Monday 15th September 2009

Kate Moore
Technology Appraisal Project Manager
National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
LONDON
WC1V 6NA

BY E-MAIL

Dear Kate,

SINGLE TECHNOLOGY APPRAISAL –
Bevacizumab in combination with oxaliplatin and either 5-fluorouracil or capecitabine for the treatment of metastatic colorectal cancer

Thank you for providing us with the opportunity to comment on the Appraisal Consultation Document (ACD) for the above appraisal. Please find Roche's response below under the standard headings.

We hope this feedback is useful to support the further deliberations of the Committee.

Yours sincerely,

[redacted]

Roche Products Limited
6 Falcon Way
Shire Park
Welwyn Garden City
Hertfordshire
AL7 1TW

Healthcare Management

Registered Number
100674 London

Tel: 01707
Fax: 01707
Mobile:
E-mail: [redacted]

1. Whether you consider that all of the relevant evidence has been taken into account

No comments

2. Whether you consider that 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

2.1. Comments on the level of innovation of bevacizumab

'As a final consideration, the Committee did not consider bevacizumab represented a sufficiently innovative technology in the treatment of metastatic colorectal cancer because it did not result in a substantial improvement in progression-free or overall survival.' (Second ACD2 paragraph 4.17)

The committee appear to be confusing innovation with degree of clinical benefit. Something could be considered to provide modest clinical benefit and be innovative due the novel attributes of the technology; for instance that it provides an advance in science of treating a disease area. Bevacizumab was the first in an innovative class of drugs that act as anti-angiogenic agents, and the only one to show a statistically significant overall survival advantage in mCRC, which has been demonstrated in both 1st and 2nd line treatment (Hurwitz et al 2004 and the E3200 study). Since its launch in January 2005, bevacizumab has become the standard of care for 1st line mCRC in the vast majority of developed countries.

NICE STA process guide indicates 'the potential for long-term benefits to the NHS of innovation' should be accounted for by the committee. Other factors are also considered such as equity, as these factors are not considered to be adequately captured with the ICER calculation. Hence when considering innovation it is our understanding that this in relation to additional factors that haven't already been captured within the ICER.

Finally the wording in paragraph 4.17 in the ACD2 appears to comment on bevacizumab in mCRC generally rather than solely to the evidence considered as part of the scope of the appraisal (ie oxaliplatin containing regimens). The main source of evidence considered as part of this appraisal is the NO16966 study the result of which are inconsistent with the other pivotal trials of bevacizumab in mCRC, which demonstrated substantial and statistically significant improvement in both PFS and OS. The first pivotal study resulted in a median increase of 4.7 months in OS (Hurwitz et al, 2004) when bevacizumab was added to irinotecan-based therapy in 1st line. The other is the E3200 study which resulted in a median increase of 3 months from the addition of bevacizumab to oxaliplatin-based therapy in 2nd line where patients in the comparator arm had a median survival of only 12.8 months.

2.2. Interpretation of the evidence

The second ACD (refered to from hereon as ACD2) states that *'the Committee noted its earlier conclusions that all of the ICERs with and without the patient access scheme were likely to be underestimates.'* Whilst not explicitly, it appears the committee were referring to the following elements of the economic model:

- Pooling of the XELOX and FOLFOX arms for efficacy
- Adverse Event Costs
- Treatment duration
- PFS utility values
- Operating costs
- Incremental costs associated with administering bevacizumab
- Oxaliplatin price

Roche consider that the conclusion drawn by the committee that the elements above are all favourable to bevacizumab and that therefore all the ICERs are underestimated is not consistent with the evidence.

Whilst it is acknowledged that, as with any appraisal there is uncertainty around the ICERs, we consider the ICER's presented without the APAS to be reasonable central estimates and there are plausible reasons for why these in fact may be overestimates including the fact that no vial sharing has been assumed as well as that a reduction in the price of oxaliplatin would reduce the ICER's without the APAS.

Below, under a separate heading for each element, is the rational behind this statement.

