Bevacizumab, sorafenib, sunitinib and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma - additional analyses for consultation

Background

NICE is currently appraising the use of bevacizumab, sorafenib, sunitinib and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma. The Appraisal Consultation Document (ACD) was issued in July 2008.

A late submission of data was received from the marketing authorisation holder of sunitinib detailing final intention to treat results and results of analyses for a subgroup of patients in which the estimates of effectiveness of the comparator technology were proposed to better reflect current clinical practice. This late submission was provided as a response to consultation on the assessment report and was not detailed enough for consideration at the first Appraisal Committee meeting. Further details on the subgroup analyses were received from the manufacturer of sunitinib during consultation on the ACD.

Having received the new data from the manufacturer of sunitinib, and also having received further data from the manufacturer of bevacizumab, the Institute commissioned the Decision Support Unit (DSU) and the Assessment Group (AG-PenTAG) to review the submissions made during consultation.

The Appraisal Committee discussed the new data submissions from manufacturers together with the DSU and the AG-PenTAG reviews of these submissions at its meeting in September. They also discussed the responses to consultation on their preliminary recommendations. The DSU and AG-PenTAG were instructed to explore further the impact of the Appraisal Committee's preferred assumptions pertaining to the subgroup on both the manufacturer's economic model and on the AG's economic model for sunitinib.

This set of papers summarises the details of the additional analyses conducted, alongside the results. You are invited to comment on these additional analyses for the above appraisal.

Documents included for consultation:

1. Pfizer's submission made in response to the assessment report and the submission made in response to the ACD.

This document contains Pfizer's (manufacturer of sunitinib) response on the assessment report and the response on the ACD as issued in July 2008. It includes details on a group of participants in the key sunitinib trial who did not receive any further treatments after the trial had ended. The document also includes cost effectiveness analyses based on this group of participants.

2. Roche Products' response to the ACD.

This document is the response from Roche Products (manufacturer of bevacizumab) on the ACD as issued in July 2008. It includes details of the request for four parameter changes for bevacizumab to the AG-PenTAG's economic model.

3. AG-PenTAG review of Pfizer's original submission and the submission in response to the ACD.

This document details a review of the Pfizer submissions (document 1) as conducted by the Assessment Group (PenTAG). It includes analyses using the updated effectiveness data submitted by Pfizer (document 1) applied to the AG-PenTAG economic model.

4. DSU review of Roche's request for parameter changes.

This document details the review conducted by the Decision Support Unit (DSU) of the suggested parameter changes requested by Roche including analyses using the parameter changes as requested by Roche (document 2) applied to the Assessment Group's economic model.

5. Appraisal Committee's preferred assumptions after considering the responses to consultation, the submissions by Pfizer and Roche and the reviews of the manufacturer submissions by DSU and AG-PenTAG.

This document details the judgments of the Appraisal Committee for the estimation of survival benefit for the subgroup of people who do not receive second line treatments

These have been applied to the economic model submitted by the manufacturer of sunitinib (Pfizer) and to economic model of AG-PenTAG.

6. DSU report on Pfizer's cost effectiveness model for sunitinib in the subgroup with no systemic post study treatment incorporating the Committee's preferred assumptions.

This document is the report produced by the DSU containing the review of the Pfizer response to the assessment report before the first meeting, a review of the submission made in response to the ACD and analysis exploring the cost effectiveness estimates when the Appraisal Committee's preferred assumptions for the 'no systemic post study treatment group' are incorporated into Pfizer's model.

7. AG-PenTAG's report on the cost effectiveness model for sunitinib in the subgroup with no systemic post study treatment, including using Committee's preferred assumptions.

This document is the report produced by AG-PenTAG containing analysis exploring the cost effectiveness estimates when the Appraisal Committee's preferred assumptions for the 'no systemic post study treatment group' are incorporated into AG-PenTAG's model.

Document 1. Pfizer's submission made in response to the assessment report and the submission made in response to the ACD.

Health Technology Appraisal
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Pfizer's original (late) submission

Submission of cost-effectiveness analyses based on final results from study A6181034

The curves presented in figures 1 and 2 are based upon the modelling undertaken for the NICE technology appraisal using the data within the Interim analysis 2 clinical study report (Motzer 2007 paper). Figure 1 shows the IFN curve diverging resulting in a potential underestimate of IFN benefit.

Figure 1: Progression free survival - Interim analysis 2

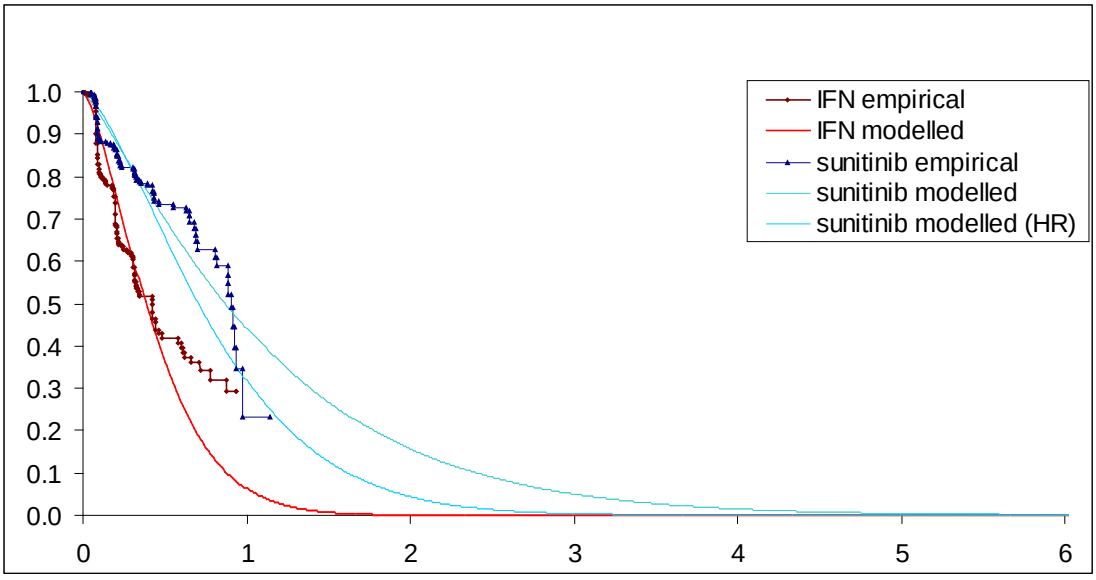
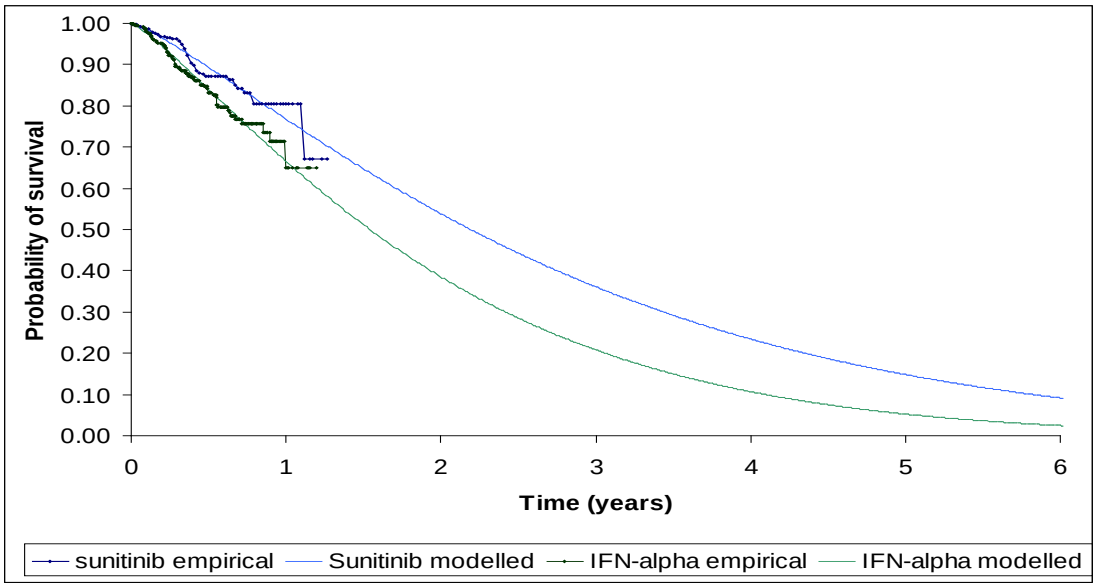


Figure 2: Overall survival - Interim analysis 2



The original cost-effectiveness analysis presented to NICE and those included below include the first cycle of sunitinib treatment as being free to the NHS.

Table 1: Cost effectiveness analysis originally presented to NICE

	Sunitinib	**IFN**	**Sunitinib vs IFN**
Life years	2.76	1.95	0.82
Progression free years	0.83	0.45	0.38
QALYs	1.96	1.36	0.60
Drug costs	£17,210	£2,587	£14,622
Follow-up costs	£1,303	£1,684	-£381
Diagnostic tests	£575	£313	£262
AEs	£63	£4	£59
BSC in progressed disease	£16243	£13,536	£2,707
Total costs	£35,393	£18,124	£17,269
ICERs			
Cost/LYG			£21,116
Cost/QALY			£28,546

***Final results - ITT Population**:*

The overall survival and progression free survival curves used to derive the cost-effectiveness results below have not been adjusted. As in our original submission, the sunitinib curve has been calculated by applying the hazard ratio to the IFN curve. Figures 3 and 4 show the fit of the modelled data against the empirical trial data for both progression free survival and overall survival.

Figure 3: Progression free survival - ITT analysis (final)

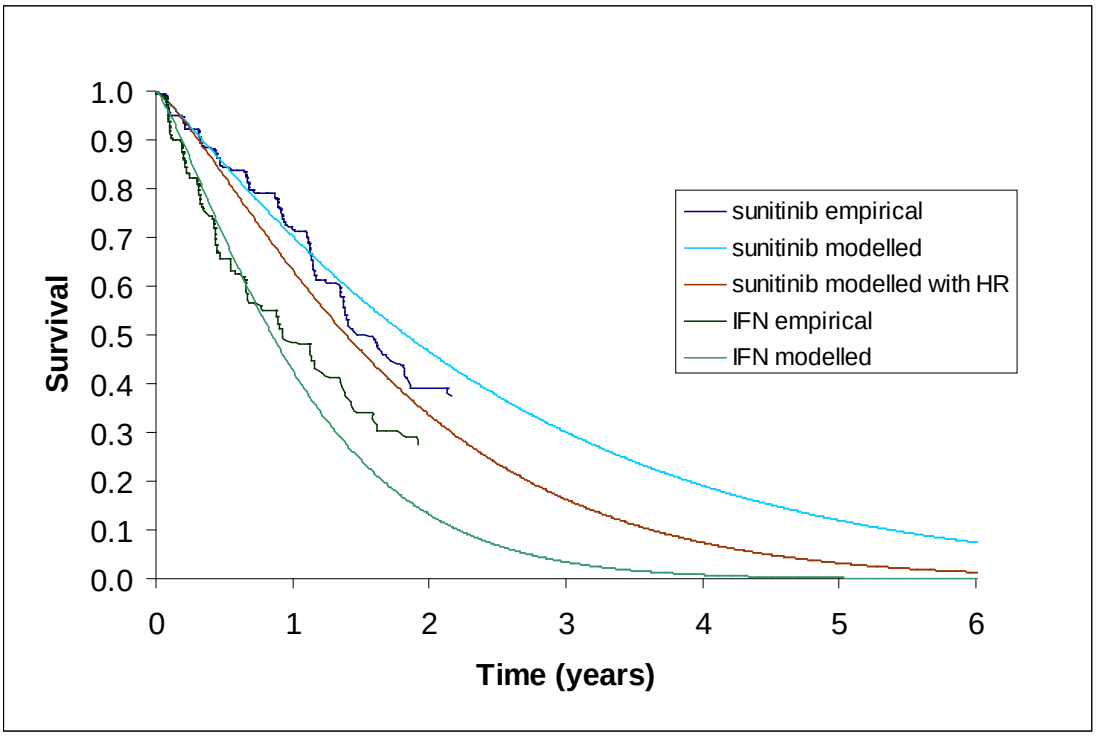
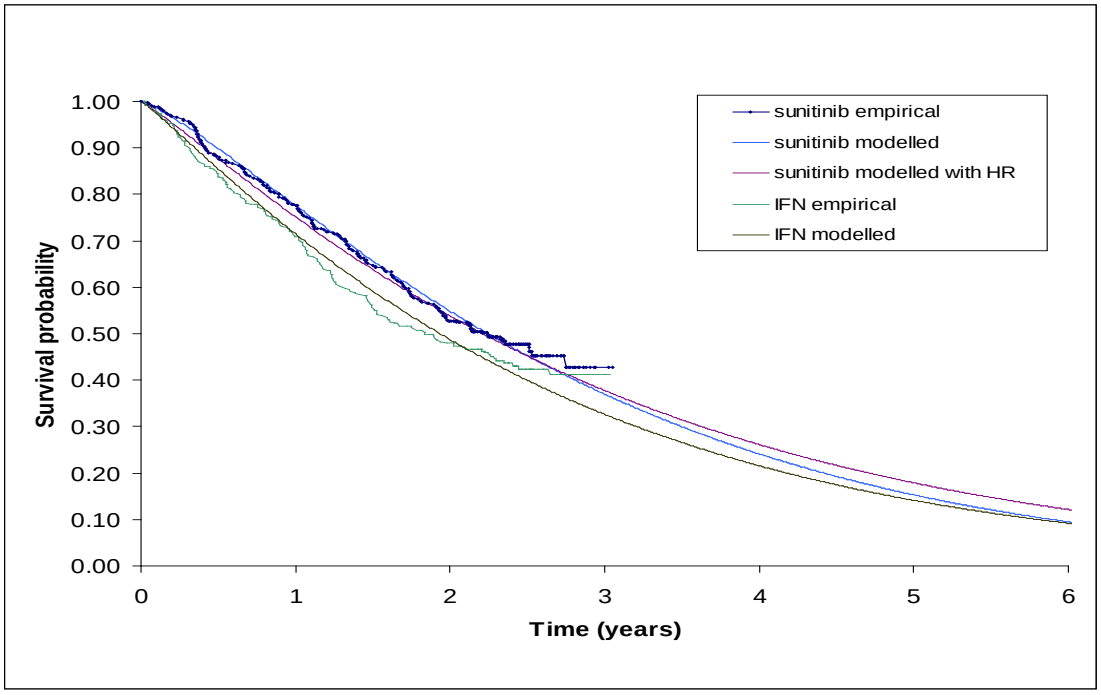


Figure 4: Overall survival - ITT analysis (final)



Within this analysis the overall survival and progression free survival curves for IFN have not been adjusted to give a visually better fit. All assumptions for this cost-effectiveness analysis remain the same as in the originally submitted model.

Table 2: Cost effectiveness analysis from ITT analysis (final)

	Sunitinib	IFN	Sunitinib vs IFN
Life years	3.13	2.61	0.52
Progression free years	1.74	1.06	0.68
QALYs	2.25	1.85	0.40
Drug costs	£37,582	£6,096	£31,485
Follow-up costs	£2,476	£3,953	-£1,477
Diagnostic tests	£1,191	£736	£455
AEs	£73	£4	£69
BSC in progressed disease	£12,898	£14,334	-£1,435
Total costs	£54,220	£25,123	£29,096
ICERs			
Cost/LYG			£56,442
Cost/QALY			£72,003

ITT analysis cross over censored

Within this analysis the progression free survival remains the same as in the ITT analysis. The curve below shows the fit of the modelled data to the overall survival curve. This curve has not been adjusted to give a better visual fit between empirical and modelled data.

Figure 5: Overall survival - cross over censored (final)

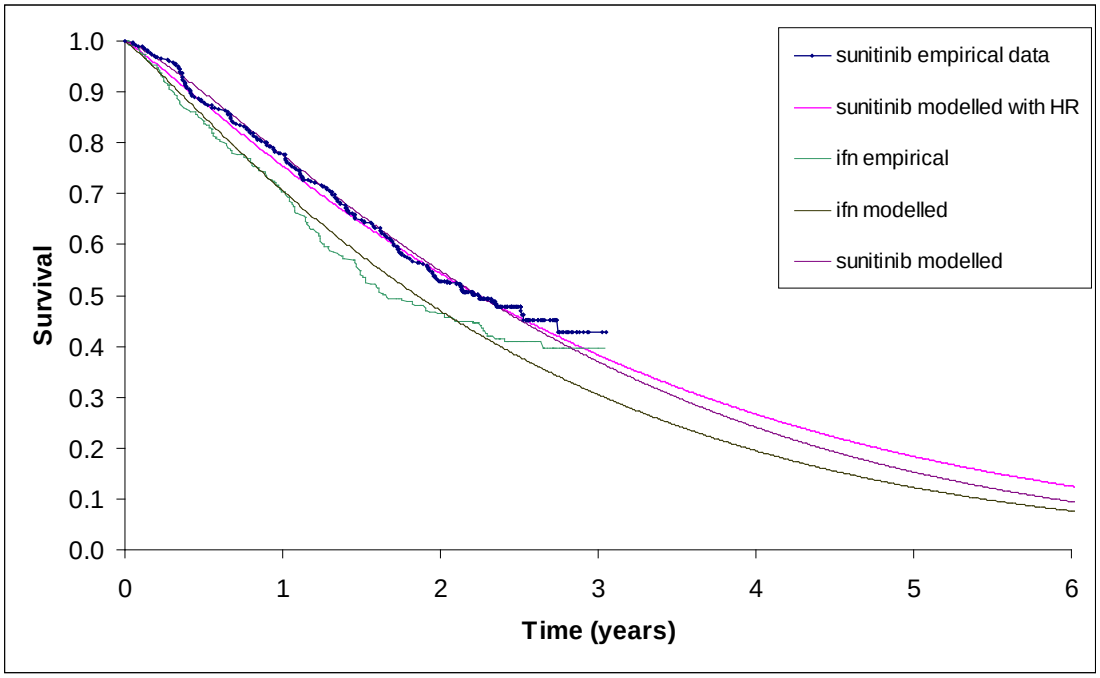


Table 3: Cost effectiveness analysis from ITT -cross over censored analysis

	Sunitinib	IFN	Sunitinib vs IFN
Life years	2.99	2.47	0.52
Progression free years	1.74	1.06	0.68
QALYs	2.16	1.76	0.41

Drug costs	£37,582	£6,096	£31,485
Follow-up costs	£2,476	£3,953	-£1,477
Diagnostic tests	£1,191	£736	£455
AEs	£73	£4	£69
BSC in progressed disease	£12,024	£13,397	-£1,373
Total costs	£53,346	£24,186	£29,160
ICERs			
Cost/LYG			£56,019
Cost/QALY			£71,760

Analysis in patients who did not receive any post study treatment

The efficacy curves within this analysis relate to the survival of patients who did not have any therapy following progression. The overall survival data has been presented at ASCO 2008 – the progression free survival data has not been presented. The modelled curves as shown below have not been adjusted to give a better visual fit between the empirical and modelled data.

