35,794 |
| **£8,929 (Merck revised)** | FOLFOX<br>Cetuximab+FOLFOX | £23,729<br>£42,880 | 1.35<br>1.87 | £36,489 |
| £10,502 | FOLFOX<br>Cetuximab+FOLFOX | £24,051<br>£43,538 | 1.35<br>1.87 | £37,129 |
| £17,724 | FOLFOX<br>Cetuximab+FOLFOX | £25,529<br>£46,558 | 1.35<br>1.87 | £40,066 |

**Table 7 – Merck 16 Week Stopping Rule Model - Summary of ICERs**

| ***Cost of Liver Resection Surgery*** | ***ICER (cost per QALY) Cetuximab+Folfox compared to FOLFOX*** | | |
|---|---|---|---|
| | ***43% Resection Rate*** | ***35% Resection Rate*** | ***30% Resection Rate*** |
| **£2,271 (original basecase)** | **£19,013** | **£22,896** | **£26,404** |
| £3,792 (DSU revised basecase) | £19,207 | £25,079 | £31,390 |
| £6,024 (Beard et al estimate) | £20,011 | £25,767 | £31,954 |
| £7,222 | £20,442 | £26,136 | £32,257 |
| **£8,929 (Merck revised)** | **£21,056** | **£26,662** | **£32,688** |
| £10,502 | £21,622 | £27,147 | £33,085 |
| £17,724 | £24,222 | £29,372 | £34,908 |

**Table 8 - Treat until Progression Model - Summary of ICERs**

| ***Cost of Liver Resection Surgery*** | ***ICER (cost per QALY) Cetuximab+Folfox compared to FOLFOX*** | | |
|---|---|---|---|
| | ***43% Resection Rate*** | ***35% Resection Rate*** | ***30% Resection Rate*** |
| **£2,271 (original basecase)** | **£24,664** | **£30,900** | **£36,535** |
| £3,792 (DSU revised basecase) | £26,498 | £36,389 | £47,021 |
| £6,024 (Beard et al estimate) | £27,302 | £37,077 | £47,584 |
| £7,222 | £27,733 | £37,446 | £47,887 |
| **£8,929 (Merck revised)** | **£28,347** | **£37,972** | **£48,318** |
| £10,502 | £28,913 | £38,457 | £48,715 |
| £17,724 | £31,513 | £40,682 | £50,539 |

## *2.3 Liver resection rates*

Throughout the manufacturers report, results are provided using liver resection rates of 30%, 35% and 43% for the CTX+ FOLFOX group and the CTX+FOLFIRI group, and 22% for the FOLFOX alone group. These results have been reproduced and verified by the DSU when re-running the model through these different scenarios.

Figure 1 and Figure 2 provide the ICERs for the CTX+FOLFOX vs FOLFOX model, with a range of different costs of liver resection surgery given.