2.2.1. Pooling of the XELOX and FOLFOX arms for efficacy

Referring to the 2*2 analysis excluding patients that had received prior adjuvant treatment:- *'The Committee heard from the manufacturer that the study was designed to pool the XELOX and FOLFOX arms and that interaction testing had been undertaken that demonstrated that pooling was appropriate. However, the Committee noted the original analysis and when the XELOX and FOLFOX arms were subsequently un-pooled the ICER for B-XELOX compared with XELOX increased slightly and the ICER for B-FOLFOX-6 compared with FOLFOX-6 increased markedly.'*

It is incorrect that the ICER for B-XELOX increased when the efficacy was unpooled. Table 3 (replicated below) of Roche's response to the ERG's clarification questions Part III shows that the ICER for B-XELOX vs XELOX decreases rather than increases (see figures highlighted in yellow).

This is consistent with what one might expect since if 'unpooling' the efficacy was to affect the ICER's, then one of the ICER's would increase and the other decrease, reflecting the fact that unpooling would cause the efficacy of one the comparisons to worsen and the other improve. Indeed this is what occurred when the efficacy was unpooled in the earlier analysis (ie the analysis when including patients with prior adjuvant treatment).

Table 3: Summary of ICERs

	Analysis	Intervention	COMPARATOR: XELOX	COMPARATOR: FOLFOX-6
1	Chemo+Bev vs Chemo+-Placebo (all 6 arms)	B-XELOX	£35,912	Dominant
		B-FOLFOX-6		£36,569
2	Chemo+Bev vs Chemo+Placebo (2*2 only)	B-XELOX	**£48,111**	Dominant
		B-FOLFOX-6		£39,771
3	XELOX+Bev vs XELOX+Placebo (2*2 only) FOLFOX+Bev vs FOLFOX+Placebo (2*2 only)	B-XELOX	**£35,662**	Dominant
		B-FOLFOX-6		£62,714
4	2*2 analysis without prior chemotherapy	B-XELOX	£36,006	Dominant
		B-FOLFOX-6		£31,174

The reason for the difference in ICER's seen between analysis 2 and 3 (table 3 above) is that in the 2*2 part of the study the placebo+FOLFOX arm performed implausibly well compared to the other arms in the study, thus reducing the observed difference in survival between the B-FOLFOX and placebo+FOLFOX arms, and when pooled with the placebo+XELOX arm, it also negatively affects the B-XELOX vs XELOX comparison. It was established that this anomaly in the results was as a result of an imbalance in an important prognostic factor, the importance of which was unknown at the time of the study. This point was accepted by the committee and it is noted in the ACD2 that removing the patients that had received prior adjuvant therapy removed this imbalance (see paragraph 4.4; ACD2).

With the imbalance removed there would be no reason to believe that XELOX and FOLFOX would result in different survival outcomes and likewise B-XELOX and B-FOLFOX would also be expected to have the same survival outcomes as each other. As discussed in the ACD2 this is supported by the statistical analysis which showed XELOX to be non-inferior to FOLFOX and no interaction between bevacizumab and the chemotherapy regimen used. This is further validated when comparing the ICERs for analyses 2,3, and 4 (table 3 above) the only instance where the ICER for B-XELOX *versus* XELOX comparison increases is where the placebo+FOLFOX arm including patients with prior adjuvant chemotherapy were pooled with the placebo+XELOX arm thus worsening the assumed treatment effect for B-XELOX vs XELOX.

2.2.2. Adverse event costs

'The Committee was also aware that the costs of adverse events had not been included in the economic model' (paragraph 4.13 ACD2)

This is incorrect. The cost of adverse events are included in the economic model (see pages 138 to 140 in Roche's submission). Hence it is untrue to say that ICER is underestimated as a result of their exclusion.