Figure 5: Progression free survival - no post study treatment analysis

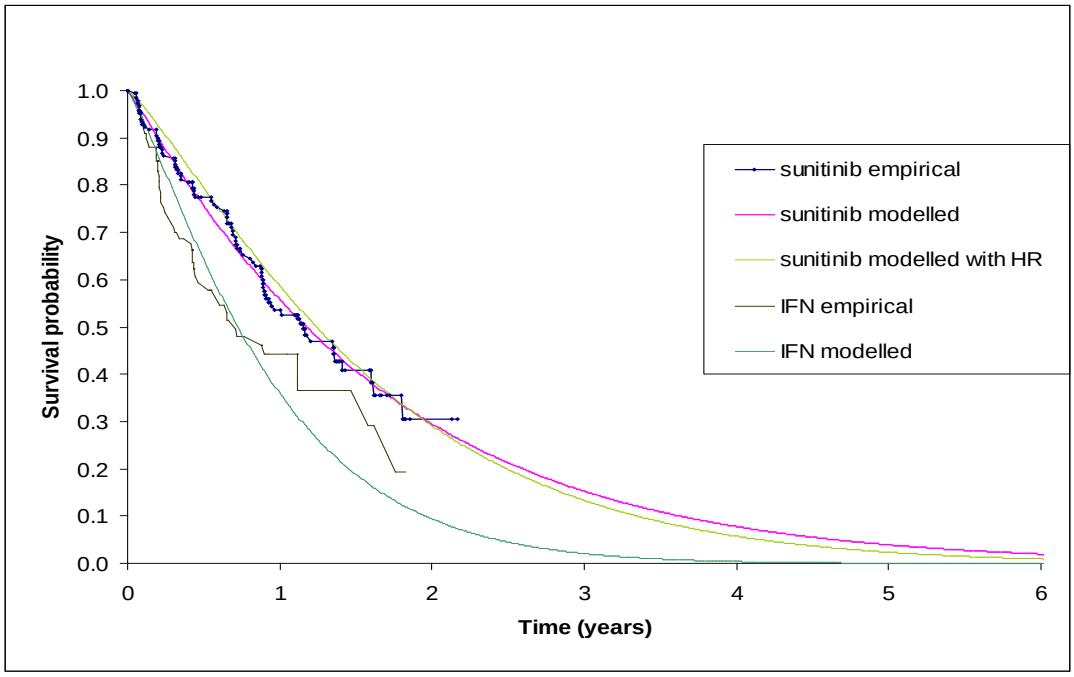


Figure 6: Overall survival – no post study treatment analysis

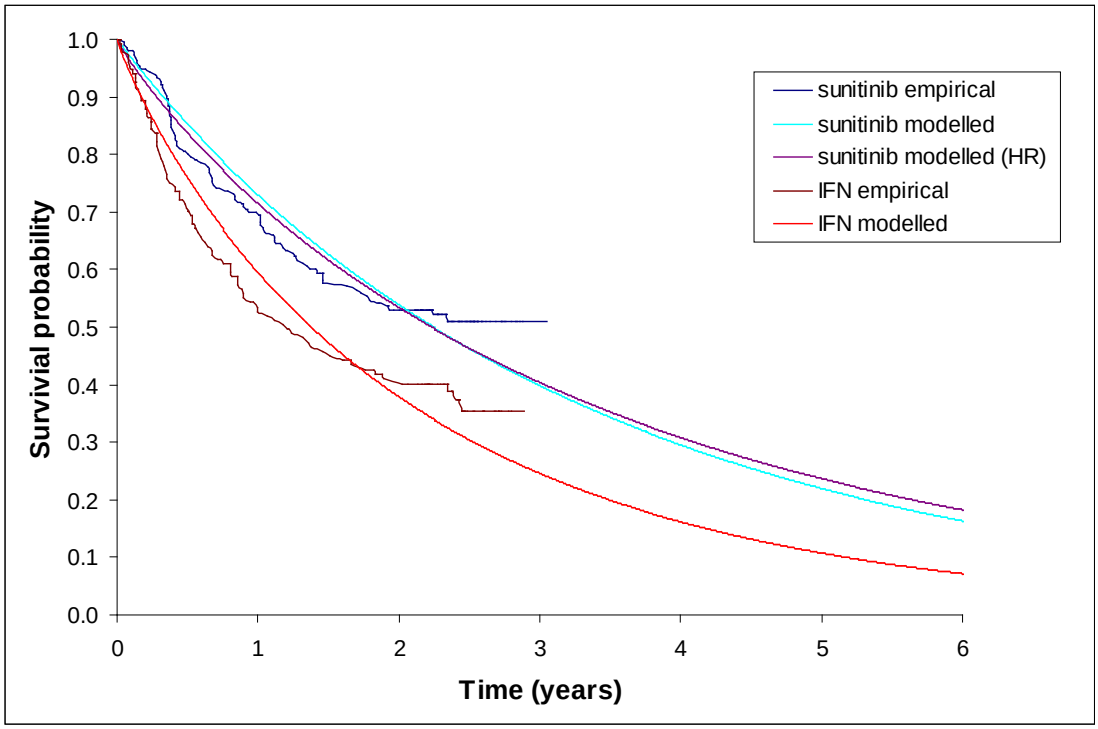


Table 4: Cost effectiveness analysis from no post study treatment data

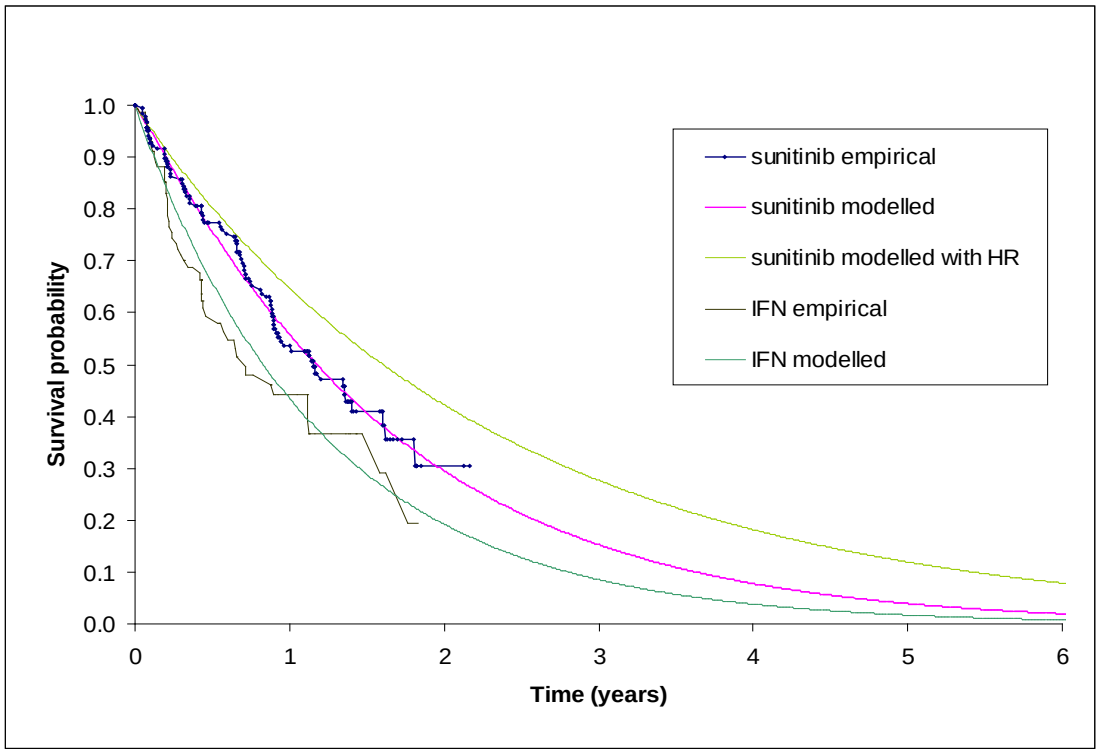
	Sunitinib	**IFN**	**Sunitinib vs IFN**
Life years	3.51	2.17	1.34
Progression free years	2.04	0.92	1.09
QALYs	2.51	1.55	0.96
Drug costs	£43,867	£5,318	£38,549
Follow-up costs	£2,813	£3,463	-£650
Diagnostic tests	£1,377	£643	£734
AEs	£76	£4	£72
BSC in progressed disease	£13,444	£12,339	£1,106
Total costs	£61,578	£21,767	£39,811
ICERs			
Cost/LYG			£29,761
Cost/QALY			£41,472

No post study treatment analysis – adjusting IFN PFS curve

As can be seen from Figure 5, the IFN PFS modelled curve does not visually fit the empirical data. Consequently it could be argued that the model underestimates the IFN PFS benefit. In their assessment of sunitinib, PenTAG adjusted the IFN curve we

submitted by fitting one data point per moth to remove the bias caused by outliers in the regression. The TAR does not give specific details for which points were used, in our analysis the data point at complete month has been used (1,2,3,4,etc). This adjustment gives the following PFS curve.

Figure 7: No post study treatment analysis – adjusted PFS curve



It is now evident that the IFN curve fits the data better, although applying the HR to this curve to create the sunitinib curve risks overestimating the sunitinib benefit. In the cost effectiveness analysis presented in table 5, the PFS value for sunitinib is read from the sunitinib modelled curve. The OS curves have not been changed.

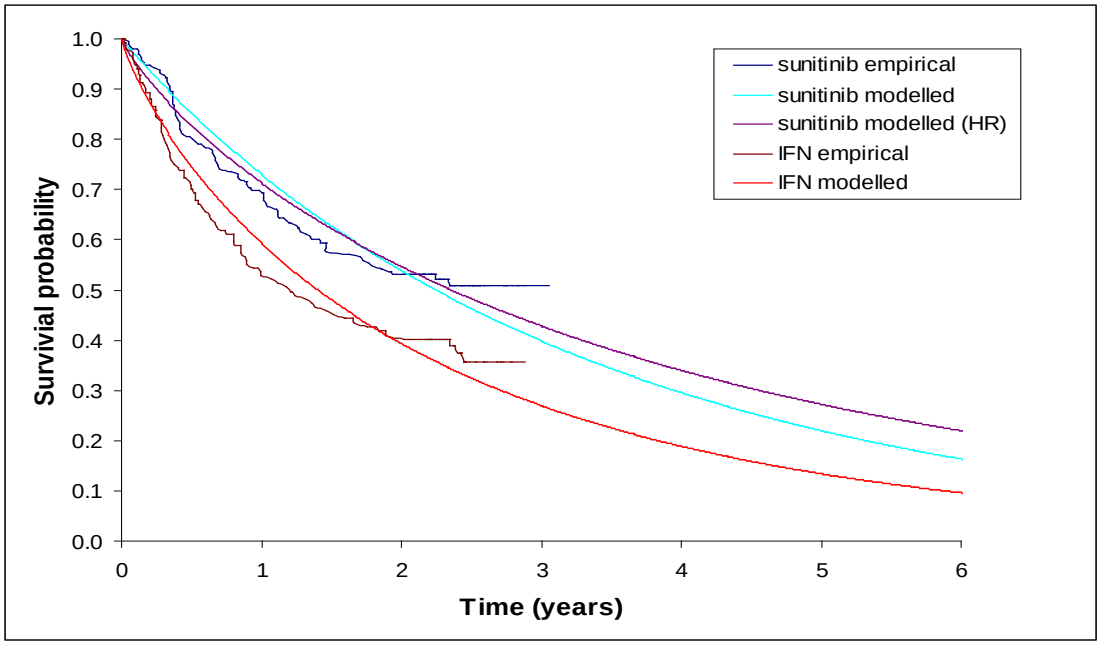
Table 5: Cost-effectiveness analysis from no post study treatment data (adjusted IFN curve)

	Sunitinib	**IFN**	**Sunitinib vs IFN**
Life years	3.51	2.17	1.34
Progression free years	1.62	1.21	041
QALYs	2.49	1.58	0.91
Drug costs	£34,902	£6,956	£27,946
Follow-up costs	£2,333	£4,470	-£2,137
Diagnostic tests	£1,112	£838	£274
AEs	£72	£4	£67
BSC in progressed disease	£16,206	£10,321	£5,885
Total costs	£54,625	£22,589	£32,036
ICERs			
Cost/LYG			£23,948
Cost/QALY			£35,245

No post study treatment analysis – adjusting OS and PFS IFN curves

The modelled OS curves appear to underestimate the longer term survival as the curves diverge towards the tail. Using the same principle to fit the OS curve as used to fit the PFS curves gives adjusted curves as shown in Figure 8. In this instance the sunitinib modelled (HR) curve fits the data better than the sunitinib modelled curve. In the cost effectiveness analysis presented in Table 6 the sunitinib modelled (HR) curve has been used to derive mean OS for sunitinib. The PFS curves shown in Figure 7 have been used to estimate mean PFS.

Figure 8: No post study treatment analysis – adjusted OS curve



The cost-effectiveness results presented in table 6 give the best case for sunitinib (lowest ICER) and the use of marginally different approaches to derive the OS and PFS curves needs to be considered.

Table 6: Cost effectiveness analysis from the no post study treatment data (adjusted OS and PFS IFN curves)

	Sunitinib	**IFN**	**Sunitinib vs IFN**
Life years	4.01	2.39	1.63
Progression free years	1.62	1.21	041
QALYs	2.81	1.72	1.10
Drug costs	£34,902	£6,956	£27,946
Follow-up costs	£2,333	£4,470	-£2,137
Diagnostic tests	£1,112	£838	£274
AEs	£72	£4	£67
BSC in progressed disease	£19,478	£11,744	£7,735
Total costs	£57,897	£24,012	£33,885
ICERs			
Cost/LYG			£20,818
Cost/QALY			£30,904

In the absence of a fully executable version of the PenTAG it has not proved possible to evaluate the impact of the use of the final data set excluding patients who received post study treatment, rather than the Escudier or Motzer Interim Analysis 2 data from the perspective of the Assessment Group. We do believe however that the incorporation of this data would lead to a more credible evaluation of the cost effectiveness of sunitinib that was also more in line with the drugs demonstrated clinical efficacy.

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Bevacizumab, sorafenib, sunitinib and temsirolimus for renal cell carcinoma
Pfizer response to the Appraisal Consultation Document

Summary

Pfizer believes that sunitinib is both clinically efficacious and cost-effective, compared to other systemic therapies, when used to treat patients with metastatic Renal Cell Carcinoma (mRCC) in England and Wales.

We are therefore disappointed that the Committee has not recommended sunitinib, a drug that has now become the standard of care in treating this condition across the rest of Europe.

We understand that one of the major impediments to reaching a positive decision lay around understanding the applicability and robustness of a key analysis within the final study results presented to the Institute. This analysis, which excluded patients who received additional systemic treatment, is most reflective of relative drug efficacy in settings where clinicians will not realistically have the opportunity to prescribe, or individual patients receive, more than one systemic therapy. Further data obtained by Pfizer in relation to this analysis, presented here, support the applicability of the data to help guide decision making regarding the use of sunitinib.

Pfizer also highlighted a number of issues in our response to the Assessment Report (TAR) around the approach taken to the clinical data and the relative cost-effectiveness of sunitinib, which significantly modified the Assessment Group base case, that are not reported on in the ACD and we are therefore unclear whether they have been considered.

Pfizer is in discussion with the Department of Health in relation to formalising our commitment to offering the first cycle of treatment free to all patients commencing treatment for mRCC with sunitinib. We hope that discussions will be concluded promptly and will advise NICE when they are completed. In the interim we would request that the free cycle is reflected in any re-analyses undertaken in response to feedback regarding the ACD.

This failure to recommend sunitinib is particularly disappointing given that the drug was given the first ever positive opinion on the granting of a conditional marketing authorisation (designed to facilitate early access to medicines) by the CHMP effective July 2006 for second line use in mRCC and GIST. This decision is strongly aligned with the proposals in the Cooksey Report, subsequently adopted by the UK

Government, for Conditional Licensing to be granted to medicines which demonstrate evidence of appropriate efficacy and safety, especially in patient populations with significant unmet clinical need

We believe that a re-appraisal of evidence, incorporating these points, explored in more detail below, should conclude that sunitinib is not only clinically efficacious in relation to other systemic therapies available but also cost-effective when applying the threshold used by the National Institute for Health and Clinical Excellence.

Clinical efficacy

The clinical efficacy of sunitinib has been significantly underestimated in the ACD because of a failure to accept the validity of the survival analysis excluding patients who received further systemic treatment post study discontinuation. The validity has been questioned under three broad headings:

1. The applicability of post hoc analyses.
2. The appropriateness of the specific analytical approach.
3. The availability of sufficient information regarding demographics and patient characteristics.

