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Tuesday 3rd March 2009

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BY E-MAIL

Dear Christopher,

MULTIPLE TECHNOLOGY APPRAISAL – Bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma

Thank you for sending us the Appraisal Consultation Document (ACD) for the above technology appraisal.

Roche welcomes the acceptance by the Appraisal Committee at its last meeting of a number of key points of feedback which were made regarding the economic modelling for bevacizumab which has resulted in a revised ICER of approximately £82,700.

In the light of this position, Roche has proposed a Patient Access Scheme in order to further reduce this base case ICER to a level which can be considered as being cost effective. Ministers have given permission for this Scheme, which was submitted to NICE in advance of this ACD response on 1st March, to be evaluated as part of the ongoing appraisal.

Alongside the evaluation of the tabled Patient Access Scheme, there are two important points which the Committee needs to consider at its next meeting. These are:

1. The tolerability profile of the combination of bevacizumab and interferon (IFN) which appears to have been particularly focussed upon by the Committee at its last meeting; and

2. The application of the End of Life criteria (EoLC) to bevacizumab.

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Roche was surprised that in the consideration of the end-of-life criteria in relation to bevacizumab, particular emphasis appeared to be uniquely placed on the combination of bevacizumab plus IFN being poorly tolerated as one reason for rejecting the applicability of the end of life criteria. This appears to us to be arbitrary and unreasonable particularly because adverse events have already been taken into account in the costs and benefits calculations used to generate the ICER. We deal with this issue further in our main response below.

It can perhaps be inferred from the positive recommendation already given for sunitinib that the Committee believe that bevacizumab plus IFN is significantly less well tolerated than sunitinib. We describe below the empirical evidence which suggests that overall the tolerability of bevacizumab plus IFN appears at least no worse than that of sunitinib. This is based on a review of safety datasets that are comparable in terms of treatment duration and which were included in our original submission. We would also point out that the Committee appear to have considered safety analysis from an immature dataset (at 6 months median treatment duration) whilst considering a more mature dataset for efficacy.

The ACD suggests that the Committee accepted that three out of the four end-of-life criteria should apply to bevacizumab, apart from the small patient population criterion. Roche believes that, as for sunitinib, this criterion should also apply positively to bevacizumab and we put forward argumentation to support this position in our response below.

In summary, Roche considers that the combination of bevacizumab plus IFN - when considered in the context of the Patient Access Scheme approved by Ministers for evaluation by NICE as part of this appraisal – can now be regarded as being clinically and cost effective. The combination of bevacizumab and IFN provides similar efficacy benefits as sunitinib in the first line setting, and in accordance with the above conclusions appears to have a similar frequency of adverse events, albeit with a very different toxicity profile.

With similar cost effectiveness to sunitinib in the context of the proposed Patient Access Scheme, we believe that bevacizumab plus IFN should be recommended for use by the Committee to provide NHS cancer patients with a choice of treatment options which is supported by the patient choice agenda set out in England's Cancer Reform Strategy.

1 WHETHER YOU CONSIDER THAT ALL OF THE RELEVANT EVIDENCE HAS BEEN TAKEN INTO ACCOUNT

Avastin Patient Access Scheme (APAS)

Roche welcomes the acceptance by the Appraisal Committee at its last meeting of a number of key points of feedback which were made regarding the economic modelling for bevacizumab which has resulted in a revised ICER of approximately £82,700.

Roche has proposed a patient access scheme (PAS), which further reduces this ICER we believe to a level which can be regarded as being cost effective and indeed in line with the cost effectiveness estimates for first-line sunitinib use (approximately £54,000).

Under the PAS any bevacizumab that a patient receives beyond a cumulative dose of 10g in any treatment year will be rebated. Additionally the drug acquisition cost of all IFN used for each patient will be reimbursed.

We submitted details of this scheme to NICE on 1st March for evaluation.