2.2.3. Treatment duration

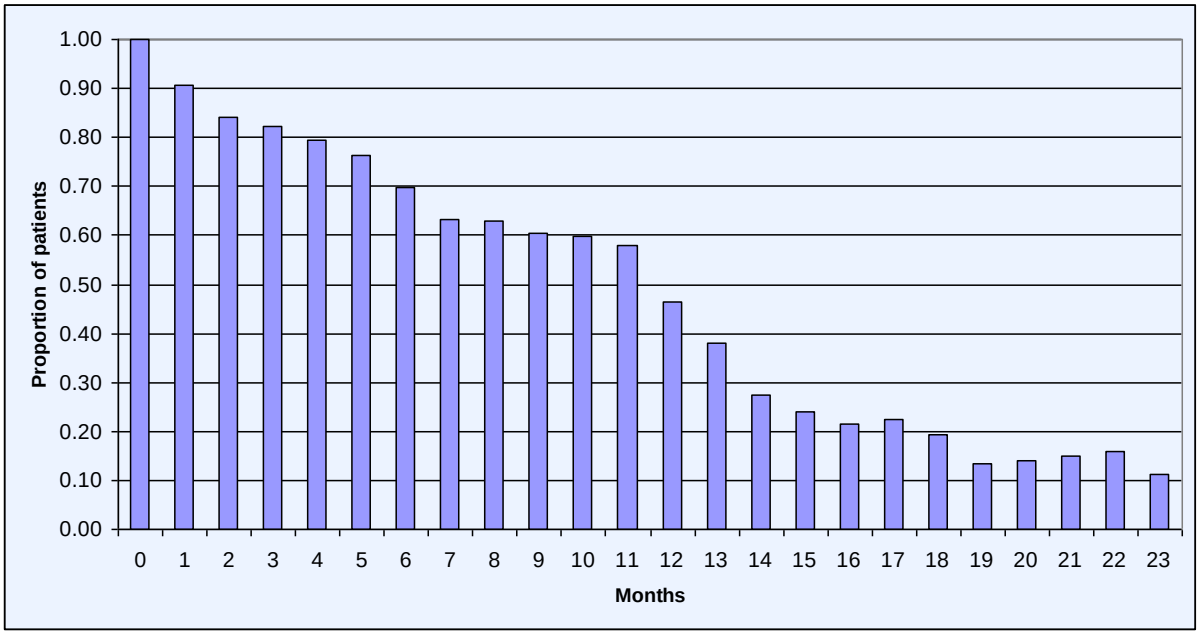
2.2.3.1. Longer treatment duration in clinical practice and the subsequent effect on the ICER

Paragraph 4.12 the ACD states: *'The Committee noted that stopping oxaliplatin treatment 1 month before the other treatment agents or receiving bevacizumab for 1 month after oxaliplatin treatment had increased the ICERs. It noted that both analyses assumed no increase in progression-free or overall survival. However, the Committee considered that if such increases in progression-free and overall survival were accounted for, the extra bevacizumab costs would outweigh any additional survival benefits of bevacizumab, given the previously noted modest impact on progression-free and overall survival'…. 'in practice bevacizumab treatment would be expected to continue until disease progression in patients treated with a continuous therapy policy. This could potentially increase the ICERs.'*

The fact it is possible the ICER could increase with an increase in treatment duration is undeniable. However one cannot know for sure what the incremental benefit of treating for longer would be and it is equally plausible the ICER might decrease or remain the same. The above paragraph seems to imply that it is more likely that the ICER would increase based on the costs outweighing the benefits, but it is not clear what is precisely meant by 'outweigh' in this instance. The committee clearly consider that the high ICER for the comparison without the APAS demonstrates that the cost outweighs the benefit however if for each additional month of treatment patients received the same magnitude of benefit as the average observed across all patients in the NO16966 then this ICER would be expected to remain roughly the same. It is not clear whether the committee considered this.

In addition there are credible hypotheses for why the ICER might decrease with longer treatment:- Patients in the NO16966 study typically stopped treatment on bevacizumab at the same time as oxaliplatin. This was primarily, either as a result of disease progression, or due to the cumulative toxicity of treatment with oxaliplatin, which typically can only be given for a maximum of around 6 months. Patients with PFS longer than 6 months then had a greater chance of stopping oxaliplatin, and thus bevacizumab prior to progression. This is borne out in the observed treatment durations in the study where the proportion of patients on treatment relative to those remaining in PFS reduces over time (see Figure 1 below). It is reasonable to consider that patients that remained in PFS for longer did so in part due to a greater response to bevacizumab. If this is the case then continued treatment with bevacizumab could result in greater incremental benefit than in the patients that stopped treatment due to disease progression. Hence treating to progression would lead to a reduction in the ICER as the patients that receive the greatest benefit would receive longer treatment. Indeed a possible reason for why the first appraisal of bevacizumab in mCRC resulted a lower ICER (~£62k) than seen in this appraisal may be a result of the fact that patients in the study being analysed in that appraisal were treated until progression.

