Health Technology Appraisal
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
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%

[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.

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)

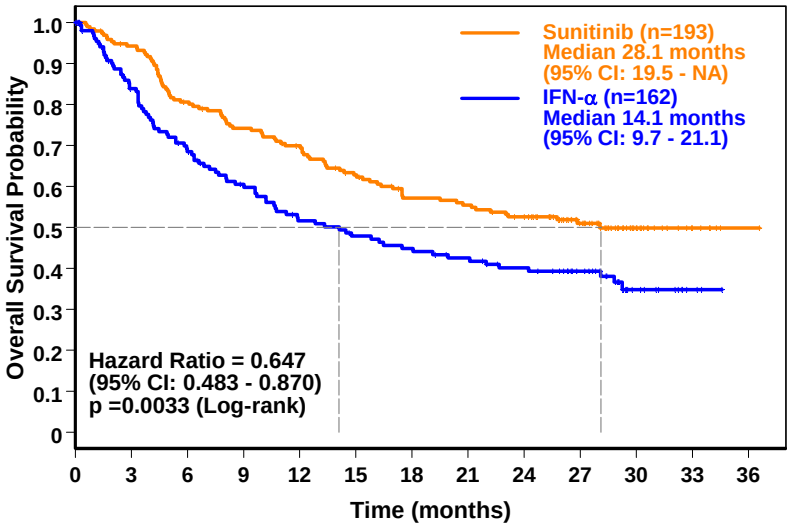
	Sunitinib, n (%) (n=323)	IFN-α, n (%) (n=359)
Any post-study treatment	182 (56)	213 (59)
Sunitinib	36 (11)	117 (33)
Other VEGF* Inhibitors	106 (33)	115 (32)
Cytokines	63 (20)	47 (13)
mTOR** Inhibitors	28 (9)	16 (4)
Chemotherapy	21 (6)	20 (6)

*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.



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.

[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).