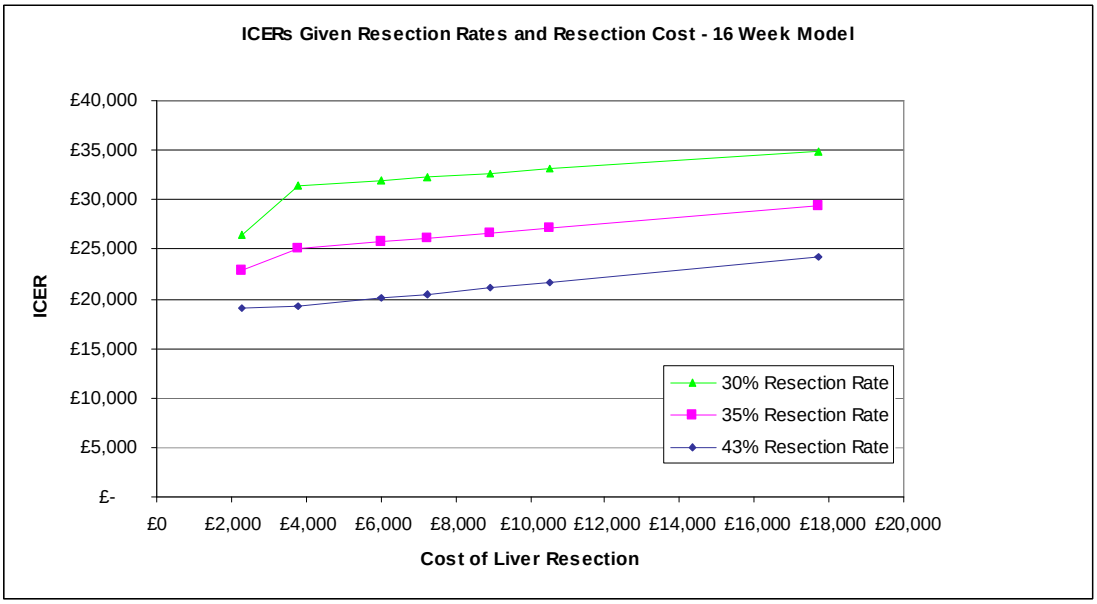


**Figure 1 – Base case ICERs - 16 week model**

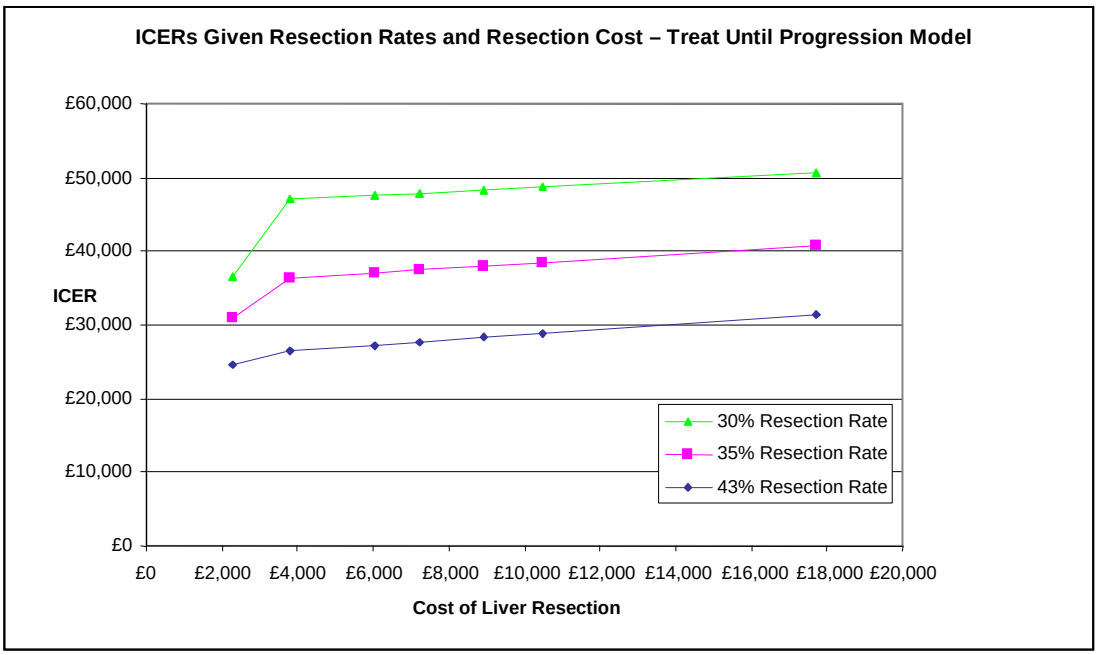


**Figure 2 – Base case ICERs - Treat until progress model**

## *2.4 16 week cetuximab stopping rule*

The appraisal committee requested that the manufacturer submits a revised version of their cost-effectiveness analysis, where treatment with cetuximab is stopped after 16

weeks of treatment. This is the time when patients are assessed for their eligibility for liver resection surgery. The implications of stopping treatment on cetuximab will be seen both through the cost and the effectiveness of the treatment strategies assessed in the cetuximab arms of the model. The appraisal of the methods used by the manufacturer to implement this stopping rule has been split into cost and effectiveness subheadings.