Figure 1: Proportion of Patients on Treatment out of Those in PFS



In conclusion whilst one cannot know for sure the incremental benefit of treating for longer, and thus how the ICER would be affected, there are plausible scenarios where treating to progression would either cause the ICER to remain the same or reduce. Hence paragraph 4.12 is misleading.

2.2.3.2. PFS Utility values

The ACD2, paragraph 4.13, indicates that the committee considered that the ICER's were underestimates due the utility values used in the economic analysis being overestimated, specifically:

- Patients on bevacizumab would have a worse PFS utility value than the comparator arm due to greater adverse events
- The utility values for both arms were overestimates

<u>Disutility due to adverse events</u>

Of the 5.1% excess of grade 3 and 4 tox 3.2% can be accounted for by hypertension, which in most cases will be measurable and treated but have little impact on patients utility.

The other important factor is that the adverse event rates reported for the NO16966 are not adjusted for time on treatment in the study. PFS, and hence treatment duration and OS, was longer in the bevacizumab arms so total AE's reported in this arm would increase disproportionately to any increase in AE's per unit time. Disutility / utility values are a measure of disutility / utility per unit of time. The fact that patients may experience disutility / utility for longer is already captured in the model via the fact that it incorporates time in PFS and OS

There is an argument for separating out PFS into two distinct health states and applying separate utility values for each of these health states to capture the fact that when being treated patients probably experience lower quality of life than after treatment is stopped and before disease progression. This would then more accurately reflect any disutility of treating for longer in the bevacizumab arm. However conversely this would mean that any incremental utility from being in PFS without the side-effects of treatment for the time between treatment cessation and progression would also be captured. As the incremental treatment duration in the

bevacizumab arm was less than the incremental time between treatment cessation to progression the impact of applying two different utility values actually reduces the ICER.

Finally a single utility value is currently applied to patients who are progression free, which incorporates patients with complete response (CR), partial response (PR) and stable disease (SD). Since tumour bulk is typically associated disutility it is reasonable to assume that the utility gain in PFS is greatest in patients with complete response and least in patients with stable disease. Adding bevacizumab to chemotherapy improves the degree of the response in patients (increased proportion of patients in non-progression have CR or PR). This increase in utility is not captured in the model and hence may underestimate the utility associated with bevacizumab thus overestimating the ICER.

<u>PFS utility value in both arms</u>

'The Committee agreed that the utility value of 0.77 was still high because it was similar to the utility values of people in the UK general population aged 55–64 and 65–74 rather than people with metastatic colorectal cancer. The Committee also noted that the utility values were obtained from a small study of people with metastatic colorectal cancer receiving cetuximab and chemotherapy.' (ACD2 paragraph 4.13).

The paragraph above questions the credibility of the source of utility values, however it is important to note the PFS utility values came from the EQ-5D results of a pivotal randomised controlled trial (NICE's preferred approach) in the indication of interest from patients receiving first line chemotherapy until progression.

2.2.3.3. Modelling of treatment duration as observed in NO16966

Whilst the *'ERG agreed that the manufacturer's economic model was an accurate replication of the NO16966 study' (paragraph 3.24),* a minor criticism of the model was made in Paragraph 3.14 in that *'Duration of treatment varied between treatment arms and was longer with the addition of bevacizumab and longer in the FOLFOX than in the XELOX arms. However, the model assumed that the treatment duration was the same in the B-FOLFOX and BXELOX arms.'*

Whilst a relatively minor point we wish to highlight any factual inaccuracies we identify in the document and this statement was noted as being incorrect. Treatment duration was in fact estimated and applied in the model for each arm of the NO16966. Please see pages 137 and 138 of our submission and also in response to question B6 page 91 of Roche's response to the second set of clarifications questions from the ERG.