The applicability of post hoc analyses

In the study, overall survival OS) was a pre-specified secondary endpoint; the primary endpoint being progression free survival (PFS) where sequential treatment with multiple systemic therapies is generally not regarded to have been a confounder. Pfizer acknowledges that the OS intention to treat (ITT) analysis of the full trial population is reflective of the study protocol and accepts that the statistical analysis plan failed to incorporate the need to develop strategies to handle confounding events that could reasonably be expected to occur , so as to enable application of the study results to the needs of patients, UK clinical practice and HTA bodies.

The European Medicines Evaluation Agency (EMEA) has recognised that there are significant issues with clinical trial design and measuring overall survival in the sphere of oncology, stating recently,

> *"While it is generally acknowledged that the aim of treatment is to improve quality of life and survival, restraints on the conduct of clinical trials may make these goals unattainable. It is thus recognised that investigators, patients and ethics committees may require, e.g. optional cross-over at time of tumour progression. Similarly, the use of active next-line therapies must be accepted. This may affect the possibility of detecting differences in OS as well as symptoms related to tumour progression." (EMEA 2005)*

Previous NICE Committees have also acknowledged the inadequacies of Randomised Controlled Trials (RCTs) where cross-overs or multiple treatments have played a part; the Appraisal Committee reporting on the use of RCTs in TA30 (Breast cancer - taxanes (review)) stated,

> *"Conducting and interpreting randomised controlled trials of anti-cancer drugs is complicated by a number of issues; including protocol defined and undefined cross over to alternative treatment where there is evidence of disease progression on randomised treatment, unblinded studies and differential toxicity profiles".*

and have gone further to question how the findings should be interpreted,

> *"The evidence base for the management of advanced colorectal cancer includes a number of randomised controlled trials. However, results for overall survival from RCTs need cautious interpretation because the disease is often managed with sequences of either mono- or combination therapy, with the frequent use of unplanned second- or third-line salvage chemotherapy." (TA93 (Irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer (review of TA33))*

and we would strongly argue that similar caution needs to be applied to interpreting the recent sunitinib RCT data relating to the current appraisal.

The appropriateness of the analytical approach

Discussion relating to the overall survival (OS) benefit of sunitinib centres on the validity of alternative final analyses to that of the full Intention To Treat (ITT).

The full ITT analysis incorporates patients who were permitted to cross over from interferon alfa (IFN-α) after the first interim analysis as well as including patients who received further treatment post study discontinuation.

An analysis was performed in which patients who crossed over from IFN-α to sunitinib were censored at the time of crossover. Allowing crossover in a study has the potential to confound any demonstration of improvement in OS with censoring at the point of cross-over a legitimate means of addressing it. This analysis demonstrated a statistically significant benefit in OS for patients treated with sunitinib but still failed to fully explain the value of sunitinib to clinical practice in the UK.

This ITT analysis, with cross overs censored, appears to demonstrate a survival benefit for IFN-α significantly greater than that reported in other clinical trials or experienced in clinical practice. This has been attributed solely to the overall improvement in management of patients with cancer which is simplistic and not supported by the evidence. Table 1 below shows the median survival with IFN-α for a number of studies. The Escudier 2007 (19.8m) and Figlin 2008 (20m) are the two highest. These are both confounded by the significant number of patients who went on to receive second or third line systemic therapy, as clinical trial data demonstrates that second line treatment improves overall survival in patients who have progressed on their initial systemic therapy (Escudier et al, 2007[1] Motzer et al, 2005).

Table 1: Overall Survival benefit with IFN-α from selected studies[i]

Study	Median Survival (months)
Creagan et al, 1991	8
Niedhart et al, 1991	10
Fossa et al, 1992	12
Minasian et al, 1993	11.4
MRC Collaborators, 1999	8.5
Motzer et al, 2000	15
Mickisch et al, 2001	17 (+ nephrectomy) 7
Flanigan et al, 2001	11.1 (+ nephrectomy 8.1
Aass et al, 2005	3.12
Coppin et al, 2005[§]	13.3

[i] Adapted from a table in Parton M, Gore M, Eisen T. Role of Cytokine Therapy in 2006 and Beyond for metastatic Renal Cell Cancer. *Journal of Clinical Oncology* 2006;24:5584-5592.

Escudier et al 2007[2]*	19.8
Figlin et al, 2008**	20

[§]Cochrane Systematic review of 52 trials
* IFN-α + placebo arm of AVOREN study, 39% of patients received further treatment with 20% receiving a TKI. **IFN-α arm of A6181034 study, 59% of patients received further systemic therapy.

To explore the potential confounding influence of post-study cancer treatments, the systemic treatments patients received post A6181034 study discontinuation were reviewed and analysed as shown in Table 2. Of the 359 IFN-α patients who discontinued from the study, 59% received post-study cancer treatments with 33% receiving sunitinib. The inclusion of such patients confounds any analysis of survival benefit[ii].

Table 2: Patients who received systemic therapy post study discontinuation (A6181034)

	Sunitinib, n (%) (n=323)	IFN-α, n (%) (n=359)
Any post-study treatment	182 (56)	213 (59)
Sunitinib	36 (11)	117 (33)
Other VEGF* Inhibitors	106 (33)	115 (32)
Cytokines	63 (20)	47 (13)
mTOR** Inhibitors	28 (9)	16 (4)
Chemotherapy	21 (6)	20 (6)

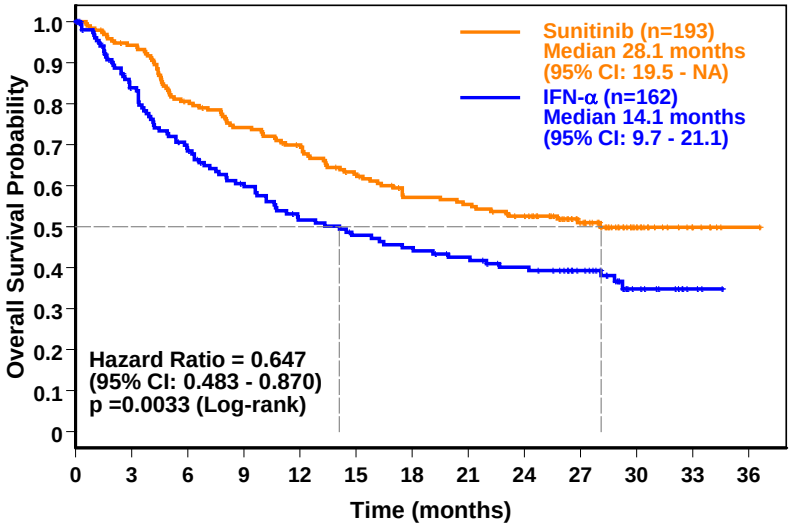
*Vascular Endothelial Growth Factor. **mTOR = mammalian Target Of Rapamycin

In the UK, outside of participation in clinical trials, patients do not routinely receive sequential treatment with a number of systemic therapies; as happened to a majority of patients in the sunitinib study (Table 2). Unless the guidance to be published by the Institute on the management of patients with mRCC specifically recommends sequential therapy, the likelihood will decrease even further. Therefore, to be applicable to the UK, a revised study analysis needs to exclude patients who have received more than one systemic agent.

This additional analysis (Figure 1), already presented to NICE, importantly appears to offer a more accurate interpretation of the efficacy of the two drugs with the median value for IFN-α of 14.1 months corresponding well to the value from the Cochrane systematic review of 13.3 months (Coppin et al, 2005).

Figure 1: Overall Survival in patients who did not receive systemic therapy post study discontinuation.

[ii] There is work ongoing using Marginal Structural modelling to handle time dependent variables such as the use of additional systemic therapies in the A6181034 study because of problems such as this (Hernan et al, 2000; Wang et al, 2008).



Patients who crossed over to sunitinib in the study (I.e. did not receive sequential therapy other than sunitinib on study) are included in this additional analysis. This will have marginally increased the median value for IFN-α.

The availability of sufficient information regarding demographics and patient characteristics.

The Committee commented on the need for further information regarding the patients included in the analysis that excluded patients who received systemic therapy post discontinuation, to understand its relevance and also to understand how representative these patients were of the overall study population.

We have generated a breakdown of the demographics and patient characteristics for patients included in this analysis. This has been incorporated into a table (Table 3) that includes the demographics and patient characteristics for the overall study population. This serves to demonstrate that there is no systematic difference in patient characteristics between the treatment groups (sunitinib vs. IFN-α) both in the overall population as well as in patients who did not receive post study systemic therapy.

Table 3: Demographics & baseline characteristics - sunitinib versus IFN-α; complete and exploratory (no post treatment systemic therapy) groups

Variable	Sunitinib Full study	**Sunitinib No post treatment systemic therapy**	**IFN-α No post treatment Systemic therapy**	IFN-α Full study
n	375	**193**	**162**	375
Age (years)				
Mean (Std)	60.6 (10.1)	**61.0 (10.1)**	**60.1 (9.4)**	60.1 (9.5)
Median	62.0	**63.0**	**60.5**	59.0
(Min,Max)	(27.0, 87.0)	**(27.0, 84.0)**	**(34.0, 79.0)**	(34.0, 85.0)
Age (years) [n (%)]				
< 65	223 (59.5)	**109 (56.5)**	**108 (66.7)**	252 (67.2)
>= 65	152 (40.5)	**84 (43.5)**	**54 (33.3)**	123 (32.8)
Sex [n (%)]				
Male	267 (71.2)	**130 (67.4)**	**120 (74.1)**	269 (71.7)
Female	108 (28.8)	**63 (32.6)**	**42 (25.9)**	106 (28.3)
Race [n (%)]				
White	354 (94.4)	**186 (96.4)**	**150 (92.6)**	340 (90.7)
Black	4 (1.1)	**0 (0.0)**	**3 (1.9)**	9 (2.4)
Asian	7 (1.9)	**5 (2.6)**	**4 (2.5)**	12 (3.2)
Not Listed	9 (2.4)	**2 (1.0)**	**5 (3.1)**	13 (3.5)
Not allowed to ask	1 (0.3)	**0 (0.0)**	**0 (0.0)**	1 (0.3)
Height (cm)				
n	354	**182**	**159**	362
Mean (Std)	171.8 (9.7)	**171 (10.1)**	**171.2 (9.3)**	171.1 (10.0)
Median	172.0	**171.0**	**172.0**	172.0
(Min,Max)	(144.8, 198.1)	**(144.8, 198.1)**	**(147.0, 189.0)**	(105.5, 194.0)
Weight (kg)				
n	370	**189**	**159**	371
Mean (Std)	83.7 (19.1)	**81.8 (17.3)**	**82.4 (17.5)**	83.1 (20.0)
Median	82.0	**81.0**	**80.0**	80.0
(Min,Max)	(44.5, 181.8)	**(47.3, 151.0)**	**(46.0, 147.7)**	(46.0, 210.5)
ECOG [n (%)]				
0	231 (61.6)	**111 (57.5)**	**88 (54.3)**	229 (61.6)
1	144 (38.4)	**82 (42.5)**	**71 (43.8)**	142 (37.9)
2*	0 (0.0)	**0 (0.0)**	**3 (1.9)**	4 (1.1)
Lactate Dehydrogenase [n (%)]				
> 1.5 x ULN	15 (4.0)	**11 (5.7)**	**14 (8.6)**	20 (5.3)
<= 1.5 x ULN	360 (96.0)	**182 (94.3)**	**134 (82.7)**	338 (90.1)
Missing	0 (0.0)	**0 (0.0)**	**14 (8.6)**	17 (4.5)
Haemoglobin [n (%)]				

< lower limit of normal	98 (26.1)	**59 (30.6)**	**53 (32.7)**	121 (32.3)
>= lower limit of normal	277 (73.9)	**134 (69.4)**	**96 (59.3)**	238 (63.5)
Missing	0 (0.0)	**0 (0.0)**	**13 (8.0)**	16 (4.3)
Corrected Calcium [n (%)]				
> 10 mg/dL	29 (7.7)	**21 (10.9)**	**6 (3.7)**	17 (4.5)
<= 10mg/dL	346 (92.3)	**172 (89.1)**	**143 (88.3)**	342 (91.2)
Missing	0 (0.0)	**0 (0.0)**	**13 (8.0)**	16 (4.3)
Nephrectomy [n (%)]				
Absence of Nephrectomy	35 (9.3)	**22 (11.4)**	**18 (11.1)**	40 (10.7)
Presence of Nephrectomy	340 (90.7)	**171 (88.6)**	**144 (88.9)**	335 (89.3)
Liver Metastases [n (%)]				
Yes	99 (26.4)	**56 (29.0)**	**40 (24.7)**	90 (24.0)
No	276 (73.6)	**137 (71.0)**	**122 (75.3)**	285 (76.0)
Lung Metastases [n (%)]				
Yes	292 (77.9)	**151 (78.2)**	**125 (77.2)**	298 (79.5)
No	83 (22.1)	**42 (21.8)**	**37 (22.8)**	77 (20.5)
Bone Metastases [n (%)]				
Yes	112 (29.9)	**60 (31.1)**	**46 (28.4)**	112 (29.9)
No	263 (70.1)	**133 (68.9)**	**116 (71.6)**	263 (70.1)
Number of Metastatic Sites [n (%)]				
0 or 1	74 (19.7)	**40 (20.7)**	**43 (26.5)**	88 (23.5)
2 or >= 3	301 (80.3)	**153 (79.3)**	**119 (73.5)**	287 (76.5)
Missing	0 (0.0)	**0 (0.0)**	**0 (0.0)**	0 (0.0)
Previous radiotherapy [n (%)]				
Yes	53 (14.1)	**24 (12.4)**	**27 (16.7)**	54 (14.4)
No	322 (85.9)	**169 (87.6)**	**135 (83.3)**	321 (85.6)
MSKCC Risk Factors** [n (%)]				
0 Risk Factors	143 (38.1)	**72 (37.3)**	**46 (28.4)**	121 (32.3)
1 or 2 Risk Factors	209 (55.7)	**106 (54.9)**	**91 (56.2)**	212 (56.5)
>= 3 Risk Factors	23 (6.1)	**15 (7.8)**	**11 (6.8)**	25 (6.7)
Missing 1 or More Factors	0 (0.0)	**0 (0.0)**	**14 (8.6)**	17 (4.5)

% = (n/N)*100

* All subjects had ECOG performance status of 0 or 1 at the time eligibility was determined; some subjects' condition deteriorated such that ECOG was 2 at the last pre-treatment assessment, which is summarized here.

**MSKCC risk factors including: ECOG>1, high LDH (>1.5 x ULN), low Hgb (<LLN), high corrected calcium (>=10 mg/dL), and time from initial diagnosis (<1 year). Only patients with data for all five risk factors are summarized.

The Assessment Group commented,

> *" On the subgroup data presented for individuals who did not receive any post study treatment, whilst the information provided is interesting, we feel it is important to highlight that this sub-group of patients was not pre-defined within the study protocol and we are unsure how such a subgroup would be identified prospectively (pre-selection?) in the clinical setting".*

and Pfizer agrees that whilst identifying these patients prospectively would be difficult it is in fact unnecessary. This analysis is of a representative sample of the overall population requiring treatment and, in a clinical setting where multiple systemic drugs are not available for use on a routine basis; the efficacy values from this analysis are more likely to reflect actual results in practice. This is supported by the comparison of demographics and patient characteristics presented in Table 3 that demonstrates no systematic difference between the analysis groups.

Further support for the representative nature of this analysis compared with the total study population can be gained by examining progression free survival (Table 4).

Table 4: Progression free survival A6181034 study

	Sunitinib	IFN-α
All study participants, Median - weeks	48.0	22.3
95% confidence intervals	(46.3, 58.1)	(17.3, 24.0)
Patients who did not receive systemic treatment post study discontinuation, Median - weeks	50.1	22.3
95% confidence intervals	(45.7, 70.4)	(14.6, 31.3)

As stated in a previous communication, had this analysis been available at the time of the original submission, we would have presented the case for it being the more appropriate for use to both position sunitinib within the care pathway and to drive any cost-effectiveness analysis. The views of clinicians expert in treating patients with mRCC support the appropriateness of this approach and is captured in the response to NICE from the Royal College of Physicians:

> *"An analysis in which patients who crossed over or received 2nd line treatment with other agents was presented confirming a huge median overall survival benefit (increased from 14months to 28months). This is the "purest" population in which it is possible to establish the survival benefit of sunitinib."*

The feed back received from UK oncologists who have seen all three analyses of the final data (ITT, ITT cross overs censored, and no systemic therapy post study discontinuation) is that the latter is the most applicable to the clinical setting in England and Wales.

Cost-effectiveness

The Committee has concluded that sunitinib is not cost-effective, with the reasons lying under four broad headings:

1. The choice of clinical data used to inform the model.

2. The modelling of the clinical data selected.
3. The failure to incorporate into a revised base case previously highlighted concerns regarding model assumptions, inputs around utility values, cost of supportive care, and death.
4. The failure to incorporate the free cycle offered by Pfizer into the base case.

The choice of clinical data used to inform the model

As discussed above, the analysis of final OS data that excludes patients who received systemic treatment post study discontinuation would have been used as the base case had it been available at the time of the original submission. We did however provide a revised cost-effectiveness analysis based on this data on June 27th 2008 as soon as the data was to hand.

It would appear from the comment by PenTAG,

> *"We suggest that such a survival profile would lead to a lower cost per QALY in this subgroup, all else equal. However the PenTAG modelling framework is structured to use data on both progression-free-survival and overall survival from the same source – consistent across all cost-effectiveness analyses undertaken for the broader review – to estimate cost-effectiveness. We believe this to be the correct approach given the modelling framework used. Therefore we are unable to provide cost-effectiveness estimates using this additionally supplied data on OS for either sub-group." (PenTAG response to comments on the TAR. Pg.2)*

that there are concerns related to the source of the efficacy data used to generate these cost-effectiveness results, which prevented the Group from developing their own cost-effectiveness estimate from this analysis. While the PFS curves for the exploratory analysis have not been published alongside the OS curves, we would like to clarify that the efficacy data used to model the sub-group population was **all** derived from the exploratory analysis.