### 2.4.1 Cost

To limit the use of cetuximab in the model, the manufacturer stopped the addition of the costs of cetuximab after 16weeks. However whilst the direct costs of cetuximab treatment have been appropriately removed after 16 weeks, the model has not removed the costs associated with adverse events associated with cetuximab treatment. This issue is discussed further in the following section

### 2.4.2 Effectiveness

The stopping of treatment at 16 weeks should be expected to alter the probability of disease progression compared to a scenario where treatment continues beyond that time. Whilst there is no direct evidence of the degree to which progression probabilities may change, an upper bound may be inferred from the comparator FOLFOX arm of the model.

The manufacturer has made no alteration to the probability of progression when implementing the 16 week stopping rule i.e. patients continue to receive the full benefit of cetuximab even though the treatment has been stopped. The stated rationale for this is:

*"…the relative impact on the ICER of patients surviving in the progression free health state as compared to the impact of patients being referred for potentially curative surgery is minimal and the PFS benefit which may have been accrued by patients in the cetuximab arm had treatment continued to progression has been reduced by the implementation of the resection strategy, hence further reducing the already marginal impact of the PFS benefit for cetuximab on the ICER".*

Merck – Clarification to NICE 26th February

Key to their rationale is the manufacturer's statement that there is minimal impact on the resulting ICER, although no evidence for this is given. Their clarification highlights that their PFS curves for the FOLFOX alone arm closely maps to the PFS curve for the cetuximab arm (see Figure 3). These curves in Figure 3 have been verified by the DSU, although they still give no indication of the impact on the ICER.

The curves show that there is a greater amount of benefit accrued in the cetuximab (pink) arm before the treatment is stopped (eligible patients receive a liver resection). The curves diverge after approximately 30 weeks, where extra benefit is accrued by the patients in the cetuximab arm. Merck considered it not necessary to adjust for efficacy as the probability of remaining in the PFS survival state after week 30 is less than 0.3.