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

Adverse-Event profile of bevacizumab + IFN

In several sections throughout the ACD, the Committee has made reference to the adverse event profile of the combination of bevacizumab and IFN as follows:

- Section 4.3.5

The Committee was persuaded that bevacizumab plus IFN-α is a clinically effective first-line treatment. However, it was mindful of the adverse effects associated with the combination of bevacizumab and IFN-α

- Section 4.3.7

'it noted there were more participants in the bevacizumab arm of the trial than the IFN-α arm that were censored. The Committee considered that this was likely to be caused by a greater number of participants withdrawing from bevacizumab plus IFN-α treatment than IFN-α plus placebo treatment, which could be because of adverse effects of bevacizumab plus IFN-α treatment '

- Section 4.3.8

The Appraisal Committee appear, in part, to presently base the guidance for bevacizumab and IFN on the opinion of patients who had commented on the appraisal: *'and its use in combination with a drug that is reported by patients to have substantial adverse effects,'*

Whilst we fully acknowledge the importance of public comment on appraisals, such comments need to be placed into context and interpreted alongside the empirical data from RCTs. We have submitted robust clinical trial data from a randomised, double-blind, placebo controlled study and believe that any appraisal of the tolerability of this combination should be based primarily upon this clinical dataset.

We were surprised by the Committee's focus on the tolerability profile of bevacizumab and IFN, which we would like to revisit through review of the data submitted from the

pivotal study AVOREN (Escudier et al., 2007).

As can be seen from the table below, patients were on study drug significantly longer in the bevacizumab plus IFN arm (median 9.7 months) compared to the IFN plus placebo arm (median 5.1 months). It is also important to note that patients also received IFN for longer in the bevacizumab combination arm, compared to IFN alone.

	IFN + placebo (n=304)	**Bevacizumab + IFN (n=337)**
Median duration of treatment, mo (range)		
Bevacizumab/placebo	5.1 (0-24)	9.7 ((0-24.4)
IFN	4.6 (0.2-12.6)	7.8 (0.2-12.6)

As can be seen from Table 1 (Appendix A), there was a similar proportion of patients who experienced adverse events in both arms of AVOREN. There were more grade ≥3 adverse events reported in the bevacizumab arm (203 for bevacizumab plus IFN vs 137 for IFN alone) and more patients in the bevacizumab + IFN arm withdrew due to adverse events compared to IFN alone (28% vs 12%, respectively). However this variance between the arms can be explained by the fact that patients were on the study treatment for almost twice as long in the bevacizumab arm. This observation is supported by the comparison of the safety data from longer follow-up of the sunitinib pivotal study, versus the less mature dataset presently considered by the Committee (Table 2, Appendix A). Whilst the incidence of adverse events changes little in the IFN arm, considerable difference in the incidence of sunitinib associated adverse events were observed as the median treatment duration increased.

Since sunitinib has received positive NICE guidance, within the same MTA, it seems pertinent to compare the adverse event profile for sunitinib with that of bevacizumab + IFN.

Unlike the AVOREN study, the sunitinib pivotal study (Motzer et al., 2007) had an open label study design, whereby both patients and investigators were aware of which study drug the patient was receiving, and as such any subjective measures may have been impacted by inherent bias. For example, 15 patients (4%) randomised to the IFN arm withdrew consent prior to receiving study drug, versus none in the sunitinib arm. Given that sunitinib at that time was the 'new /innovative therapy' with promising efficacy data from phase II studies, it is not surprising that patients chose not to participate in a study once they learned that they would receive an 'older / less effective' drug. Similarly, following publication of the second interim analysis, 25 patients who were receiving IFN and whose disease had not progressed switched to the sunitinib arm. These observations indicate how patient preference can potentially impact study outcomes in an open label setting.

With regard to the adverse event profile for sunitinib, the Committee concluded in Section 4.1.12. of the sunitinib FAD that '*The frequency of adverse events associated with sunitinib is comparable to that associated with IFN-α monotherapy.'* As mentioned earlier, the Committee has based it's findings on the adverse event profile of sunitinib on an immature dataset, first presented at ASCO in 2006 and later published in 2007 (Motzer et al., 2007). At the time of this second interim analysis, the median duration of

treatment was 6 months (range, 1 to 15) in the sunitinib group, and 66% of patients remained on treatment. However, by the third interim analysis (Motzer et al., 2007b), the median treatment duration had almost doubled to 11 months, better reflecting the efficacy of sunitinib with a median PFS of 11 months. At this data cut, only 27% of patients remained on therapy, and therefore the full safety profile for the majority of patients had been captured.