The only simplification made was that, given that oxaliplatin is free of charge under the APAS, it was assumed to be given for same duration as bevacizumab. In the study the oxaliplatin treatment duration was slightly shorter in the bevacizumab arms than the bevacizumab treatment duration. Hence the model currently overestimates the treatment duration of oxaliplatin in the bevacizumab arms and correcting this would reduce the ICER's for when the APAS is not applied. There has no affect on the ICER's when the APAS is applied as oxaliplatin is free of change.

2.2.4. Administration costs

Paragraph 3.30 of the ACD states *'The ERG noted that the source of the recalculated administration costs and patient access scheme operating costs were unclear.'*

Section 4.14 goes on to state, when referring to the administration costs, that the committee noted that *'in particular, the sources of the unit costs were unclear'*.

The source of the revised administrations costs was described in our response to the ACD under the heading *'The incremental pharmacy and administration cost associated with adding bevacizumab to XELOX or FOLFOX'* . The source of the unit costs was clearly stated as being the PSSRU (see table 7 from Roche response to the 1st ACD below). Full details of the time and motion study which these unit costs were then applied were also provide in the our response.

Table 7: Unit costs taken from the PSSRU (PSSRU, 2008) and inflated to 2009 costs

Healthcare Professional	Per hour	Per patient contact hour [T]	Per patient contact hour inflated to 2009
Hospital Pharmacist (band 6)	£32	£45	£46
Pharmacy Technician	Not available	Not available	Not available
Nurse Team Manager (band 7)	£33	£74	
Nurse Team Leader (band 6)	£29	£65	£63*
Nurse (band 5)	£23	£43	

* *Average across bands*; [T] *calculated as total annual cost divided by estimated hours of patient contact for nurses and patient related activity time for pharmacists*

2.2.5. Operating costs of the APAS

Paragraph 3.30 of the ACD states *'The ERG noted that the source of the recalculated administration costs and patient access scheme operating costs were unclear.'*

A detailed description of the methods and sources of timings and costs are provide under the heading of *'The NHS resource cost of operating APAS and the subsequent effect on the ICER'*.

Section 3.26 states *'The manufacturer revised the time per patient of operating the patient access scheme to 131 minutes and 152 minutes for the XELOX and FOLFOX regimens, respectively, based on research within the NHS. This equated to a cost per patient over years 1 to 3 of £57 and £67 for B-XELOX and B-FOLFOX, respectively.'*

The above paragraph could be misunderstood to suggest that the cost per patient was only accounted for from years 1 to 3. This is not the case. The ongoing costs of running the scheme were based on the mean duration patients are expected to be on APAS, although admittedly patients are not expect to be on the scheme for more than 3 years.

The mention of years 1 to 3 in our response to the first ACD was with regards to the average number of patients that would be expected to be enrolled on APAS in trust during the first 3 years from commencing the scheme. This was required to convert the one-off cost of a trust

setting up the scheme and the monthly accounting activities associated with the APAS to a per patient cost that could then be applied to the economic model.

2.2.6. Oxaliplatin Price

Paragraph 4.16 of the ACD2 states *'the Committee noted the view of the ERG that if the substantial price reduction of oxaliplatin was included in the model then the ICERs would also be greatly increased.'*

It is not clear from the above paragraph which ICER's are being referred to. It is not the case that all the ICERs would increase. The ICER's without APAS applied would decrease should the price of oxaliplatin reduce since patients were treated for longer on oxaliplatin in the bevacizumab arm.

3. Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS

Roche do not agree the ACD is a currently a fair reflection of the evidence. As detailed above, under heading 2, there a number of areas where the ACD is either factually incorrect or does not provide a reasonable interpretation of the evidence.

4. **Are there any equality related issues that need special consideration that are not covered in the ACD?**

No comments.

REFERENCES

Curtis L. Unit costs of health & social care. PSSRU 2008. http://www.pssru.ac.uk/uc/uc2008contents.htm Accessed May 2009

Hurwitz et al; Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer; N Engl J Med. 2004 Jun 3;350(23):2335-42

Giantonio BJ *et al* High-dose bevacizumab improves survival when combined with FOLFOX4 in previously treated advanced colorectal cancer: Results from the Eastern Cooperative Oncology Group (ECOG) study E3200. *J Clin Oncol.* 2005; **23** (16S): Abstr 2.