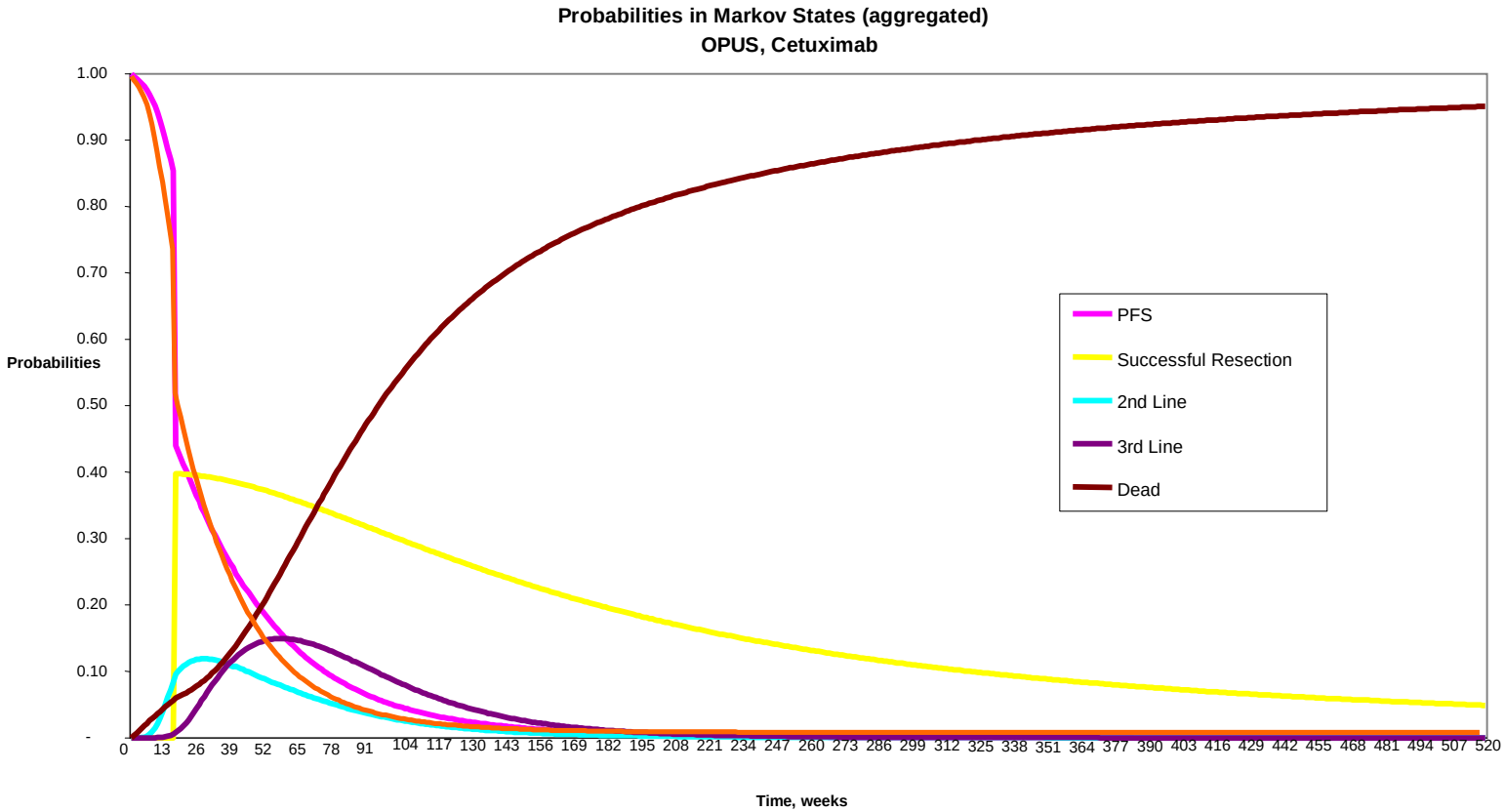


**Figure 3 - Merck Markov State Probabilities for Cetuximab arm, with FOLFOX PFS arm overlayed (orange curve)**

The DSU attempted to implement a stopping rule that saw the patients before 16 weeks follow the Cetuximab PFS curve, but then after 16 weeks switch to following the FOLFOX alone arm. The new curve (labelled New Stopping) is shown on Figure 4. This curve sees patients receive all the benefit for the first 16 weeks, but then the curve follows closely, but underneath the FOLFOX PFS arm. This reflects the impact of applying the same probability of progression as is applied in the FOLFOX arm to a smaller patient cohort. At this point, it is likely that the model is underestimating the corresponding probabilities. This is because at week 16 patients are eligible for liver resection surgery, of which a greater proportion receive in the cetuximab arm compared to the FOLFOX arm (43% of patients in the cetuximab arm receive a liver resection, as opposed to 22% in the FOLFOX arm). Patients who receive surgery are most likely to move to a curative stage (95% of patients, due to the 5% failure rate of the surgery). The curve therefore vertically falls at 16 weeks and then decreases at the steeper rate of the FOLFOX arm, as the model is now drawing from this curve.