This dataset was included in our submission for bevacizumab and IFN, as part of the indirect comparison with sunitinib. A further update relating to final analysis of overall survival (submitted by Pfizer as part of this MTA) was presented in September 2008 (Negrier et al., 2008).

The reported safety data from all of three analyses are summarised in Table 2 (Appendix A) for ease of comparison and any differences should be considered in the context of different treatment duration and proportion of patients still on therapy (i.e. patients whose disease had not progressed). Given that the median duration of sunitinib is considerably longer in the third interim analysis, the increased incidence of sunitinib adverse events was not unexpected. Patients in the sunitinib arm experienced significantly more grade≥3: diarrhoea, nausea, vomiting, hypertension, hypothyroidism, neutropenia, thrombocytopenia, and hyperlipidaemia; whereas patients in the IFN arm experienced more grade≥3 lymphopaenia ($p<0.05$ for all comparisons).

As such, when reviewing the safety dataset most relevant to the efficacy outcomes reported for sunitinib and given the very distinct toxicity profiles of the two agents, it appears that sunitinib is at best no less toxic than IFN.

Whilst acknowledging the inherent issues with indirect comparisons of data from independent clinical trials, we believe it is important to compare the tolerability profiles of bevacizumab + IFN vs sunitinib given the different guidance issued for the two technologies. Safety data from the AVOREN study is compared with the most relevant dataset from the sunitinib pivotal study in terms of treatment duration (i.e. the third interim analysis) in Table 3, which was also included in our original submission for this MTA. Overall, the tolerability of bevacizumab + IFN appears at least no worse than that of sunitinib.

Finally, we would like to remind the Committee of the IFN dose reduction analysis that formed part of the original submission for bevacizumab and IFN. Given the wealth of experience with IFN in the treatment of advanced RCC patients, an algorithm reflecting standard clinical practice of IFN dose reductions for the management of IFN-related toxicity was included in the AVOREN protocol (Melichar et al., 2007, 2008).

Approximately 40% of patient in the bevacizumab plus IFN arm reduced the dose of IFN, compared to 30% in the IFN plus placebo arm. (As expected, dose reduction resulted in decreased side effects in both groups, and interestingly the bevacizumab + reduced dose IFN demonstrated similar efficacy to the ITT study group. Thus, the AVOREN study showed that IFN side effects can be effectively managed through a standard dose reduction algorithm, without compromising efficacy. It is also interesting to note 27% patients had IFN dose reductions in the sunitinib pivotal study, whereas 50% of patients on in sunitinib had dose reductions due to adverse events (Negrier et al., 2008). Once again, when comparing the amount of dose reduction required to manage adverse events in the two pivotal studies, bevacizumab + IFN

appears at least no worse than sunitinib.

Conclusion

In summary, we believe that robust RCT data from the AVOREN study demonstrates that the tolerability profile of bevacizumab + IFN is acceptable, in the context of the significant efficacy benefits the combination provides over IFN alone. Therefore, we believe the Committee's particular focus on this issue is not substantiated by the data and is inappropriate. Moreover, review of the pivotal data for sunitinib suggests that it is at best no less toxic than IFN, and indirect comparison of the safety data for the two technologies does not suggest that sunitinib is any more tolerable than bevacizumab + IFN. Hence we believe that the Committee has been inconsistent in this regard in it's appraisal of the two technologies side by side.

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

Application of End of Life Criteria (EoLC)

Whilst we accept that the Appraisal Committee has tested the application of the end of life criteria on only a limited number of occasions so far since the Supplementary Advice was issued, it appears that bevacizumab has on this occasion been treated differently to other drugs.

The ACD indicates that the Appraisal Committee accepted that three of the four EoLC did apply to the combination of bevacizumab and IFN for this technology appraisal and we agree with the position of the Committee regarding the applicability of the first three criteria:

2.1.1
The treatment is indicated for patients with a short life expectancy, normally less than 24 months
"The Committee noted from the clinical trials that life expectancy with IFN-α treatment alone was unlikely to be greater than 24 months and was potentially as low as 12 months."

2.1.2
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment
"The Committee considered that even though the median overall survival in the bevacizumab arm of the trial had not been reached, the Committee considered that it was likely that bevacizumab plus IFN-α would increase overall survival by more than 3 months in comparison with IFN-α alone."