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

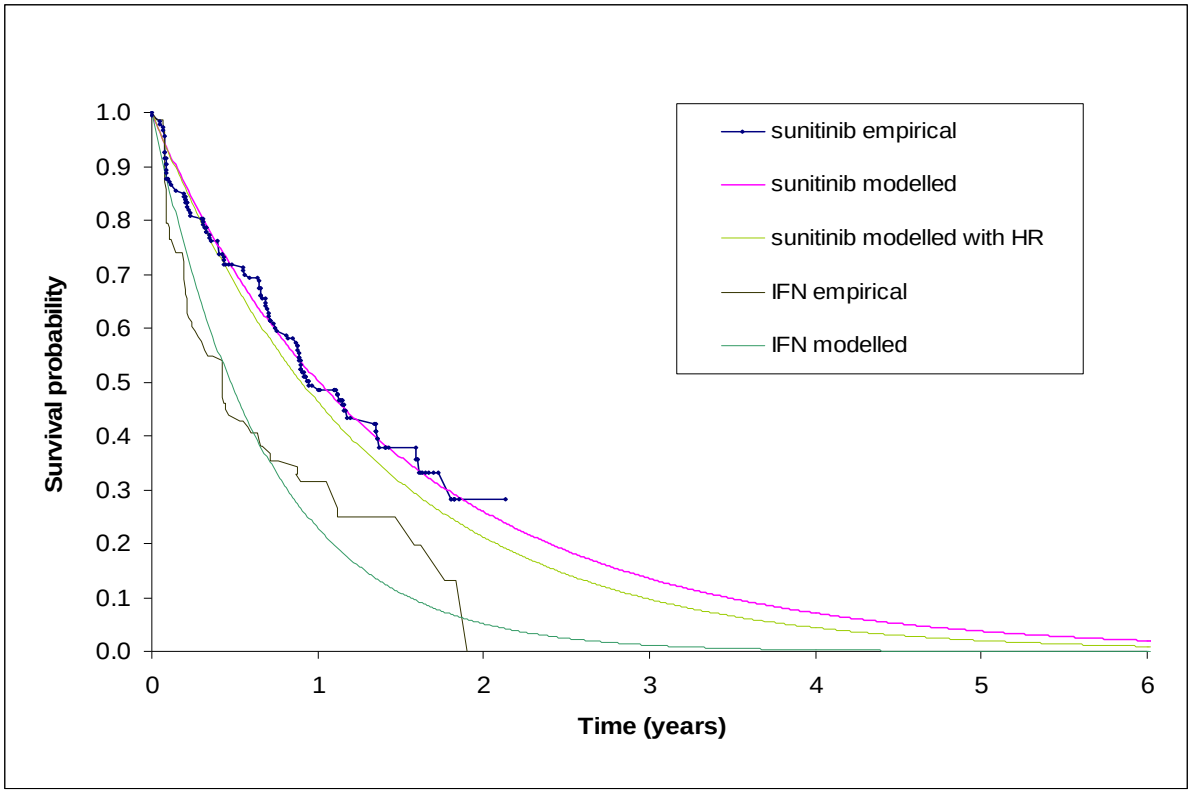
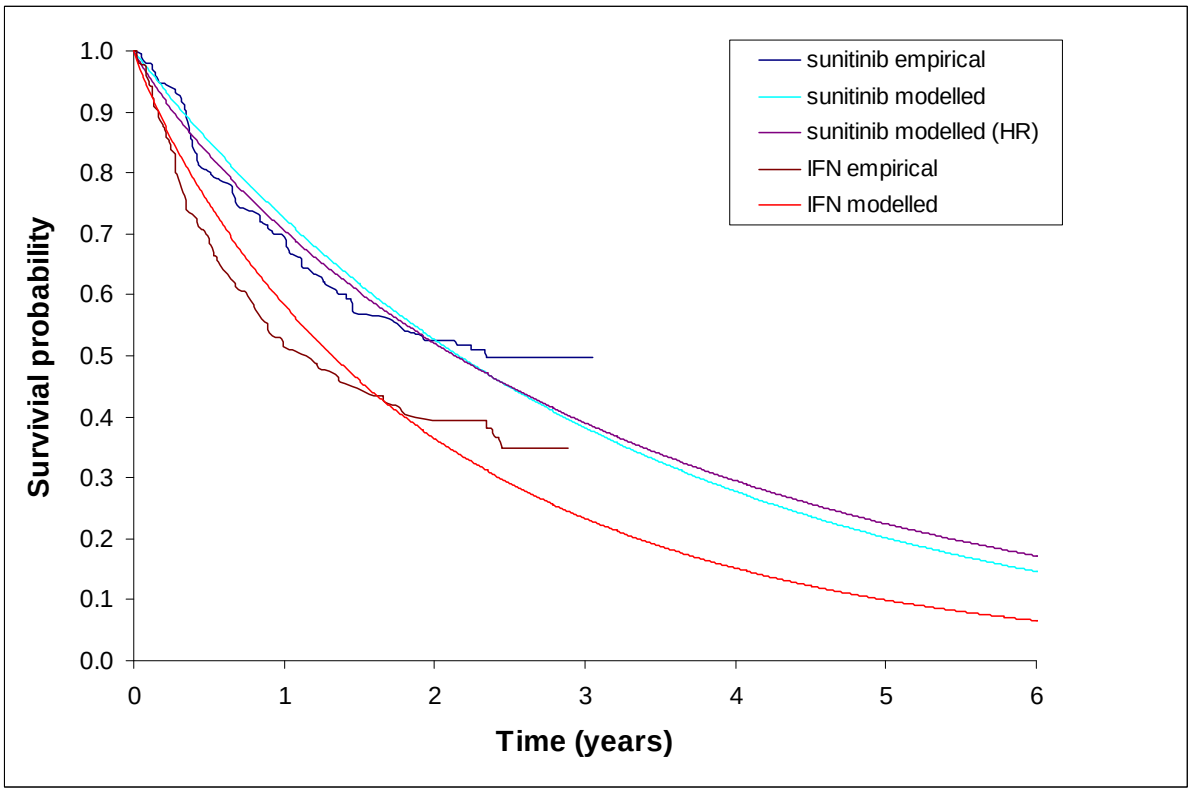


Figure 3: Overall survival - no systemic treatment post study discontinuation analysis