The modelling of the clinical data used

In modelling the OS and PFS for this analysis, the IFN-α survival data was extrapolated using regression techniques to estimate the parameters of the Weibull survival curve. The sunitinib survival curves were then modelled using the revised hazard ratios and the extrapolated IFN-α survival curve. The resulting curves and the empirical data from the exploratory analysis are shown figures 2 and 3.

Figure 2: Progression free survival – no systemic treatment post study discontinuation analysis

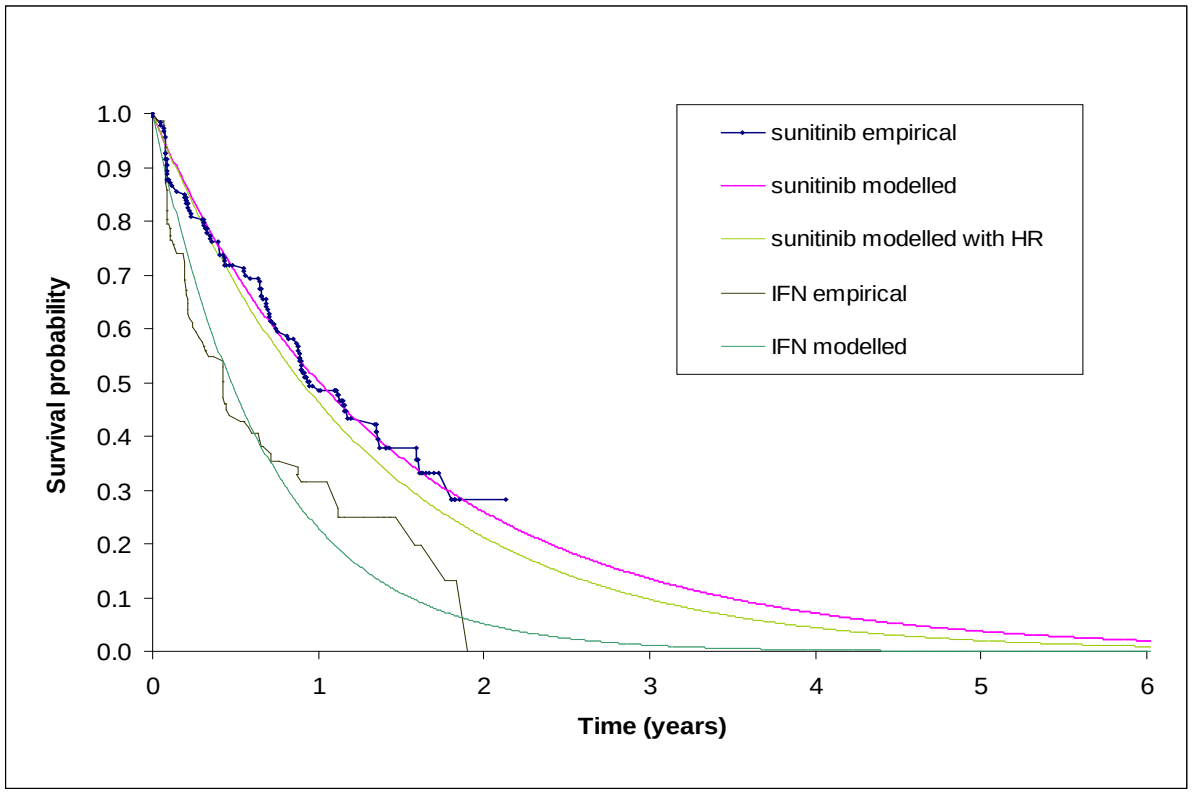
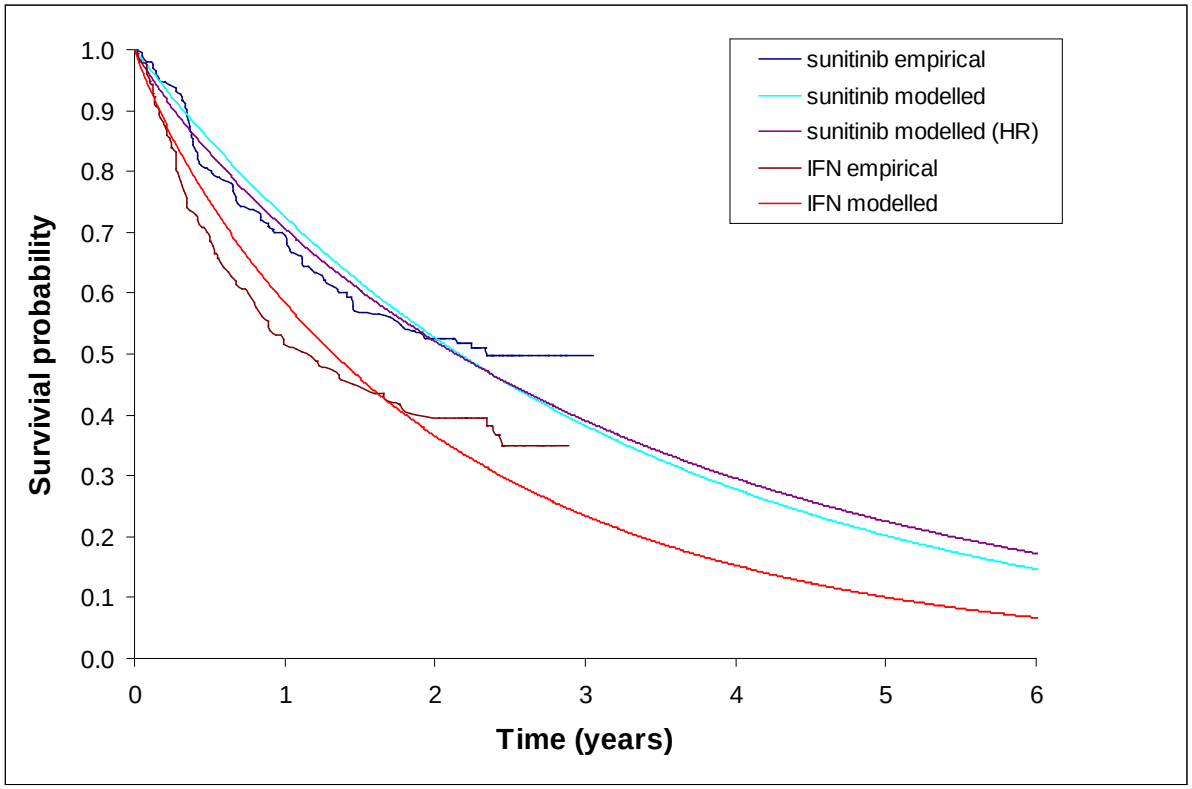


Figure 3: Overall survival - no systemic treatment post study discontinuation analysis

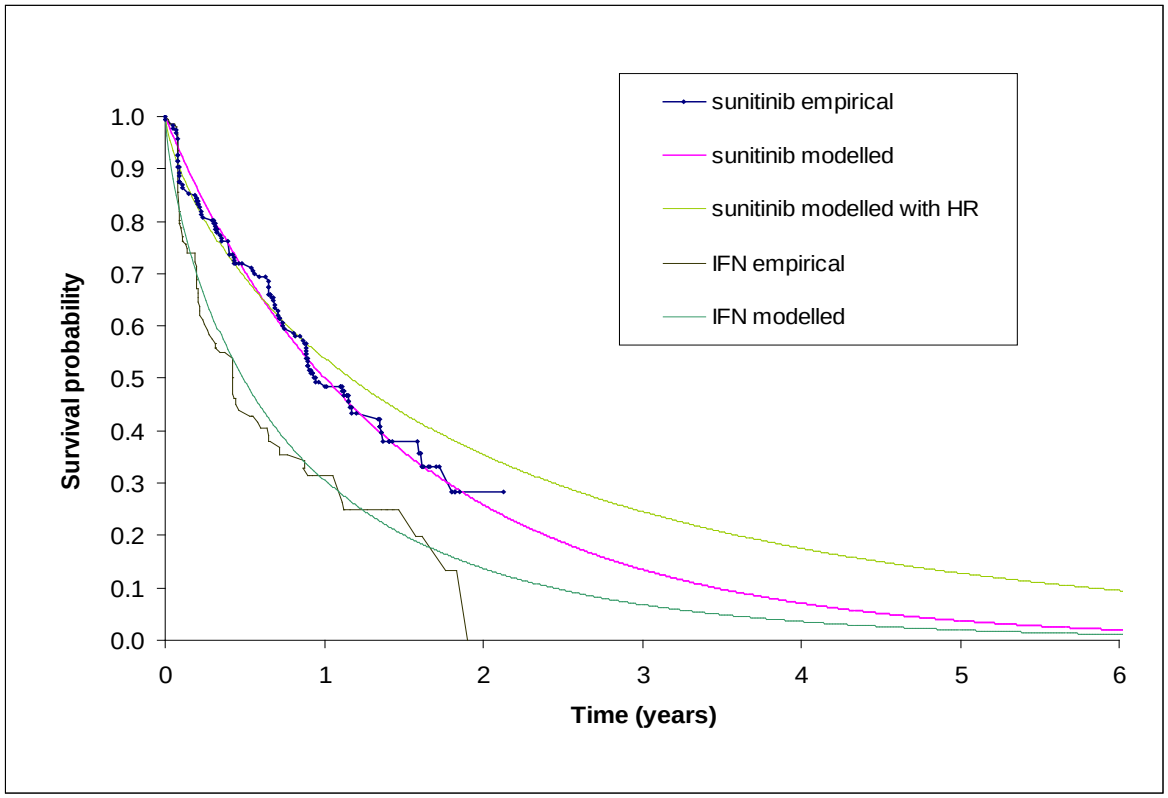


The above curves were generated from a regression that used all available data points to estimate the Weibull parameters, this approach is consistent the approach taken in our original submission. However, as in the original submission, the survival analysis for PFS is heavily influenced by the

first few data points in the Kaplan-Meier trial data and results in the model underestimating the PFS for IFN-α.

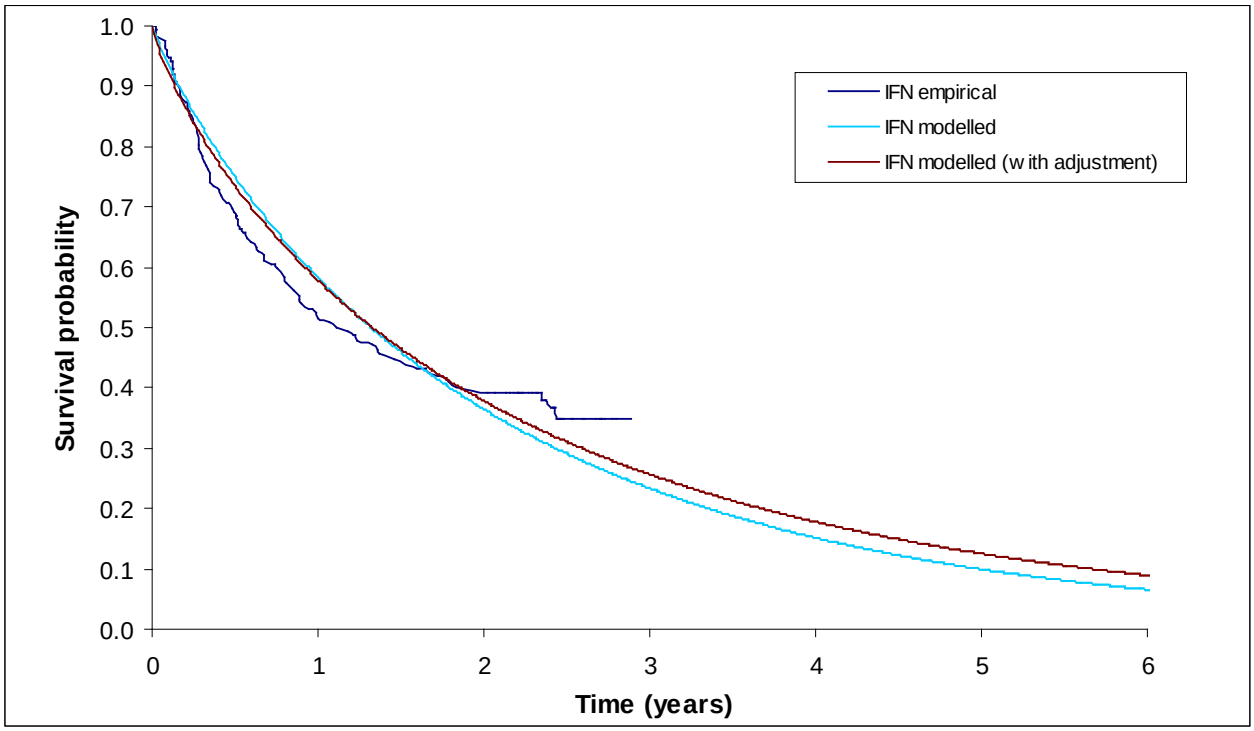
In our original model, PenTAG corrected this underestimation by fitting a Weibull curve to fewer data points (one per month). We have adopted this approach to improve the fit of the IFN-α curve shown in figure 2 and generated the survival curves for IFN-α and sunitinib as shown in figure 4. While adjusting the regression improves the fit of the IFN-α curve, applying the hazard ratio to this IFN-α curve to estimate the sunitinib curve generates one that does not fit the sunitinib trial data. When the curve for sunitinib is fitted independently (sunitinib survival data is extrapolated using regression to estimate the parameters of a Weibull curve), the modelled curve is shown to fit the data very well.

Figure 4: Adjusted PFS curves: no systemic treatment post study discontinuation analysis



The survival analysis for OS is also heavily influenced by the first few data points in the Kaplan-Meier trial data. The transformation of the Weibull survival function S(t) for regression, In(-In(S(t)) is very large and negative where S(t) is below 1. Adjusting the regression by fitting one data point per month (the approach used by PenTAG) alters the shape slightly, by reducing the underestimate observed at the end of the curve (figure 5).

Figure 5: Overall survival curves: no systemic treatment post study discontinuation analysis



To estimate cost-effectiveness of sunitinib compared to IFN-α, mean survival times have been calculated from the Weibull curves shown in figure 4 (for PFS) and figure 5 (for OS). Using the costs and utilities from our original submission, this gives the following cost effectiveness result.

Table 5: Cost effectiveness analysis of no systemic treatment post study discontinuation analysis

	Sunitinib	**IFN-α**	**Sunitinib vs IFN-α**
Life years	3.88	2.29	1.59
Progression free years	1.49	0.95	0.53
QALYs	2.72	1.63	1.09
Drug costs *	£31,920	£5,495	£26,425
Follow-up costs	£2,173	£3,577	-£1,405
Diagnostic tests	£1,024	£664	£360
AEs	£70	£4	£66
BSC in progressed disease	£19,552	£12,932	£6,621
Total costs	£54,739	£22,672	£32,067
*First cycle of sunitinib free			
ICERs			
Cost/LYG			£20,205
Cost/QALY			**£29,440**[3]

Probabilistic sensitivity analysis was undertaken to explore the impact of second-order uncertainty surrounding mean parameter values on marginal costs and health effects. The probabilistic analysis was carried out by allowing parameters to vary according to the uncertainty specified in their probability distributions, with 2,000 sets of random numbers used to generate 2,000 sets of cost-effectiveness results. The results of these simulations are presented as cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs). Figure 6 presents a

[3] In the analyses presented June 27th the ICER was reported as £30,904. An error in translating the raw data was responsible for the higher figure, uncovered when further analyses received from the study statistician were used to validate the modelling approach.

cost effectiveness plane showing the marginal costs and QALYs associated with sunitinib compared to IFN-α. Figure 7 shows the cost effectiveness acceptability curve. The CEAC shows that at a willingness to pay threshold of £30,000 the probability that sunitinib is cost effective is 51%

Figure 6: Incremental cost effectiveness scatter-plot

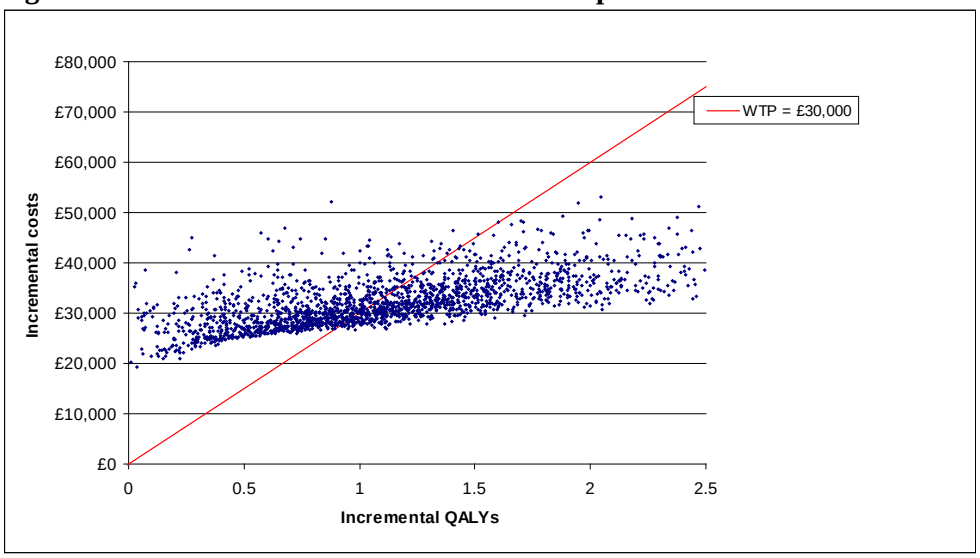
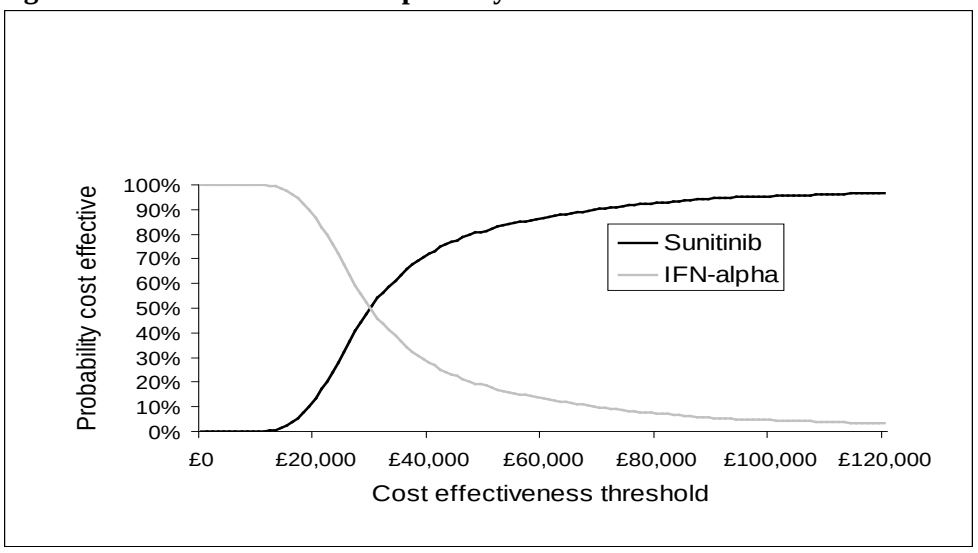


Figure 7: Cost effectiveness acceptability curve



The Committee appear confident that the approach taken to modelling the data is sound but that it could not be *'…considered a robust basis for decision making as the estimates had not been critiqued by the Assessment Group and no details about the post-hoc subgroup were provided'*. Pfizer has addressed the concerns about missing details elsewhere in this response as well as the argument for the utility of the analysis. We have also attached to this response a fully executable version of the model used to derive cost-effectiveness results for this analysis. Should any further data be required over and above that present in the model we will provide it on request.