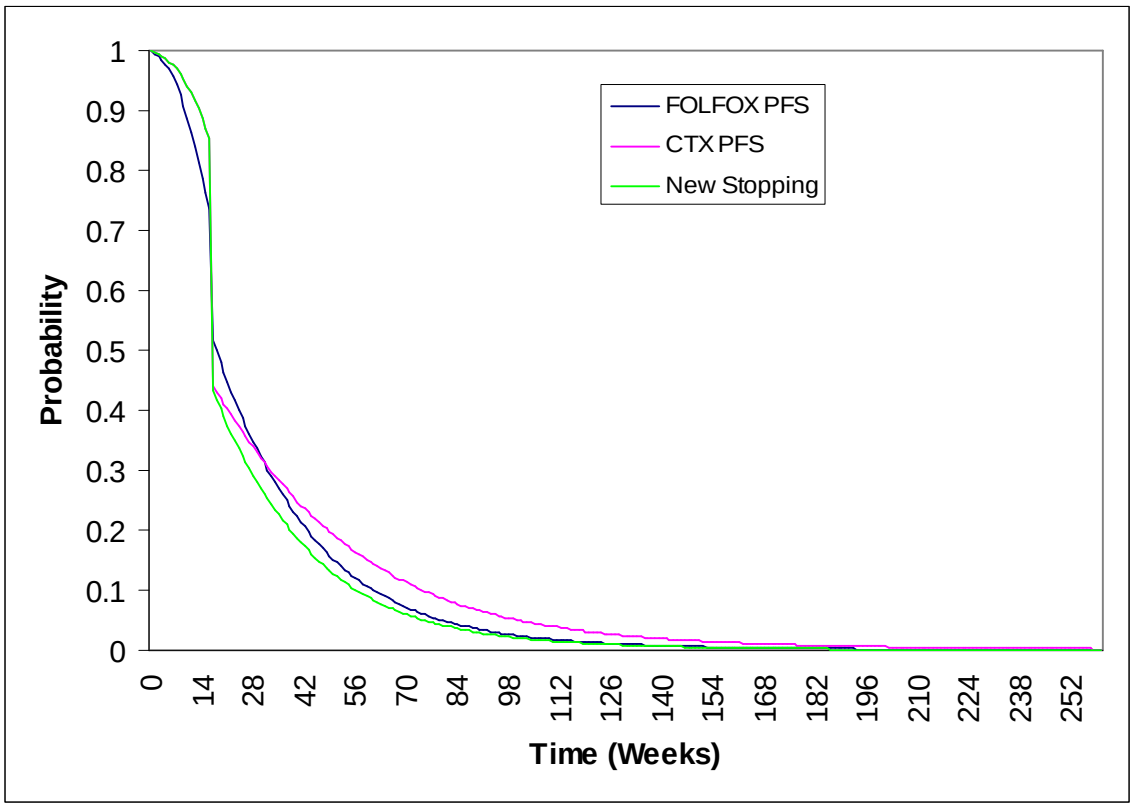


**Figure 4 - DSU stopping rule on efficacy - New PFS Curves (Until 260 weeks)**

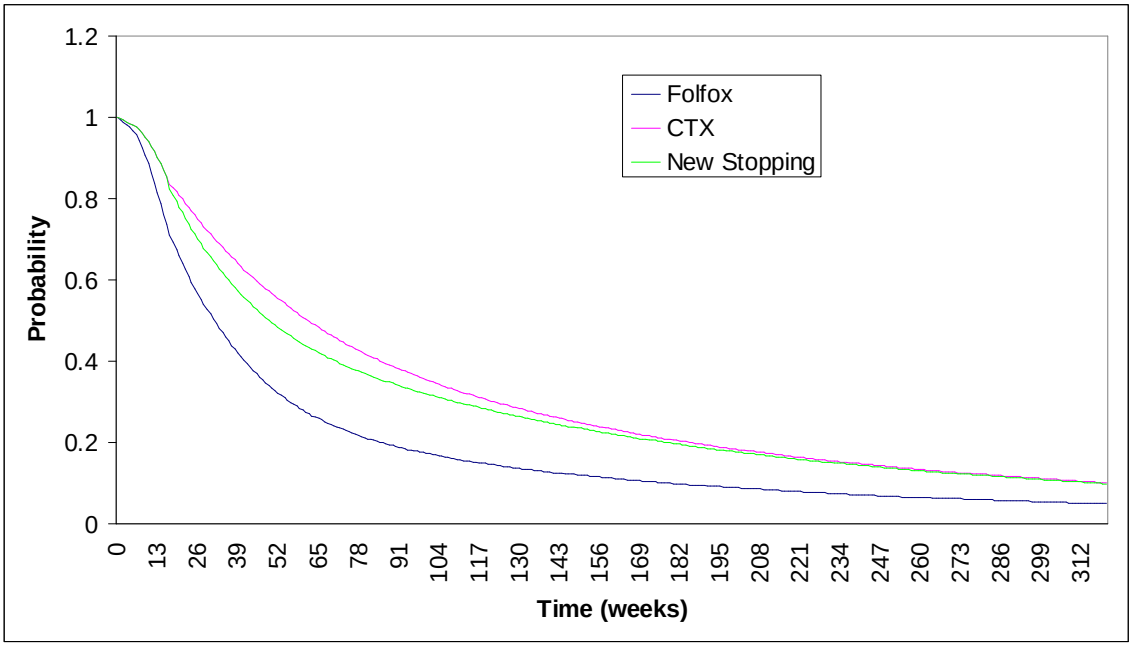


**Figure 5 - Combined PFS and Curative States (Until 320 weeks)**

Figure 5 shows the curves for PFS and curative states added together. Therefore the probability of being in either of these states is highest for the cetuximab arm, with the stopping rule curve slightly lower after 16 weeks, but considerably greater than the FOLFOX arm.

**Table 9 - DSU Stopping Rule Results**

| | ***Comparators (43% Resection rate, £8,929 liver surgery cost)*** | ***Cost*** | ***QALY*** | ***ICER (cost per QALY)*** |
|---|---|---|---|---|
| *Original Model* | FOLFOX<br>Cetuximab+ FOLFOX | £23,729<br>£42,880 | 1.35<br>1.87 | £36,489 |
| *Treat Until Progression(updated original model)* | FOLFOX<br>Cetuximab+ FOLFOX | £23,729<br>£40,544 | 1.41<br>2.01 | £28,347 |
| *Manufacturers 16 week stopping rule* | FOLFOX<br>Cetuximab+ FOLFOX | £23,729<br>£36,219 | 1.41<br>2.01 | £21,056 |
| *New DSU 16 week stopping rule* | FOLFOX<br>Cetuximab+ FOLFOX | £23,729<br>£35,752 | 1.41<br>1.91 | £24,022 |

There is a small reduction in the cost of Cetuximab+FOLFOX with the new DSU 16 week stopping rule. This is because the costs incurred due to adverse events due to cetuximab have been stopped after 16 weeks. The reduction in the cost of the cetuximab+FOLFOX arm has lowered the incremental cost, and subsequently the ICER, compared to if the cost was adjusted using the manufacturers method of just removing the direct drug cost of cetuximab.