2.1.3
No alternative treatment with comparable benefits is available through the NHS
The Appraisal Committee *"..had heard that RCC does not respond well to IFN-α and that bevacizumab represents an improvement in the treatment of advanced and/or metastatic RCC."*

However, in relation to the last criteria we disagree with the Committee's position:

2.1.4
The treatment is licensed or otherwise indicated, for small patient populations.
In summary , the Committee was not persuaded that bevacizumab plus IFN-α meets all the criteria, particularly given the size of the patient populations (in RCC and other cancers) for whom it is licensed and its use in combination with a drug that is reported by patients to have substantial adverse effects,..'

Adverse Events
It is not clear to Roche why the adverse event profile of bevacizumab and IFN has been raised as a consideration under the End of Life Criteria. The End of Life Criteria Supplementary Advice does NICE direct Committees to examine this issue. Furthermore, as demonstrated above, the adverse event profile for the combination of bevacizumab and IFN is no worse than that observed for sunitinib. This is supported by the data from the randomised clinical trial of sunitinib versus IFN, which the Committee acknowledged. There is no mention of the adverse event profile for sunitinib in the Committee's consideration of End of Life criteria in the corresponding FAD for sunitinib.

"Small Population" Criterion

Generally, .the inclusion of this particular criterion in the end-of-life supplementary advice is particularly challenging, not least because of the absence of empirical evidence to suggest that society places any greater value on treating individuals with rare diseases over those with common ones.

However, we offer up the following points in support of arguing that this criteria should be applied positively to bevacizumab in this appraisal as it has been for sunitinib:

a) Reimbursement status

Whilst bevacizumab may be licensed for the treatment of multiple cancer indications it is currently not reimbursed for any indication on the NHS. If recommended for use in this appraisal for renal cell cancer, this would effectively be the first ever indication used in the NHS. There has to date been no recovery of the development costs of bevacizumab whatsoever from any use on the NHS.

There are a number of further issues with including indications outside of the scope of the appraisal when determining the size of the population of interest including:

b) Scope of appraisal

Since the scope of this appraisal is to investigate the clinical and cost effectiveness of treatments for RCC, it seems unreasonable to base any case for endorsement at least in part on the regulatory status of other indications which are not relevant and outside

the scope of the appraisal. This would seem unfair to renal cell cancer patients.

c) First come, first served

It also seems unreasonable to potentially disadvantage renal cell cancer patients on the basis of the order and sequence within which marketing authorisations happen to be granted for other particular indications (in this case comparing for example the sunitinib licencing sequence with that of the bevacizumab licencing sequence).

d) Specific development costs

Finally, follow-on indications require the full range of clinical trials to establish safety and efficacy. Development costs are unique to each particular indication and need to be considered as such. We therefore believe that the regimen being appraised in this setting should be considered in isolation in establishing the relevant patient population.

In summary, we believe that since the number of renal cell cancer patients is within acceptable 'small population' limits (less than 4,000) that the fourth small population criterion should on this occasion equally apply positively to both bevacizumab and sunitinib alike.

4 ARE THERE ANY EQUALITY RELATED ISSUES THAT NEED SPECIAL CONSIDERATION THAT ARE NOT COVERED IN THE ACD?

Roche considers that the application of the end of life criteria within this appraisal may result in equality issues for renal cell cancer patients who may be disadvantaged if the end of life criteria within this MTA are applied inconsistently or due for example to factors outside of the particular scope of the appraisal such as sequencing of marketing authorisation applications being taken into account in decision making.