The failure to incorporate into a revised base case previously highlighted concerns regarding model assumptions and inputs around utility values and cost of supportive care and death.

In our response to the TAR, we raised the concern that the Assessment Group base case ICER represented an inflated estimate of the ICER for sunitinib compared to IFN-α. We felt that their

assumptions concerning utility values and costs associated with supportive care and death were not representative of clinical practice. The further scenario analysis we presented in response to the TAR demonstrated that the cumulative effect of changing assumptions related to baseline efficacy data, supportive care costs, 1st free cycle, inclusion of death costs resulted in a much lower ICER for sunitinib compared to IFN-α.

The Assessment Group, in their response to comments on the TAR; acknowledge the accuracy of this multi-way sensitivity analysis, however there is no evidence within the ACD that this alternative base case figure has been considered. That PenTAG have accepted the validity of a number of the sensitivity analyses, leaves Pfizer with the concern that, where there is acknowledged uncertainty within each of the two approaches, the Committee defaults to that of their Assessment Group, without exploring the validity of the arguments raised by Pfizer. This is especially concerning as some of the PenTAG assumptions are clearly built around subjective opinion within their team.

Utility values

In relation to the utility values used we note that our comments have been acknowledged and that PenTAG conducted further sensitivity analyses to explore in greater detail the uncertainty around the values used in their base case. As discussed above there is no evidence that this has been considered by the Committee as valid to modify the PenTAG base case.

In our revised analysis, presented above, we have modelled using the trial based utility values as in our original submission. These values are problematic as the values derived from the Motzer study are 'within trial' values and therefore unlikely to be an accurate reflection of the 'true' utility associated with being either progression free or progressed with a diagnosis of metastatic RCC as reflected in real world practice. In addition, as we have previously commented, there are significant concerns that the 'progressed' values within the trial were taken at the point where the patients entered the progressed state.

The failure to incorporate the free cycle offered by Pfizer into the base case.

In line with Pfizer's ongoing commitment to ensure the widest possible access to clinically effective drugs the cost of the drug was reduced by 5% in May 2007 making the UK price of Sutent the lowest within Europe.

In addition, Pfizer commenced offering the first cycle free on 08/05/2007, having confirmed with the MHRA that this revised pricing scheme did not constitute a prohibited "gift, pecuniary advantage or benefit in kind" to persons qualified to prescribe or supply medicines.

In response to the comments in the ACD regarding the scheme we have contacted the Department of Health and made them aware of its structure and function. We have answered the questions that the department had and now anticipate endorsement for the first cycle free scheme within the UK in the near future.

The cumulative effect of the price reduction and offering the first cycle free is estimated at being an effective total price reduction of 18.5%.

Conclusion

Pfizer believes that sunitinib is both clinically efficacious and cost-effective when used to treat patients with metastatic renal cell carcinoma in England and Wales.

The supporting data presented by Pfizer in relation to the final study results, demonstrates that there is no systematic difference between the patients in the analysis undertaken in those who did not receive any post study systemic therapy and the general study population. This supports the use of the analysis for demonstrating efficacy and modelling cost-effectiveness. In using this analysis, it has been shown that sunitinib can offer a doubling of overall survival benefit (28.1m) vs IFN-α (14.1m).

It appears that the Committee, in making the provisional recommendation in the Appraisal Consultation Document (ACD), have failed to take into account a number of key issues raised in previous correspondence around the Technology Assessment Report. This unfortunately has the effect of perpetuating inconsistencies in the approach to the sunitinib clinical data and also the drugs relative cost-effectiveness.

Pfizer has initiated discussion with the DoH regarding the offer of the first cycle of therapy free. This, along with the original five per cent price cut, has effectively reduced the cost to the NHS of sunitinib by 18.5%.

It is our view that a re-appraisal of evidence, incorporating the points above, should conclude that sunitinib is not only clinically efficacious in relation to other systemic therapies available, but also cost-effective when applying the threshold used by the National Institute for Health and Clinical Excellence.

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Document 2. Roche Products' response to the ACD.

MULTIPLE TECHNOLOGY APPRAISAL – Bevacizumab, sorafenib, sunitinib and temsirolimus for renal cell carcinoma

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

Roche welcomes the provisional clinical findings of the Appraisal Committee in relation to establishing the effectiveness of bevacizumab, recognising its ability to address significant unmet clinical need for patients with renal cell cancer. However, the ACD presently concludes that bevacizumab is not cost effective when based on either Roche's submission or on the analysis performed by the Assessment Group (AG).

Roche would like to request that the Appraisal Committee when reconsidering the ACD, evaluate further and deliberate on several key parameters currently included within the AG's economic model which we believe presently compromise the accuracy and validity of the final base case estimate of the bevacizumab ICER. In this context, we would also point out that the ACD is currently not clear regarding which of the alternative assumptions reported are considered to be most robust by the Appraisal Committee in establishing the base case ICER and we would like to request that these are made explicit to us.

We also present in this response to the ACD what Roche considers to be a more appropriate hazard ratio from the AVOREN trial for use in the AG's model in relation to appropriately taking into account post progression treatments and also present details of the actual dosing observed from the AVOREN trial because we believe the AG's treatment duration assumptions for bevacizumab are inaccurate.

Roche would like to request that if the points raised below are considered valid by the Appraisal Committee that they are incorporated into the AG's economic model cumulatively rather than as part of any univariate analysis in order to report a revised base case ICER for bevacizumab. Alternatively, if any of the points raised are not considered valid then we would like to request that the Committee provide a clear explanation and rationale as to why alternative assumptions are preferred.

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

It is unclear from the ACD as to whether or not Roche's response to the Assessment Group's Report discussing the validity of some of the assumptions used in their analysis was considered by the Committee. There are a number of differences between the clinical and economic analyses performed by Roche and those conducted by the AG which have a very significant impact on the final ICER and therefore it is important that each of these points be considered in turn:

A) Overall survival / post-progression treatment effect

In this section we provide a further analysis of the AVOREN pivotal trial that adjusts overall survival for second-line treatments.

Roche's original submission used an overall survival hazard ratio based on the safety population (HR 0.709) whereas the AG's analysis was based on the ITT population (HR 0.75).

Roche maintain that the safety population is the relevant population to consider in the analysis since this represents the population that actually received at least one dose of the study drug. AVOREN was a double-blinded trial and therefore the reason for a patient not receiving drug would not be related to which arm they had been randomised to. Additionally there is no incremental cost prior to the first dose between the two arms so the likelihood of patients not receiving treatment post randomisation is irrelevant. Hence patients that did not receive the study drug do not contribute to informing the decision problem and merely dilute the average costs and outcomes of the patients that did receive the study drug.

None of the analyses undertaken however account for the confounding effects of second-line treatments. This has previously been summarised in a publication by Tappenden et al *"The central difficulty in interpreting overall survival data from many existing cancer trials concerns the number of patients who crossover to alternative therapies following disease progression or treatment failure."…. "The implication for clinical effectiveness is that outcomes observed within the comparator treatment group may be exaggerated, leading to the underestimation of the incremental treatment benefit, whilst the implication for cost-effectiveness analyses is that the cost of achieving such benefits within the comparator arm will also be underestimated if these are omitted from the model."* (Methodological issues in the economic analysis of cancer treatments, Tappenden 2006)

Roche attempted to address the confounding factor of second-line treatments by including the cost of these treatments in our submission, as observed within the AVOREN trial.

However PenTAG noted in their response to comments on the AG report *"that whilst the published paper includes the statement that "Other neoplastic agents were allowed subsequent to progression or toxicity", we are unaware of any published evidence to suggest that TKIs or temsirolimus were used as second line therapies. We were therefore unable to adjust the IFN baseline overall survival data to reflect the use of second line treatment options."*

Roche interpret PenTag's comments to suggest that if they had had access to the patient level data from the AVOREN trial then they would have attempted to adjust overall survival for second-line therapies. This represents an alternative and credible method of adjusting for the confounding effect of second line therapy. Roche agree that AVOREN, being a multinational trial, does not fully reflect the decision problem in this appraisal and that adjusting for second-line therapies would therefore represent a more fit for purpose analysis.

Re-analysis of the AVOREN trial adjusting for second-line therapies by censoring patients that received novel treatments second-line (bevacizumab, sunitinib and sorafenib), results in an overall survival hazard ratio for bevacizumab of 0.613 (C.I.: 0.464; 0.811) stratified by Motzer score and region and 0.605 (CI: 0.459; 0.796) un-stratified.

There is an inevitable trade off between maintaining randomisation of the resulting cohort versus how well it represents the decision problem of interest. The validity of the revised hazard ratio relies on the assumption that the characteristics of the censored patients are balanced between the arms and are representative of the patient population as a whole. It can be seen from Table 1 below that the baseline characteristics of the censored patients are broadly similar to the ITT population except possibly with regards to Motzer score. The

hazard ratio stratified by Motzer score and region takes into account any imbalance between the arms relating to Motzer score and therefore is the most applicable estimate to use.

Table 1: Baseline characteristics of censored patients

	Censored Population		ITT Population	
	Bevacizumab + IFN	INF	Bevacizumab + IFN	IFN
Number of patients	91	56	325	316
Male	67%	82%	68%	73%
Motzer score— Favourable Intermediate Poor	 31% 62% 8%	 46% 54% 0%	 30% 61% 9%	 32% 60% 8%
Age <65	67%	56%	63%	63%
No. of metastatic sites	2.34	2.52	2.41	2.39
Karnofsky Score 100 90 85 80 75 70	 57% 25% 1% 12% 0% 4%	 52% 34% 0% 11% 0% 4%	 44% 31% 1% 17% 0% 6%	 38% 39% 0% 16% 0% 7%
Mean Weight	76.63	79.85	76.03	77.39

Second-line treatments reported in Roche's original submission were based on a table in the AVOREN clinical study report entitled "Summary of subsequent antineoplastic therapy started after disease progression by trial treatment". In the course of estimating a revised hazard ratio it was discovered that this post-progression treatment table does not include any bevacizumab administered post-progression (off licence second-line use) in the bevacizumab+IFN arm. This was because any treatment with bevacizumab had been started prior to disease progression and did not meet the definition of treatments within this specific table. This has been corrected in the re-analysis so that all second-line novel agents are censored.

Roche therefore requests that any analysis relating to bevacizumab should now use the overall survival hazard ratio of 0.613 as we believe this best reflects the treatment benefit of bevacizumab within its UK licensed indication, compared with a scenario and consequent outcomes where it is not made available (i.e, the decision problem of interest).

Analysis utilizing the ITT hazard ratio would in effect be modeling the outcomes of bevacizumab followed by a bundle of other novel agents (many off license and unlikely to be prescribed within the UK NHS) compared to IFN followed by a bundle of novel agents.

B) Average cumulative dose administered per patient

For patients who received bevacizumab there is presently a discrepancy between the cumulative dose recorded in the AVOREN trial and that estimated by the AG. This results in a cost difference between the two models of £12,535 (and an approximate difference in the ICER we estimate of approximately £47,000).

Roche used the actual mean cumulative dose as observed in the AVOREN trial to calculate drug acquisition cost. We consider this the optimal method of calculating drug acquisition costs as it is a precise reflection of drug consumption that resulted in the health benefits observed in the trial.

The AG used an estimated average cumulative dose based on the assumption of treatment until progression and an average dose intensity taken from the Escudier *et al* 2007 paper.

As can be seen in Table 2 below, the AG have also overestimated the treatment duration of first-line bevacizumab by approximately 70% and hence the drug acquisition cost is also vastly overestimated.

Table 2: Drug dosage - Bevacizumab and IFN alfa-2a in both study arms (safety population) as per protocol

	Bevacizumab + Interferon alfa-2a			
	Bevacizumab (Clinical trial)	**Interferon alfa-2a (Clinical trial)**	**Bevacizumab (Assessment Group Estimate)**	**Interferon alfa-2a (Assessment Group Estimate)**
Average No. of Administrations	15.51	84.59		
Average Treatment duration (months)	7.36	6.48	12.0	12.0
Average Dose (mg) per Administration	756.7	7.89	88% dose intensity for 12.0 months	83% dose intensity for 12.0 months
Mean Total Dose (mg)	11,733.43	667.55		
Mean drug costs per patient (Present value using standard 3.5% discount rate)	£26,627	£3,505	Not split out in modeling	Not split out in modeling
	£30,132		£42,667	

Roche would like to request that a re-analysis of the economic model is performed for bevacizumab to include the costs based on the average cumulative dose as observed in the AVOREN trial itself. (We note that the clinical outcomes of bevacizumab at the dose assumed by the AG are unknown).

C) Administration costs (number of administrations)

As per point B above regarding the assumed dose administered, the AG assumed treatment until progression at the per protocol treatment frequency when estimating the number of administrations provided.

The number of administrations of IFN and bevacizumab as observed in the AVOREN trial were considerably less than those estimated by the AG as the average treatment duration was only 7.36 months compared to 12 months assumed by the AG. Additionally on average, bevacizumab administrations actually occurred every 16.5 days as opposed to the per protocol cycle length of every 14 days, further contributing to the present overestimate.
Roche would like to request that a re-analysis of the economic model is performed for bevacizumab to include the costs based on the actual number of administration observed in the pivotal trial.

D) Administration costs (cost per administration)

The administration of bevacizumab is more rapid than for chemotherapy regimens and as such applying the cost of an average chemotherapy administration (£189 in 2006/7 reference costs (HRG code SB15Z), uprated to £197 for 2007/8 by the Assessment Group) places an inappropriately high cost on the administration of bevacizumab. Roche suggests that it would be more appropriate to consider the lower interquartile range figure for the relevant reference cost (£95 in 2006/7 reference costs, uprated to £98 for 2007/8). This is appropriate given the average administration time of bevacizumab of approximately 30 minutes (from the second administration) compared to commonly administered agents such as irinotecan, leucovorin, and other combination therapies which take an average of two hours to infuse (see relevant Summaries of Product Characteristics). Applying this more appropriate administration cost would further reduce the treatment cost of bevacizumab + IFN whilst ignoring this we believe biases the results against bevacizumab + IFN.

Conclusion

Roche believes that the cumulative impact of all of these model parameter refinements upon the final ICER of bevacizumab is highly significant. However, it has not been possible for us to estimate a revised ICER ourselves as we only have access to the “read-only” version of the AG’s Economic Model which has limited our ability to understand the impact of these changes and to respond fully to this consultation.

We would therefore like to request that the AG’s economic model is re-run with our proposed revised assumptions and that the results are shared in a fully transparent manner, along with details of all of the final assumptions relied upon by the Committee in determining a revised base case ICER which can subsequently be used as the basis for continued engagement and dialogue going forwards.

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

Please refer to our response to question 1 above.

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 would like to request that the issues raised in response to question 1 are addressed by the Appraisal Committee and appropriate changes incorporated into a re-analysis of the baseline ICER of bevacizumab which is shared transparently with stakeholders.

Roche would also like to point out that for this particular appraisal of bevacizumab in renal cell cancer we believe that other relevant factors (such as those listed in Section 6 of the revised Guide to Methods) should be explicitly taken into account by the Appraisal Committee. These factors include “severity of disease” and the “degree of clinical need of patients with the disease”. We would like to request that the position of the Appraisal Committee is made clear and transparent in relation to whether and how these factors have been considered when interpreting the final ICER for bevacizumab.

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

We believe there are none.

We hope that these comments are helpful to the Appraisal Committee.

Document 3. AG-PenTAG review of Pfizer's original submission and the submission in response to the ACD.