Due to the lack of clinical data providing follow-up on patients who have been withdrawn from cetuximab treatment, at least from the clinical trials sourced, the DSU and the manufacturer have been unable to fully implement the stopping rule based on clinical evidence. The manufacturer's assumption that patients receive the full benefit of cetuximab, even once treatment has stopped is the most optimistic way to assume the impact of a treatment stopping rule. The DSU has looked to demonstrate that using less optimistic assumptions, with patients future probabilities of disease progression determined by the comparator arm, the ICER is substantially worse.

## *2.5 Results of CETUXIMAB+FOLFIRI compared to FOLFOX*

The manufacturer was asked to present their results for cetuximab+FOLFOX compared to FOLFOX, and for cetuximab+FOLFIRI compared to FOLFOX. The manufacturer explains that with no consistent comparator arms across the clinical trials, and with no other direct sources of evidence, a direct comparison between cetuximab+FOLFIRI compared to FOLFOX in not possible. To provide a cross-comparison, the costs and QALYs of each appropriate arm of the model have been compared to provide incremental costs and QALYs. As the Patient Access Scheme is only implemented for Cetuximab + FOLFOX, the cost of Cetuximab should be the original value of £1.365 when used in combination with FOLFIRI. However in the manufacturers estimates, they have run the model with the 16% PAS reduction in the price of cetuximab, which is inappropriate with regards to the remit of the PAS. Their results, along with results generated without the PAS applied are summarized in Table 10 below.