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

Yours sincerely,

Appendix A

Table 1: Overview of Adverse Events for the AVOREN Study

	All Grades		Grade ≥ 3	
	Pla + IFN	**Bev + IFN**	**Pla + IFN**	**Bev + IFN**
	N = 304	**N = 337**	**N = 304**	**N = 337**
All AEs	328 (97%)	287 (94%)		
AEs with Frequency ≥ 2%				
Fatigue	83 (27%)	110 (33%)	25 (8%)	40 (12%)
Asthenia	84 (28%)	109 (32%)	20 (7%)	34 (10%)
Proteinuria	8 (3%)	59 (18%)	0	22 (7%)
Neutropenia	20 (7%)	24 (7%)	7 (2%)	15 (4%)
Hypertension	28 (9%)	88 (26%)	2 (<1%)	13 (4%)
Bleeding	28 (9%)	112 (33%)	1 (<1%)	11 (3%)
Influenza-like illness	77 (25%)	82 (24%)	6 (2%)	10 (3%)
Anorexia	92 (30%)	121 (36%)	8 (3%)	10 (3%)
Depression	31 (10%)	41 (12%)	4 (1%)	10 (3%)
Anaemia	41 (13%)	33 (10%)	17 (6%)	9 (3%)
Pyrexia	130 (43%)	152 (45%)	2 (<1%)	8 (2%)
Thromobcytopaenia	12 (4%)	21 (6%)	3 (<1%)	7 (2%)
Headache	49 (16%)	79 (23%)	4 (1%)	7 (2%)
Diarrhoea	47 (15%)	69 (20%)	3 (<1%)	7 (2%)
Venous Thromboembolic Event	3 (<1%)	10 (3%)	2 (<1%)	6 (2%)
Dyspnoea	38 (13%)	44 (13%)	7 (2%)	2 (<1%)
Additional Targeted Events				
Arterial Thromboembolic Event	2 (<1%)	5 (1%)	1 (<1%)	4 (1%)
GI Perforation	0	5 (1%)	0	5 (1%)
Wound healing comp.	3 (1%)	5 (1%)	0	2 (<1%)
Congestive Heart Failure	38 (13%)	44 (13%)	0	1 (<1%)
AE leading to study discontinuation				
Bev/Pla	17 (6%)	63 (19%)		
IFN α-2a	35 (12%)	76 (23%)		
Death not due to PD [5]	7 (2%)	8 (2%)		

Table 2: Overview of sunitinib vs IFN attached below (A3 paper layout)

Full Sun vs IFN AE Table.doc

Table 3. Indirect comparison of adverse events for sunitinib and the combination of bevacizumab and IFN from Phase III pivotal studies.

Study **Agent – Treatment duaration**	**Study A6181034[a]** **(sunitinib 11 months)** **n= 375**		**AVOREN[b]** **(Bev + IFN 10 months)** **n= 337**	
Event (%)	**All Grade**	**Grade 3/4**	**All Grade**	**Grade 3/4**
Fatigue	54	11	33	12
Asthenia	--	--	32	10
Diarrhoea	60	8†	20	2
Nausea	52	4†	--	--
Stomatitis	30	1	--	--
Vomitting	31	4†	--	--
Anorexia	--	--	36	3
Bleeding	--	--	33	3
Proteinuria	--	--	18	7
Hypertension	30	12†	26	3
Headache	--	--	23	2
Depression	--	--	12	3
Hand-foot syndrome	29	8†	--	--
Ejection fraction decline	13	3	--	--
Hypothyroidism	11	2†	--	--
Pyrexia	8	1	45	2
Chills	7	1	--	--
Myalgia	8	<1	--	--
Flu-like symptoms	2	0	24	3
Dyspnoea	--	--	13	<1
Venous thromboembolic event	--	--	3	<1%
Arterial thromboembolic event	--	--	1	1
Gastrointestinal perforation	--	--	1	<1
Wound healing complications	--	--	1	<1
Congestive heart failure	--	--	<1	<1
Laboratory Abnormalities				
Neutropaenia	77	16†	7	4
Anaemia	78	6	10	3
Thrombocytopaenia	68	9†	6	2
Lymphopaenia	67	17	--	--
Increased lipase	56	17†	--	--
Increased amylase	34	6	--	--
Hypophosphataemia	30	6	--	--

[a] Motzer RJ, Figlin RA, Hutson TE, et al. (2007b). Sunitinib versus interferon-alfa (IFN-α) as first-line treatment of metastatic renal cell carcinoma (mRCC): Updated results and analysis of prognostic factors. J Clin Oncol; 25 (supp): Abstract 5024 and oral presentation

- *No definition of AE listing provided*

† The comparison between the sunitinib group and the IFN-α group was significant (P<0.05) with the use of Fisher's exact test applied to the sum of grade 3 and 4 AEs.

[b] Escudier B, Pluzanska A, Koralewski P, et al. (2007c) Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet;370:2103-11.

- *Adverse events with a frequency of 2% or more, and additional targeted events were reported*.

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