BEVACIZUMAB, SORAFENIB TOSYLATE, SUNITINIB AND TEMSIROLIMUS FOR RENAL CELL CARCINOMA:

A SYSTEMATIC REVIEW AND ECONOMIC EVALUATION

Addendum to the report submitted on 2nd May 2008

Report commissioned by: NHS R&D HTA Programme

On behalf of: NICE

Produced by: Peninsula Technology Assessment Group (PenTAG)
Peninsula College of Medicine and Dentistry
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Date of addendum: 30th September 2008

Expiry date:

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The additional analyses presented within this addendum have been performed in response to requests by NICE on receipt of additional data and analyses from the manufacturer of sunitinib (Pfizer). For simplicity we have referred to the various submissions from Pfizer as 'submission 1', 'submission 2' and 'submission 3' throughout this document (Table 1).

Table 1: Key to Pfizer submissions

	Details	**Date**
Submission 1	Original submission	
Submission 2	Additional data and analysis submitted immediately prior to the first appraisal committee meeting	27/06/08
Submission 3	Additional data and analysis submitted in response to the ACD consultation	29/08/08

Additional analyses presented to NICE on 9th September 2008

These analyses were performed on request by NICE to aid clarification and understanding of the impact of the additional data provided by Pfizer on 27th June 2008 on the cost effectiveness estimates produced by the PenTAG cost effectiveness model. All analyses refer to the comparison of sunitinib versus IFN as first line therapy in people with advanced and/or metastatic RCC.

Comparison of the results of these additional analyses with those submitted by Pfizer is presented in Table 2 below.

Additional analysis PenTAG CEA 2.1 - OS 'no post-study treatment group', PFS from final ITT group

Using:

- Empirical data* on OS from the IFN group with 'no post-study treatment group' (Fig 8, Pfizer submission 2);
- HR of 0.647 for OS (sunitinib), from Pfizer submission 2 (ASCO presentation, 2008);
- Empirical data* on PFS from the IFN group for the full trial group, ITT censored (Fig 3, Pfizer submission 2);
- HR of 0.488 for PFS (sunitinib), from ASCO abstract reported by Motzer et al 2007;
- Other base case assumptions as in the PenTAG CEA (see Assessment Report);

* *PenTAG model weibull function/curve using empirical data*

We report a cost per QALY for sunitinib vs. IFN of **£65,464** (£62,365 when first cycle of sunitinib is free to purchaser).

Additional analysis PenTAG CEA 2.2 - OS and PFS data from 'no post-study treatment group'

Using:

- Empirical data* on OS from the IFN group with 'no post-study treatment group' (Fig 8, Pfizer submission 2);
- HR of 0.647 for OS (sunitinib), from Pfizer submission 2 (ASCO presentation, 2008);
- Empirical data* on PFS from the IFN group with 'no post-study treatment group' (Fig 5, Pfizer submission 2);
- HR of 0.488 for PFS (sunitinib), from ASCO abstract reported by Motzer et al 2007;
- Other base case assumptions in the PenTAG CEA (see Assessment Report);

* *PenTAG model Weibull function/curve using empirical data*

We report a cost per QALY for sunitinib vs. IFN of **£63,182** (£60,094 when first cycle of sunitinib is free to purchaser; £59,881 with HR of 0.52 for PFS sunitinib [Pfizer submission 3], and when first cycle of sunitinib is free to purchaser).

Table 2: CEA analysis presented by Pfizer (submission 3, amended from submission 2), compared to additional PenTAG CEA results above. In the PenTAG analysis we have assumed no pricing strategy and IFN is administered for a maximum of 12 months

	Pfizer (submission 3)			PenTAG OS 'no post-study treatment group', PFS from final ITT group			PenTAG OS & PFS data from 'no post-study treatment group'		
	Sunitinib	IFN-α	Sunitinib vs IFN-α	Sunitinib	IFN-α	Sunitinib vs IFN-α	Sunitinib	IFN-α	Sunitinib vs IFN-α
Life years	3.88 **	2.29 **	1.59	3.25	2.15	1.1	3.25	2.15	1.1
Progression free survival	1.49	0.95	0.53	2.71	1.37	1.33	2.61	1.24	1.37
Time on treatment #†	1.49	0.95	0.53	2.71	0.70	2.01	2.61	0.65	1.96
QALYs	2.72	1.63	1.09	2.47	1.6	0.87	2.46	1.6	0.862
Drug costs	£31,920*	£5,495	£26,425	£59,119	£4,224	£54,895	£57,088	£3,945	£53,143
Other costs	£3,267	£4,245	-£978	£4,936	£3,241	£1,695	£4,767	£2,958	£1,809

BSC in progressed disease	£19,552	£12,932	£6,621	£2,814	£3,169	-£355	£3,139	£3,631	-£491
Total costs	£54,739	£22,672	£32,067	£66,869	£10,633	£56,236	£64,994	£10,533	£54,461
Cost/LYG			£20,205			£51,473			£49,848
Cost/QALY			£29,440[1]			£65,464			£63,182

* Pfizer assumption of first cycle free of charge

** In Pfizer analysis life-years presented (as in Table) are not discounted. PenTAG analysis reports discounted life-years. Where PenTAG do not discount life-years (for comparison with Pfizer analyses) the results are 3.64 years for sunitinib and 2.35 years for IFN (the same data for both of the above PenTAG analyses).

In Pfizer analysis PFS = time on treatment, in PenTAG analysis there is an assumption that IFN treatment is given for a maximum of 12-months, therefore PFS is not equal to estimated time on treatment.

†Not subject to discounting

All cost estimates and QALY estimates in the Table are based on discounting of future costs and QALYs. PenTAG estimates of life-years are based on discounting of future life-expectancy.

[1] In Pfizer submission 2 the ICER was reported as £30,904. An error in translating the raw data was responsible for the higher figure, uncovered when further analyses received from the study statistician were used to validate the modelling approach.

Additional comments:

i) Table 2 reports CEA findings from Pfizer (submission 3) and PenTAG CEA related to the use of clinical effectiveness data presented by Pfizer in submission 2 (with some info from submission 3). We note that the primary difference between Pfizer CEA results and PenTAG results relate to estimates of modeled time on treatment (in PFS health state) and the subsequent drug treatment costs. There is also a slight difference in the survival profiles.

ii) PenTAG note that the Pfizer submissions 2 and 3 are not specifically clear on the approach taken by Pfizer, and suggest (it appears) that they are (may be) using the OS data with a HR for modeling sunitinib OS, and using PFS empirical data for IFN and sunitinib to model Weibull curves for each. We suggest NICE (or NICE DSU) explore this.

iii) At the time of the Pfizer submission 2, there were no details provided on the characteristics of this patient group, or the comparison of this group with the full trial group. Pfizer have now provided further information on the characteristics of the 'no post-study treatment group', in their submission 3. Based on information provided by Pfizer in submission 3 (received by NICE 29/09/08) the 'no post-study treatment group' and the full trial patient group look very similar, however it is clear from the survival curves provided that the two groups have a different profile against PFS, and this is an interesting observation (given the fact that switching treatment when in 'progressive disease' might not be expected to influence PFS.

iv) PenTAG could see the OS data from the 'no post-study treatment group' as a potentially appropriate source of effectiveness data, where clinical practice was characterised by the absence of available alternative treatments; i.e. where only one treatment was available this analysis might provide the closest approximation of the clinical situation.

v) PenTAG could see the use of the OS data from the 'no post-study treatment group' as data that is available from a smaller patient group, but for use in generalizing to the broader patient group. However, PenTAG would see the full trial analysis (ITT, censored) as the most appropriate PFS data for use in the assessment of clinical and cost-effectiveness. The use of PFS data from

the ‘no post-study treatment group’ to generalise to the broader patient group would not seem sensible, given (i) the apparent differences in PFS profiles, and more importantly (ii) the availability of PFS data from the full patient/treatment sample.

vi) PenTAG note that Pfizer have raised the concern over the use of the sunitinib HR to model PFS data, based on the initial PFS survival analysis in the PenTAG report (their Fig 2 and Fig 4, submission 3), PenTAG have not explored this further, but note that the same situation may not be present in the analysis of PFS data for the final analysis ITT patient group (see Fig 3 in Pfizer submission 2), NICE (NICE DSU) may explore further.

vii) ** PenTAG note, when comparing Pfizer submissions 2 and 3 that empirical survival curves for PFS from the ‘no post study treatment’ group appear to be different, and would suggest that NICE (NICE/DSU) explore this.

viii) ** PenTAG note that in Pfizer submission 2 (and subsequent) that the differences in empirical survival curves is not explained (e.g. data on PFS from Fig 1 submission 2 and Fig 3 submission 2; why are the curves so different?) and suggest NICE (NICE DSU) may wish to explore further.

Document 4. DSU review of Roche's request for parameter changes.

BEVACIZUMAB, SORAFENIB, SUNITINIB AND TEMSIROLIMUS FOR RENAL CELL CARCINOMA.

DECISION SUPPORT UNIT

Keith Abrams, Steve Palmer, Allan Wailoo

28th September 2008

Introduction

The DSU were asked to provide commentary on additional analyses submitted by the manufacturers Pfizer and Roche as part of this appraisal.
It is worth noting at the outset how the estimates of treatment effectiveness for overall survival (OS) and for progression free survival (PFS) influence estimates of cost effectiveness. There are three (inter related) issues which drive cost effectiveness:

1) The hazard ratios themselves
2) Baseline progression free and absolute survival estimates (i.e. the same HR applied to different baselines will result in higher absolute gains)
3) Impact of incremental gains in PFS and OS (i.e. because treatments are given until progression it is preferable in cost-effectiveness terms to minimise differences in PFS and maximise differences in OS).

These issues are important when considering the various sets of ICERs calculated below.

Response to Roche ACD commentary

Overall survival / post progression treatment effect.

The hazard ratio used by both the AG and Roche is derived from the AVOREN trial.

In the AG cost effectiveness model, the HR for overall survival was taken from the intention to treat population, stratified according by MSKCC risk group and region (hazard ratio of 0.75 (95% CI 0.58 to 0.97); p=0.02670). The unstratified analysis that was not used in the model gave similar results (hazard ratio of 0.79 (95% CI 0.62 to 1.02); p=0.0670). (see page 51 of the assessment report).

In their original submission Roche based their analysis on the safety population (i.e. patients that had at least one dose of the treatment), stratified according to the trial protocol, which gave a slightly lower hazard ratio (HR of 0.709 (CI 0.55 to 0.91). Their justification for using this population, as opposed to the ITT population, is that

this ensures that patients have received at least one dose of the treatment. There were 2 patients in the bevacizumab arm and 6 in the IFN arm that withdrew before the first treatment according to the published study paper (Escudier et al, 2007. p 2106). The HR for this population is 0.71. It is not clear if this is the definition used by Roche since in their letter they refer to 641 patients in the ITT population (Table 1), which would appear to be the safety population using the figures in the Escudier et al. paper. In their original submission they refer to 649 in the ITT population

The ITT analysis should be considered preferable to the safety analysis since this is the basis on which patients were randomised. The safety analysis permits patients originally randomised to the IFN arm to be analysed as part of the bevacizumab arm if they received one or more doses. Efficacy analyses should be conducted on the ITT population as in the PenTAG model with appropriate consideration of costs for patients that did not actually receive treatment, thus allowing appropriate modelling of patients that do and do not comply with treatment.

Table 5 reports the revised ICERs, based on the PENTAG model, incorporating the safety population estimates for (i) the HR for OS and (ii) the HR for OS and PFS.

Table 5: Revised cost-effectiveness for bevacizumab using safety population

Scenario	**Inputs**	**ICER using PENTAG model**
Bevacizumab – Base Case	*HR OS = 0.75* *HR PFS = 0.63*	*£171,301*
i) Bevacizumab – Revised OS data Safety population	HR OS = 0.709 HR PFS = 0.63	£144,303
ii) Bevacizumab – Revised OS and PFS data Safety population	HR OS = 0.709 HR PFS = 0.609	£147,718

In their response to the ACD, Roche raise an additional issue. Overall survival may be confounded in trials where patients switch to other treatments after disease progression or treatment failure. In this situation, the comparator group may gain survival benefits from these second line treatments. Therefore, the cost effectiveness modelling should either include the costs of providing these additional treatments to

patients in the comparator arm (as Roche argued their model did) or factor out the survival benefits attributable to the second line treatments. Since the assessment group did not have access to the patient level data, they were unable to perform such an adjustment. Roche present results based on censoring all patients that received second line treatments and stratifying as in the previous analyses (hazard ratio of 0.613 (CI 0.46 to 0.81). This results in a substantial reduction in the numbers of patients included in the analysis from 641 in the ITT population, although see previous paragraph for concerns about whether this is in fact the safety population (325 bevacixumab + IFN vs 316 IFN) to 147 (91 bevacixumab + IFN vs 56 IFN).

The impact of implementing this revised estimate in the PenTAG model is reported below in Table 6.

Table 6: Revised cost-effectiveness for bevacizumab using adjusted HR for OS

Scenario	**Inputs**	**ICER using PENTAG model**
Bevacizumab – Base Case	*HR OS = 0.75* *HR PFS = 0.63*	*£171,301*
Bevacizumab – Revised OS data Adjusted analysis	HR OS = 0.613 HR PFS = 0.63	£101,340
Bevacizumab – Revised OS HR equivalent to HR for PFS	HR OS = 0.63 HR PFS = 0.63	£107,489

There is a difficulty that arises from these differences in approach. The ITT overall survival analysis respects the original trial randomisation whilst the censored analysis is based on particularly small numbers of patients. The patient groups are not entirely balanced in terms of their baseline characteristics between the censored treatment and control groups or between the censored groups and the ITT population, although it is difficult to assess whether these differences should be considered significant. Furthermore, there is a risk of unobserved differences between the treatment and control censored groups influencing the estimated treatment effect. It should also be noted that the revised estimate is more favourable than the HR for PFS which seems optimistic. For this reason we have also included a scenario that considers a HR of 0.63 for OS, equivalent to PFS.

The DSU suggest that provision of the individual patient data (IPD) would permit detailed consideration of the performance and credibility of alternative modelling strategies. In the absence of provision of this data a number of alternative analyses could be presented that demonstrate the impact of different approaches to censoring.

The alternative modelling approach would be to amend the PenTAG model to include the costs of second line therapies whilst maintaining the survival benefit estimates from the ITT population. This may then result in modelling of treatment strategies that do not reflect current UK NHS practice.

Average cumulative dose administered per patient

The AG calculate the cost of bevacizumab from three elements: the BNF unit cost, mean dose intensity reported from Escudier et al. (2007) and the mean duration of treatment.

Roche suggest that the actual mean dose observed in the trial safety population should be used to estimate the drug costs, as in the Roche model. However, it is not clear the source of the Roche calculations. In their original submission (p. 67), the dosages based on the safety populations are presented. However, these are based on populations larger (n= 336) than those reported randomised to this arm of the trial (n=327). PenTAG highlighted inconsistencies between these data and the dose intensities reported elsewhere in the original Roche submission and the trial publication (see page 119 of the AG report).

Nevertheless, the key area of disagreement between the PenTAG and Roche approaches relates to the definition of dose intensity. Mean dose intensity should report the amount of drug administered in a clinical trial as a proportion of the amount that would have been administered had there been no withdrawals or dose reductions. According to the protocol in the AVOREN trial, no dose reductions were permitted (Escudier et al. 2007, p 2105). Therefore, were the trial protocol adhered to, the figure of 88% used in the PenTAG model should reflect patients with disease progression,

toxicity, or withdrawal of consent. Provided the PenTAG model appropriately reflects withdrawals from treatment for these reasons, the application of this figure until progression would be appropriate and reflects the study protocol.

Roche argue that the dose intensity figures are only applicable to the actual treatment period of the trial i.e. the dose intensity figures do not reflect withdrawals at all but only the dose administered to those still receiving treatment.
Since the mean treatment duration is significantly shorter than the time to progression, due in large part to withdrawals due to adverse events, there is a difference in the drug costs calculated by the Roche and PenTAG methods.
This requires clarification from Roche.

One additional issue relates to how this is reflected in the model. Clearly, if patients remain in the progression free state beyond the 24 months of the trial then it is reasonable to extrapolate drug costs beyond that time in order to be consistent with the modelling of health benefits. Solely using the drug use reported within the trial would therefore be an underestimate. Due to censoring, not all patients have progressed at final follow up.

If the definition of dose intensity is as implied by the Roche comments, then the true drug cost is likely to lie somewhere between the PenTAG and Roche estimates.

Number of administrations.

The issue raised by Roche is similar to b) discussed above. PenTAG model the per protocol drug use and are consistent between the costing approach and the modelling of benefits.

Roche highlight two reasons why this approach does not correspond to the actual drug use in the trial. Firstly, as in the previous point, treatment duration was shorter than time to progression. This is likely to be mainly because of patients who withdrew from treatment due to toxicity. In addition, the protocol defined infusions every two weeks was not in fact followed. Infusions were given on average every 16.5 days, not every 14 days.

With regard to the second point, if the dose intensity figures cited above were correct, then the decreased frequency of infusions would form part of the dose intensity figure. It is therefore important that any corrections do not double count this element of drug costs.

The relevance of the difference between treatment duration and time to progression is as discussed above. However, in relation to this issue it is important to reiterate that censoring of patients within the trial means that a failure to model costs beyond that observed within the trial period would lead to an underestimate.

Unit cost of administrations

Roche argue that it is inconsistent to apply a unit cost using reference costs that relate to an average chemotherapy administration when bevacizumab requires a relatively short infusion of approximately half an hour.

The SPC for bevacizumab indicates that the first two infusions should be given over a longer period and subsequent infusions would then take approximately half an hour provided there has been no intolerance. The frequency with which intolerance is experienced should be considered in adjusting these administration costs.

The PenTAG model applies the same cost to administration of temsirolimus which requires a 30 to 60 minute infusion. Patients should be given intravenous diphenhydramine 25 to 50 mg (or similar antihistamine) approximately 30 minutes before the start of each dose. It does therefore seem appropriate to apply a lower cost to bevacizumab infusions.