**Table 10 - Results of cetuximab plus FOLFIRI compared to FOLFOX**

| ***Model*** | ***Comparators*** | ***ICER (cost/QALY)*** | | |
|---|---|---|---|---|
| | | **Liver resection rate 43%** | **Liver resection rate 35%** | **Liver resection rate 30%** |
| *Original Model (original price of CTX. Liver resection cost £2,271)* | Cetuximab+FOLFOX FOLFOX | £33,780 | £46,053 | £58,754 |
| | Cetuximab+FOLFIRI FOLFIRI | £28,024 | £35,194 | £41,606 |
| *Updated Model – Treat Until Progress (PAS scheme. Liver resection cost £8,929)* | Cetuximab+FOLFOX FOLFOX | £28,347 | £37,972 | £48,318 |
| | Cetuximab+FOLFIRI FOLFIRI | £32,345 | £45,058 | £60,211 |
| *Updated Model – 16 week stopping rule (PAS scheme. Liver resection cost £8,929)* | Cetuximab+FOLFOX FOLFOX | £21,056 | £26,662 | £32,688 |
| | Cetuximab+FOLFIRI FOLFIRI | £23,626 | £30,908 | £39,588 |
| *Updated Model – Treat Until Progress (**original price of CTX**. Liver resection cost £8,929)* | Cetuximab+FOLFOX FOLFOX | £32,288 | £43,563 | £55,684 |
| | Cetuximab+FOLFIRI FOLFIRI | £37,048 | £52,054 | £69,940 |
| *Updated Model – 16 week stopping rule (**original price of CTX**. Liver resection cost £8,929)* | Cetuximab+FOLFOX FOLFOX | £23,608 | £30,099 | £37,076 |
| | Cetuximab+FOLFIRI FOLFIRI | £26,667 | £35,209 | £45,390 |
| ***MANUFACTURERS RESULTS*** *Updated Model - Treat Until Progress (**PAS scheme**. Liver resection cost £8,929)* | **Cetuximab+FOLFIRI FOLFOX** | **£26,641** | **£32,496** | **£37,786** |
| ***MANUFACTURERS*** | **Cetuximab+FOLFIRI** | **£20,990** | **£24,492** | **£27,655** |

| | | | | |
|---|---|---|---|---|
| ***RESULTS***<br>*Updated Model -*<br>*16 week stopping rule*<br>***(PAS scheme**. Liver*<br>*resection cost £8,929)* | **FOLFOX** | | | |
| ***DSU RESULTS***<br>*Updated Model - Treat*<br>*Until Progress*<br>***(Original price of CTX**.*<br>*Liver resection cost £8,929)* | **Cetuximab+FOLFIRI**<br>**FOLFOX** | **£29,669** | **£36,464** | **£42,540** |
| ***DSU RESULTS***<br>*Updated Model -*<br>*16 week stopping rule*<br>***(Original price of CTX**.*<br>*Liver resection cost £8,929)* | **Cetuximab+FOLFIRI**<br>**FOLFOX** | **£22,944** | **£26,929** | **£30,482** |

# 3 SUMMARY AND IMPLICATIONS

## *3.1 Conclusion*

For all the additional documentation submitted by the manufacturer, PSA has not been performed for any of the results. The model requires approximately one day to run full PSA, and so it has not been performed for any of the DSU additional modeling. It is important to highlight that the manufacturer's methods of incorporating a stopping rule on cetuximab treatment after 16 weeks provide the most optimistic results. The manufacturer has based their rationale for not adjusting the efficacy of cetuximab therapy once cetuximab is withdrawn by claiming that the ICER would not be affected. However the DSU's stopping rule highlights that accounting for a reduction in the probability of having progressive free disease will have an impact on the estimated QALYs and see a considerable increase in the ICER, when compared to the manufacturers stopping rule model.

Adjusting the length of the model horizon is unlikely to have a significant impact on the results, and this change, along with the revised cost of liver resection, and the implementation of the liver resection rates and the liver resection failure rate have all been appropriately reported and incorporated. The manufacturer has implemented the patient access scheme as a 16% reduction in the list price of cetuximab, however the manufacturer inappropriately included the PAS scheme applied to the cetuximab + FOLFIRI arm, and so this analysis has been re-run with the original cetuximab cost.

# 4 REFERENCES

[1] Guide to the methods of technology appraisal – National Institute for Health and Clinical Excellence. June 2008
http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf

[2] Beard et al. Hepatic Resection for Colorectal Liver Metastases: A Cost-Effectiveness Analysis. Annals of Surgery. 232(6) 763-776. 2000