Reference costs based on HRGs are not ideal for differentiating between treatments in this situation. Roche suggest the application of the lower quartile which is £95 compared to £189 (at 2006/7 prices), a near halving of the cost. This is an arbitrary figure.

It should also be noted that in the appraisal of erlotinib, Roche argued that a unit cost of £299 is applicable for docetaxel infusions, which last approximately one hour. In

this appraisal, the ACD states "the Committee noted that the most appropriate NHS reference cost (SB12Z) puts it in this range (at £170 per case)."

The degree to which this cost should be reduced requires consideration of the resources used in providing infusions. There are likely to be elements of this activity that do not vary with the duration of the infusion e.g. the set up, putting away equipment, preparation of patients, and this should inform the extent to which the unit cost is reduced from that used for an average infusion.

Table 7: Revised cost-effectiveness for bevacizumab using alternative costing assumptions

Costing Assumption	**Base-Case** *HR OS = 0.75* *HR PFS = 0.63*	**Scenario 1** *HR OS = 0.613* *HR PFS = 0.63*	**Scenario 2** *HR OS = 0.63* *HR PFS = 0.63*
Bevacizumab – Base case costings	£171,301	£101,340	£107,489
(i) Bevacizumab – Revised dosage only	£124,402	£74,008	£78,406
(ii) Bevacizumab – Revised dosage AND Revised number of adminstrations	£114,624	£68,561	£72,610
(iii) Bevacizumab – Revised dosage AND revised number of administrations AND revised unit cost of administration	£108,835	£65,213	£73,146

Table 7 shows revised cost effectiveness estimates based on the PenTAG model using the parameter values suggested by Roche in relation to costings. Because of the issues highlighted above in relation to the post hoc analyses, we present results for different overall survival HRs.

The table shows the impact of reducing (i) the dosage only, (ii) reducing dosage and number of administrations, (iii) reducing dosage and number of administrations and the unit cost of administrations.

Document 5. Appraisal Committee's preferred assumptions

The Committee understood that in the sunitinib study not only had there been crossover after disease progression, but also that participants had received second-line treatment after the study had ended. This could be expected to exaggerate overall survival estimates for people in the UK receiving IFN-α in the future, as the Committee accepted testimony from clinical experts that current UK practice is likely to preclude treatment with second-line therapies. The Committee therefore considered that the investigation of outcomes in the participants who received no 'post-study treatment' was appropriate.

The Committee was concerned about the data and approach used by the manufacturer of sunitinib. The Committee was mindful that this group was not pre-specified and represented less than half of the original trial population. The Committee noted that even though the baseline demographics of the group appeared similar to those of the whole trial population the findings were suggestive of an unbalanced comparison. The Committee noted that in the model the overall survival of those people who only received sunitinib was now higher than those people who had received sunitinib as well as further treatments after the study had ended. This finding would imply that having a second-line treatment was less beneficial compared to participants who only received sunitinib and the Committee considered that this was implausible.

The Committee considered that the estimate of overall survival might have been inflated by the curve fitting techniques used in the manufacturer's model. The overall survival curve for sunitinib appeared to have been estimated by applying the study hazard ratio to the IFN-α overall survival curve. The Committee considered that the use of this technique when the empirical data were highly censored (that is based on a small number of the total trial participants) and with a relatively short follow-up period could have exaggerated the true effect of sunitinib on overall survival. The Committee considered that the estimates of overall survival associated sunitinib treatment from the 'no post study treatment' group were overestimated. The Committee

concluded on balance that the most appropriate estimate of overall survival associated with sunitinib treatment was that from the full ITT population.

The Committee then considered the estimate of overall survival associated with IFN-α as derived from the ‘no post study treatment’ group. The Committee noted that in the updated Pfizer model that the overall survival for those people who only received IFN-α was lower than those people who had received IFN-α and further treatments after the study had ended. The Committee accepted that this was plausible and concluded that the ‘no post study treatment’ group provided an acceptable estimate for overall survival associated with IFN-α treatment.

The Committee then considered the estimates of progression-free survival associated with sunitinib and IFN-α treatment. The Committee considered that the estimates of progression-free survival from the ITT population should be similar to the estimates derived from the 'no post study treatment' group. This is because participants would generally receive further therapy after the transit from the progression-free state to progressive disease. The Committee therefore understood that it was not necessary to use the findings from the ‘no post study treatment’ group. The Committee concluded that, to estimate progression free survival in the ‘no post study treatment group’, it is preferable to use all the data from the ITT population rather than using an analysis that did not contain over half of the trial participants. Therefore, the Committee concluded that, even when accepting the use of the ‘no post study treatment group’ the use of the ITT population data to inform the progression-free survival modelling for sunitinib and IFN-α treatment was appropriate.

Therefore, the Committee requested additional analyses using the following preferred assumptions:

- Estimates of progression-free survival for people receiving IFN-α should be based on the overall ITT population
- Estimates of progression-free survival for people receiving sunitinib should be based on the overall ITT population

- Estimates of overall survival for people receiving IFN-α should be based on the population who received no further second-line treatments after the sunitinib trial had ended
- Estimates of overall survival for people receiving sunitinib should be based on the overall ITT population

Document 6. DSU report on Pfizer's cost effectiveness model for sunitinib in the subgroup with no systemic post study treatment, including using Committee's scientific value judgments.

BEVACIZUMAB, SORAFENIB, SUNITINIB AND TEMSIROLIMUS FOR RENAL CELL CARCINOMA.

DECISION SUPPORT UNIT

Keith Abrams, Steve Palmer, Allan Wailoo

28th September 2008

Introduction

The DSU were asked to provide commentary on additional analyses submitted by the manufacturers Pfizer and Roche as part of this appraisal.
It is worth noting at the outset how the estimates of treatment effectiveness for overall survival (OS) and for progression free survival (PFS) influence estimates of cost effectiveness. There are three (inter related) issues which drive cost effectiveness:

1) The hazard ratios themselves
2) Baseline progression free and absolute survival estimates (i.e. the same HR applied to different baselines will result in higher absolute gains)
3) Impact of incremental gains in PFS and OS (i.e. because treatments are given until progression it is preferable in cost-effectiveness terms to minimise differences in PFS and maximise differences in OS).

These issues are important when considering the various sets of ICERs calculated below.

Response to Pfizer additional analyses of clinical effectiveness

In their response to the ACD and in a previous letter dated 27th June 08, Pfizer submitted additional analyses on the clinical effectiveness of sunitinib. At the time of the original submission made by Pfizer, the trial A6181034 had only reported interim results. Median overall survival had not been reached.

When the final results from the trial are incorporated into the Pfizer cost-effectiveness model, the ICER rises from £29k per QALY to £72k per QALY. This is assumed to be based on a hazard ratio for OS rising from 0.65 in the interim analysis to 0.82 in the full ITT final analysis. Pfizer argue however that there is potential bias in the ITT estimates of overall survival and therefore an underestimate of the cost effectiveness of sunitinib. There are two potential sources of bias:

i) the IFN group that were allowed to cross over to sunitinib after the first interim analysis

ii) patients in both study arms that received second line systemic therapies

Pfizer present an analysis where patients in group (i) were censored at the time of cross over. The HR for OS is 0.81 in this situation. This makes little difference to the ICER compared to the full ITT analysis.

Pfizer argue that the appropriate estimate of both OS and PFS comes from their analysis that:

a) exclude all patients that received second line therapies. This results in a HR for OS of 0.65.
b) Adjust the PFS curve to obtain a better fit
c) Adjust the OS estimate

These three changes in combination result in an ICER of £31k per QALY.

In order to estimate the potential impact of these changes in the PenTAG model, a number of alternative ICERs are presented in Table 1 below. The base case scenario refers to the original hazard ratios applied by PenTAG for OS (0.65) and PFS (0.42). Alternative scenarios are based on the revised PFS data (investigator led or central reviewer analyses) and the revised full ITT OS data. The first 5 sets of results do not include the agreed pricing strategy of the first cycle of sunitinib free to the NHS. The last row of Table 1 reports the impact of the agreed pricing strategy based on the results of the central reviewer analysis. Table 2 reports more detailed results based on this scenario.

Table 1: DSU revised cost-effectiveness estimates for sunitinib using final HRs and PENTAG model

Scenario	**Inputs**	**ICER using PENTAG model**
Sunitinib – Base Case	*HR OS = 0.65* *HR PFS = 0.42*	*£71,462*
Sunitinib – Revised PFS data Investigator led HR PFS	HR OS = 0.65 HR PFS = 0.52	£61,487
Sunitinib – Revised PFS data Central Reviewer analysis HR PFS	HR OS = 0.65 HR PFS = 0.54	£59,819

Sunitinib – Revised PFS + OS data Investigator led HR PFS + Revised HR OS	HR OS = 0.82 HR PFS = 0.52	£120,474
Sunitinib – Revised PFS + OS data Central Reviewer analysis HR PFS + Revised HR OS	HR OS = 0.82 HR PFS = 0.54	£118,005
Sunitinib – Revised PFS + OS data Central Reviewer analysis HR PFS + Revised HR OS *+ 1st cycle sunitinib free*	HR OS = 0.82 HR PFS = 0.54	£104,715*

* see detailed breakdown below

Table 2: Detailed cost-effectiveness analysis estimates from DSU analysis using PENTAG model

	Sunitinib	**IFN-α**	**Sunitinib vs IFN-α**
Life years	1.85	1.63	0.22
Progression free years	1.12	0.62	0.50
QALYS	1.39	1.19	0.20
Drug costs	£24,299	£2,952	£21,347
Drug admin	£0	£491	-£491
Monitoring costs	£1,494	£825	£669
Diagnostic costs	£669	£370	£299
AEs	£78	£4	£74
BSC in progressed disease	£2,766	£3,798	-£1,032
Total costs	£29,306	£8,438	£20,868
ICER			
Cost per QALY			**£104,715**

In relation to the analysis that excludes all patients that received a second line therapy, several cautions are appropriate.

Firstly, the use of second line therapies in the UK NHS must be considered in order to identify the appropriate subgroups of patients. Table 3 reports the systemic treatments received by patients post study discontinuation.

Table 3: Patients who received systemic therapy post study discontinuation (A6181034)

	Sunitinib, n (%)	IFN-α, n (%)

	(n=323)	(n=359)
Any post-study treatment	182 (56)	213 (59)
Sunitinib	36 (11)	117 (33)
Other VEGF* Inhibitors	106 (33)	115 (32)
Cytokines	63 (20)	47 (13)
mTOR** Inhibitors	28 (9)	16 (4)
Chemotherapy	21 (6)	20 (6)

Secondly, excluding patients who progress and therefore require 2nd line therapy (regardless of whether their demographics are similar or not to those who remain included) will almost certainly produce inappropriate results since their reason for exclusion is inextricably linked to outcome, i.e. death. A more appropriate strategy would be to censor at the time at which they began 2nd line therapy, though this should be undertaken with caution too.

Modelling of clinical efficacy data adopts the approach used by PenTAG (estimated Weibull model using monthly data). Although Figure 4 shows that by modelling PFS for sunitinib and IFN groups separately a reasonably 'good fit' is achieved (though not when the HR estimate is used to adjust the IFN curve), Figure 5 for OS in the IFN group displays considerable 'lack of fit', and the input of 3.88 life-years in Table 5 for sunitinib is derived from the survival curve in Figure 5 using the HR, which must cast serious doubt on the validity of the associated ICER.

An additional scenario was considered by the DSU using the Committee's preferred assumptions for the scenario of no systemic treatment post study discontinuation analysis based on the Pfizer model. This scenario was based on the PFS data from the ITT final analysis for both the IFN-α and sunitinib arms (1.06 [12.72 months] and 1.74 [20.88 months] progression-free years respectively). For overall survival, data from the IFN-α 'no post study treatment' arm of 2.29 (27.48 months) life years was inputted and 3.13 (37.56 months) life years taken from the ITT final analysis was used for the sunitinib arm. The results are presented in Table 4. This approach resulted in an ICER of £49,304 per QALY gained for sunitinib compared with IFN-α.

Table 4: Cost effectiveness analysis of no systemic treatment post study discontinuation analysis – DSU analysis based on Committee's preferred assumptions using Pfizer model

	Sunitinib	**IFN-α**	**Sunitinib**

			vs IFN-α
Life years	3.13	2.29	0.84
Progression free years	1.74	1.06	0.68
QALYs	2.33	1.69	0.64
Drug costs	£37,582	£6,096	£31,485
Follow-up costs	£2,476	£3,953	-£1,477
Diagnostic tests	£1,191	£736	£455
AEs	£73	£4	£69
BSC in progressed disease	£12,898	£11,758	-£1,140
Total costs	£54,220	£22,547	£31,673

*First cycle of sunitinib free

ICERs

Cost/QALY **£49,304**

It is worth noting that this ICER is still likely to be an underestimate since the mean overall survival estimate applied to sunitinib in this scenario was based on the results from the overall ITT population. This estimate will include any additional survival benefits conferred to the proportion of subjects who subsequently received post-study treatments. Consequently, employing this estimate directly within this scenario represents the most optimistic assumption in relation to the estimate of mean overall survival for sunitnib in the absence of subsequent treatments i.e. that post-study treatments conferred no additional survival benefits within the ITT population.

Document 7. AG-PenTAG report on the cost effectiveness model for sunitinib in the subgroup with no systemic post study treatment, including using Committee's preferred assumptions.

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BEVACIZUMAB, SORAFENIB TOSYLATE, SUNITINIB AND TEMSIROLIMUS FOR RENAL CELL CARCINOMA:

A SYSTEMATIC REVIEW AND ECONOMIC EVALUATION

Addendum to the report submitted on 2nd May 2008

Report commissioned by: NHS R&D HTA Programme

On behalf of: NICE

Produced by: Peninsula Technology Assessment Group (PenTAG)
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2.2. Question 2: Provide further explanation as to why use of the HR from ASCO Motzer (0.488 - applied to the PFS estimate for IFN) to estimate the PFS estimate for SUN (resulting in 32.5 months or 2.71 years) is the most appropriate way of modelling PFS for the 'no-post-study-treatment' patient group.

2.3. Question 3: Provide an estimate for the ICER for the comparison of sunitinib and IFN based on the Committee's preferred assumptions [Table 3], modelled using the PenTAG model, to compare with the ICER of £62k from the PenTAG August submission.

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Table 5: Results from CEA using PenTAG model and OS and PFS data from Figure 2. We have assumed the 1st cycle of sunitinib is free of charge, no restriction on time of administration of IFN. All other assumptions as the PenTAG base case (see Assessment report

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Figure 1: PenTAG curves fitted to IFN and sunitinib empirical data. The IFN Weibull curve is estimated by fitting to the empirical data and the sunitinib curve is modeled by applying the hazard ratio to the IFN curve
Figure 2: Weibull survival curves derived by PenTAG using the assumptions requested by the NICE Appraisal Committee. Time is measured in years on the x-axis

The additional analyses presented within this addendum have been performed in response to requests by NICE on receipt of additional data and analyses from the manufacturer of sunitinib (Pfizer). For simplicity we have referred to the various submissions from Pfizer as 'submission 1', 'submission 2' and 'submission 3' throughout this document (Table 1).

Table 3: Key to Pfizer submissions

	Details	**Date**
Submission 1	Original submission	
Submission 2	Additional data and analysis submitted immediately prior to the first appraisal committee meeting	27/06/08
Submission 3	Additional data and analysis submitted in response to the ACD consultation	29/08/08

Additional analyses presented to NICE on 17th September 2008

These analyses were performed in response to a series of questions posed by NICE on 15th September 2008.

Question 1: Provide further explanation as to why the PFS estimates for IFN differ between PenTAG (16.44 months or 1.37 years) and Pfizer (12.72 months or 1/06 years) when both come from the same data source (Pfizer submission 2).

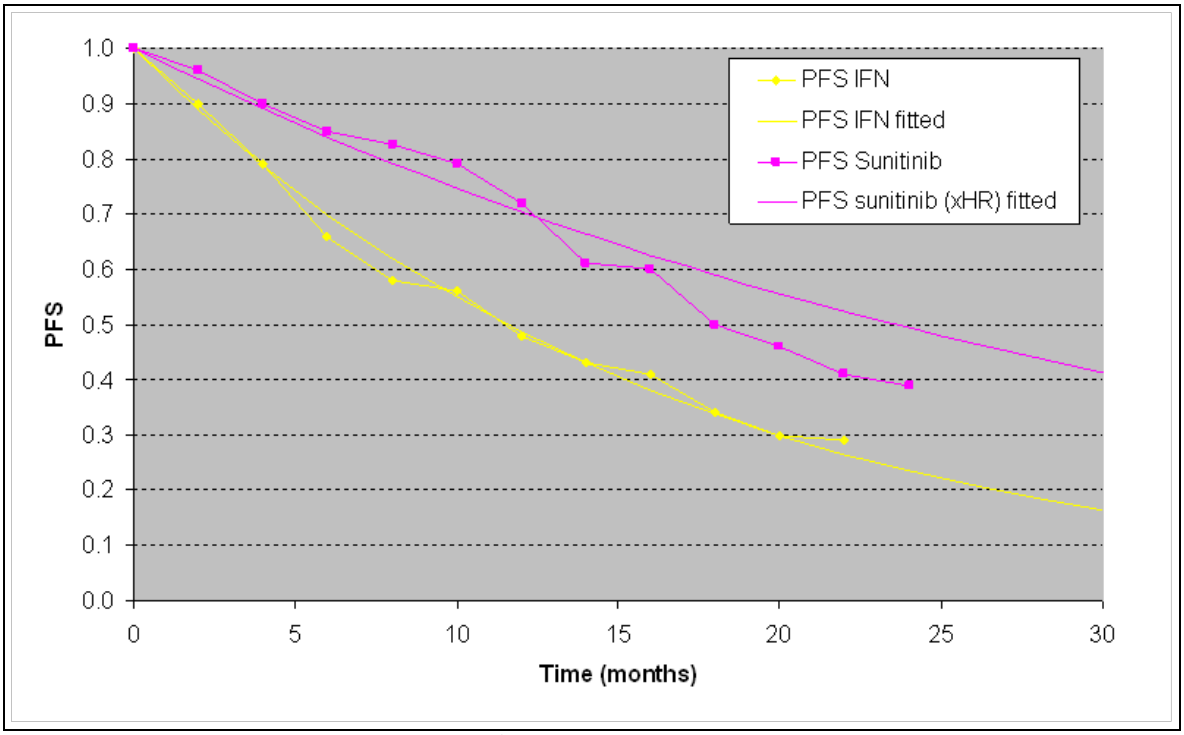
When PenTAG use the empirical Kaplan-Meier data for PFS, as presented in Pfizer submission 2, Figure 3 [submitted in 'paper' form only, i.e. no accompanying Excel model] we use this data to fit a Weibull curve for IFN (see Fig 1 below), with this Weibull curve estimating 16.44 months (1.37 years) in PFS in the model. When using the PenTAG base case assumption of a max of 12 months on IFN treatment, the model predicts a time period of 8.4 months on IFN treatment (although mean time in PFS is 16.44 months).

The Pfizer prediction of 12.72 months (1.06 years) in the PFS health state, when using the same empirical Kaplan Meier data (submission 2, Fig 3) is due to the different Weibull fit to

the data by Pfizer. It is 'very clear' from the Pfizer Figure 3 (submission 2) that from 9-10 months the Pfizer Weibull curve for PFS (their green curve) is predicting fewer people in the PFS state at each time point thereafter, i.e. fewer than reported in the empirical KM curve. The PenTAG Weibull curve presents as a closer fit to the empirical KM data. We see this as the explanation for the difference noted for time in PFS.

Pfizer have suggested that using a Weibull curve that fits the empirical IFN data better (as in the PenTAG model) leads to a poorer fit to the sunitinib treatment data, when using the hazard ratio (from the clinical trial). This is dealt with further in our response to question 2 below.

Figure 1: PenTAG curves fitted to IFN and sunitinib empirical data. The IFN Weibull curve is estimated by fitting to the empirical data and the sunitinib curve is modeled by applying the hazard ratio to the IFN curve



*Modelled using empirical survival curves presented in Pfizer submission 2, Figure 3

Question 2: Provide further explanation as to why use of the HR from ASCO Motzer (0.488 - applied to the PFS estimate for IFN) to estimate the PFS estimate for SUN (resulting in 32.5 months or 2.71 years) is the most appropriate way of modelling PFS for the 'no-post-study-treatment' patient group.

For clarification, PenTAG have used the HR of 0.488 reported in an abstract by Motzer and colleagues (ASCO 2007) to model PFS for the final ITT patient group (as reported in Pfizer

submission 2, Figure 3). PenTAG suggest that the ITT data for PFS from the final analysis (Pfizer submission 2, Figure 3) is the most appropriate data. This being due to the fact that any 'post-study treatment' is expected to be after progression i.e. after the recording of the transit from PFS to progressive disease - we note that in the published Motzer et al paper it states *'After the interim analysis had been performed and discussed with the data and safety monitoring committee, patients in the IFN group with* progressive disease *were allowed to cross over to the sunitinib group.'*

PenTAG suggest that the use of data from the 'no-post-study-treatment' patient group for PFS would only be useful if it were necessary to generalise findings back (from the 'no-post-study-treatment' patient group) to the broader patient group due to lack of appropriate PFS data for the broader patient group (as is/may be the case with the use of OS data). This is plainly not the case with PFS data, where PFS data 'are' available for the broader patient group, as reported in Pfizer submission 2 (fig 3).

In the additional analysis presented by PenTAG (for discussion being held between NICE and DSU, 9th Sept). PenTAG present ICERs calculated for sunitinib versus IFN using the data on PFS and OS presented by Pfizer in their submission 2 (identified as PenTAG CEA 2.2). This analysis used the HR of 0.488 for PFS (from Motzer et al ASCO abstract) to be consistent with our response to submission 2 (the note from PenTAG was responding primarily to Pfizer submission 2, and that was the only HR available to us at that time). In the Pfizer submission 3 they present a HR of 0.52 for PFS for the 'no-post-study-treatment' patient group. PenTAG suggest that, where this HR is correct for the 'no-post-study-treatment' patient group (i.e. at present it remains unpublished), it would be the most appropriate for this patient group, and the data for this patient group. That is why PenTAG also presented an ICER (cost per QALY) for their CEA 2.2 based on a HR of 0.52.

PenTAG suggest that the use of a baseline IFN model (Weibull curve/model from Kaplan-Meier data) and the use of the HR for sunitinib, to model sunitinib PFS, is an appropriate way to model the two treatment options. This methodological approach is accepted as an appropriate approach.

Given the research question set out for PenTAG (see Assessment Report, our question 1) is the comparison of sunitinib, bevacizumab+IFN, and IFN alone, it is necessary to consider alternatives to IFN (current practice) on the basis of a common comparator, and to use HRs to estimate the treatment effectiveness from alternative treatments (sunitinib, bev+IFN). In our initial analysis (in the Assessment Report) we used IFN data from the AVOREN trial as the base case (with analysis using Motzer trial data in sensitivity analyses). Using such a

framework for CEA it is appropriate to use baseline progression with relevant hazard ratios. It is not possible to perform a 3-way comparison by fitting all curves independently.

Pfizer, who are primarily concerned with a comparison between sunitinib and IFN, initially used a similar framework (baseline IFN, and HR for sunitinib). Pfizer are now suggesting (applying) the Kaplan-Meier empirical data for PFS for both IFN and sunitinib, and modeling Weibull curves for both i.e. not using the HR approach (this is the approach from Pfizer in their submission 3, Fig 4, Table 5). This is based on a view that use of a PFS HR to model sunitinib will overestimate the effect of sunitinib on PFS (and subsequently incurring greater treatment costs).

Where the research question for PenTAG is changed (by NICE) to one that considers only sunitinib as an available alternative to IFN, removing bevacizumab+IFN from the treatment options, it would be appropriate to consider the use of Weibull curves (modeled from KM data) for both IFN and sunitinib PFS, where the HR approach was thought to overestimate treatment effect of sunitinib on PFS.

Both approaches, given the context stated, are appropriate. Which is the most appropriate is an issue of judgment, for example, based on the research question being addressed, and considerations over use of clinical effectiveness data (i.e. hazard ratios used to establish treatment effectiveness, using trial patient level data).

We suggest that the hazard ratio approach to modeling treatment effect offers some potential benefits, as it models using the relative treatment effect (measured by the HR). The relative treatment effect may not be reflected accurately when fitting curves independently (treatment and control), as curve fitting is applied across the whole of the curve, include the 'tail' of the Kaplan-Meier curve, and there can be a large degree of uncertainty in the 'tail' of the Kaplan-Meier curve.

Question 3: Provide an estimate for the ICER for the comparison of sunitinib and IFN based on the Committee's preferred assumptions, modelled <u>using the PenTAG model</u>, to compare with the ICER of £62k from the PenTAG August submission.

Table 4: Committee's preferred assumptions [provided by NICE 15/9/08]

Committee					**PenTAG**[#]
					Data source used by PenTAG
PFS		**Months*** **	**Years*** **		

	IFN	12.72	1.06	ITT-Final Jul08 (table 2)	Pfizer submission 2, Fig 3 (hard copy only, no model/data)
	SUN	20.88	1.74	ITT-Final Jul08 (table 2)	Pfizer submission 2, Fig 3 (hard copy only, no model/data)
	Diff	**8.16**	**0.68**		
OS					
	IFN	27.5	2.29	No-post Rx-Pfizer Aug 08 (table 5)	Pfizer submission 3, Fig 5 (Excel model and data available)
	SUN	37.6	3.13	ITT-Final Jul08 (table 2)	Pfizer submission 2, Fig 4 (hard copy only, no model/data)
	Diff	**10.1**	**0.84**		

[#] Data used by PenTAG in response to NICE request.

***PenTAG note that the months/years calculated by Pfizer in their analysis are not discounted (undiscounted), whilst the QALYs have been discounted.

PenTAG have the following comments on the Committee's preferred assumptions. Firstly, PenTAG have concerns over using the approach taken by Pfizer in their Submission 2, Figure 3, when modeling PFS from the ITT full analysis. The Weibull curves used for PFS are both underestimating the proportions of people in PFS over time, when compared to the empirical Kaplan-Meier data. And secondly, PenTAG have concerns over the approach requested by NICE to estimating OS i.e. using survival curves from different patient groups for OS, (ITT OS curve for sunitinib and the 'no post-study-treatment group' for IFN OS).

However, PenTAG have responded to the NICE request and present below the curves derived for use in the PenTAG model, based on the NICE Appraisal Committee preferred assumptions.

PFS ITT curves (from Pfizer submission 2, Fig 3)

We note that Pfizer have not provided an Excel model (data) with the analyses presented in their submission 2. Therefore, PenTAG have not been given the values of the two parameters of the Weibull curve for PFS ITT for IFN, nor the 2 parameters for PFS for sunitinib. PenTAG have therefore estimated these parameters from reading off data from their hard copy curve fits in Figure 3 submission 2.

PenTAG modeling with time measured in months calculates the Weibull parameters as (i) for IFN, gamma= 1.25, and lambda = 0.038 (ii) for sunitinib, gamma= 1.27, and lambda = 0.019.

Using these parameters PenTAG derive estimates of the mean PFS time that are almost identical to those presented by Pfizer (for IFN PenTAG PFS = 12.73 mths vs. 12.72 mths from Pfizer; for sunitinib PenTAG PFS = 20.87 mths vs. 20.88 mths from Pfizer).

OS curve IFN (from Pfizer submission 3, Table 5 / Figure 5)

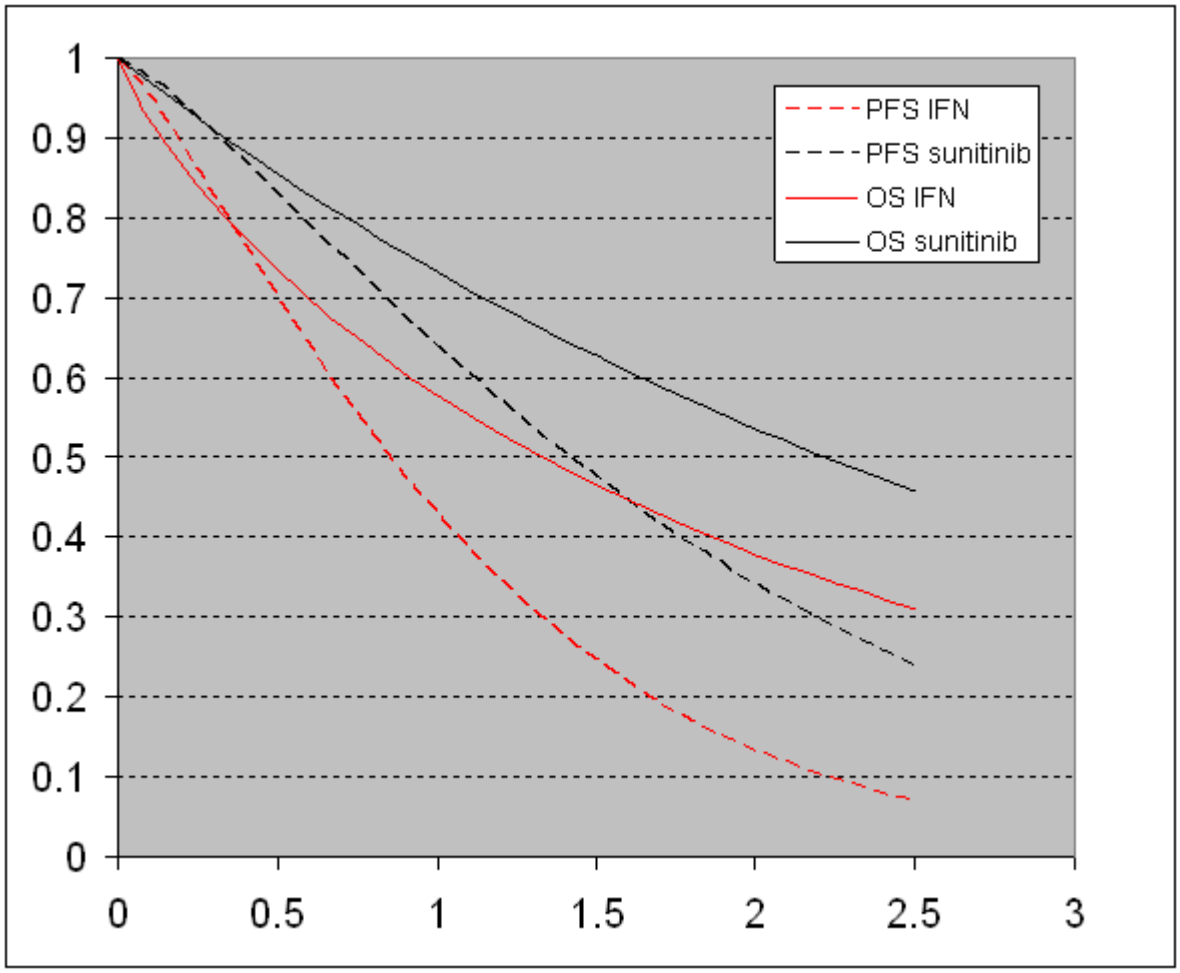
For IFN, the Committee requested PenTAG to use Pfizer's submission 3 (Figure 5). PenTAG have used the Pfizer model (Excel data) to obtain Weibull parameters; gamma = 0.83 and lambda = 0.547, where they measure time in years, not months. These values correspond to gamma = 0.83, lambda = 0.070, where time is measured in months, which is the framework used for the PenTAG model.

OS curve sunitinib (form Pfizer submission 2, Figure 4)

For sunitinib OS, the Committee requested PenTAG to use data from Pfizer's submission 2 (Figure 4 OS curve). As for the PFS data, Pfizer have not provided an Excel model with the analyses presented in their submission 2. PenTAG have not been given the values of the two parameters of the Weibull curve (OS sunitinib), and these have been estimated from reading off data from the hard copy curve fit in submission 2 (Figure 4). PenTAG modeling, with time measured in months, calculates parameters gamma= 1.00, lambda = 0.026. Using these parameters PenTAG derive estimates of the mean PFS time that are almost identical to those presented by Pfizer (PenTAG mean sunitinib OS = 37.68 mths vs. 37.56 mths from Pfizer).

Using the above data/assumptions in the PenTAG model gives the survival curves presented in Figure 2 (below).

Figure 2: Weibull survival curves derived by PenTAG using the assumptions requested by the NICE Appraisal Committee. Time is measured in years on the x-axis



Note that when using the above OS and PFS data in the PenTAG model/analyses, to present the results below, the (undiscounted) PFS years are virtually identical to those as given by the Committee (from Pfizer model) in their listed 'preferred assumptions'. However, the (undiscounted) life years are a little lower in the PenTAG results (compared to Pfizer results). This finding, is due to the fact that Pfizer have calculated their values assuming an infinite time horizon, whereas PenTAG assume a 10-year time horizon (to fit the PenTAG model framework). For comparison with Pfizer outputs, when we assume an infinite time horizon in the PenTAG model, the values are virtually identical to the Pfizer values.

Requested PenTAG cost effectiveness analysis

Table 5: Results from CEA using PenTAG model and OS and PFS data from Figure 2. In this analysis we have assumed the 1st cycle of sunitinib is free of charge and the IFN is administered for a maximum of one year. All other assumptions are as the PenTAG base case (see Assessment Report)

	Sunitinib	IFN	Sunitinib - IFN
Life years (undiscounted)	3.07*	2.21**	0.86***
Progression-free years (undiscounted)	1.75	1.06	0.70
QALYs (discounted)	2.10	1.51	0.59
Drug costs (disc)	£37,262	£4,179	£33,082
Other costs (disc)	£3,329	£2,678	£651
BSC in PD (disc)	£4,262	£3,826	£435
Total costs (disc)	£44,852	£10,683	£34,169
Cost / LYG (disc)			£44,667
Cost / QALY (disc)			£58,195

* estimate is 3.14 when assuming infinite time horizon (Pfizer model output = 3.13)
** estimate is 2.29 when assuming infinite time horizon (Pfizer model output = 2.29)
*** estimate is 0.85 when assuming infinite time horizon

Table 6: Results from CEA using PenTAG model and OS and PFS data from Figure 2. We have assumed the 1st cycle of sunitinib is free of charge, no restriction on time of administration of IFN. All other assumptions as the PenTAG base case (see Assessment report)

	Sunitinib	IFN	Sunitinib - IFN
Life years (undiscounted)	3.07*	2.21**	0.86***
Progression-free years (undiscounted)	1.75	1.06	0.70
QALYs (discounted)	2.10	1.51	0.59
Drug costs (disc)	£37,262	£6,116	£31,145
Other costs (disc)	£3,329	£2,989	£340
BSC in PD (disc)	£4,262	£3,826	£435
Total costs (disc)	£44,852	£12,931	£31,921
Cost / LYG (disc)			£41,729
Cost / QALY (disc)			£54,366
* estimate is 3.14 when assuming infinite time horizon (Pfizer model output = 3.13) ** estimate is 2.29 when assuming infinite time horizon (Pfizer model output = 2.29) *** estimate is 0.85 assuming infinite time horizon			

Further to the CEA above, when using the above data (Figure 2) in the PenTAG model, we report additional CEA results:

- Assuming the 1st cycle of sunitinib is not free (no price scheme), and an assumption that IFN given for a max of 12 months, results in a cost per QALY of £62,773.
- Assuming the 1st cycle of sunitinib is not free (no price scheme), and no restriction on time for administration of IFN, results in a cost per QALY of £58,944.