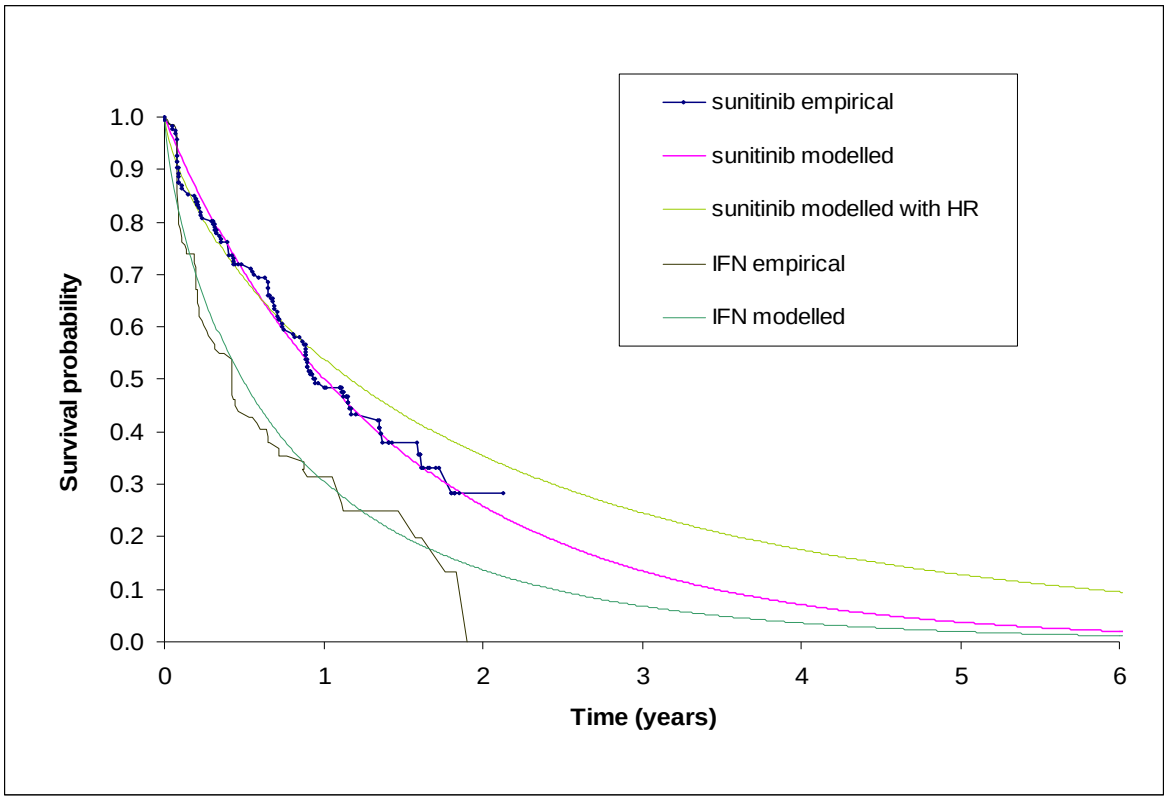


The above curves were generated from a regression that used all available data points to estimate the Weibull parameters, this approach is consistent the approach taken in

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.

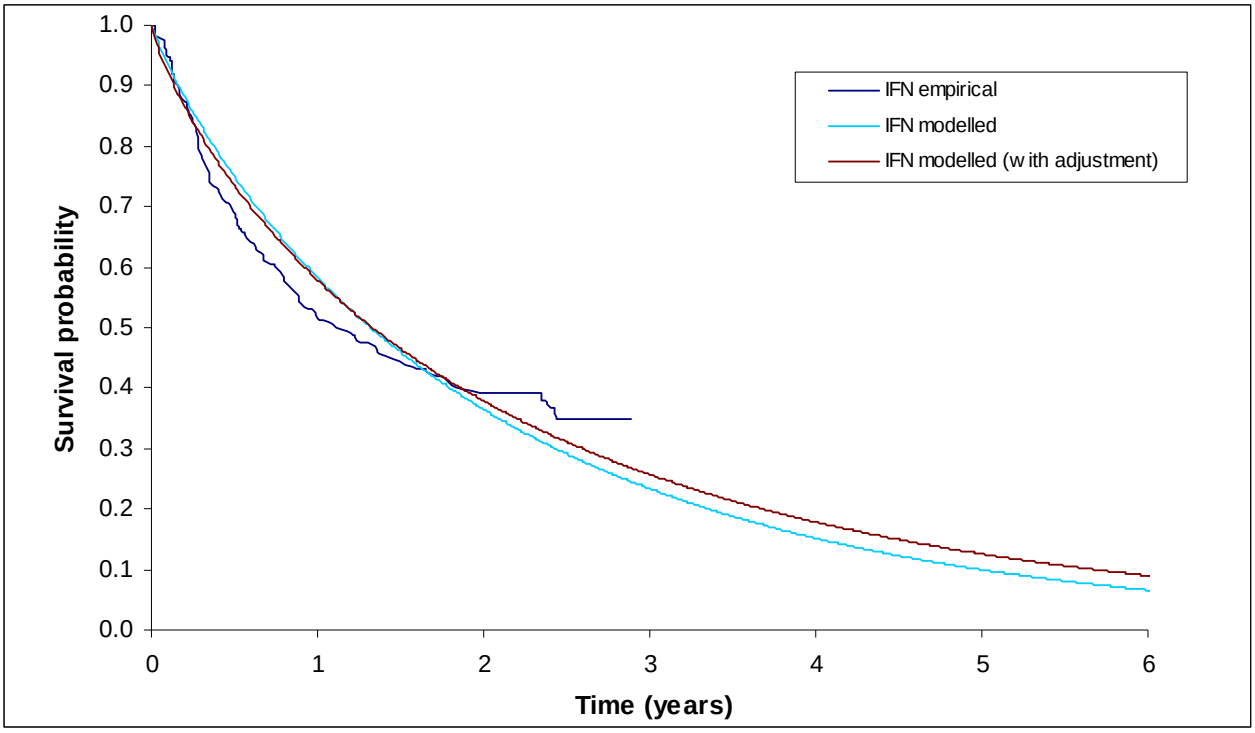
In our original model, PenTAG corrected this underestimation by fitting a Weibull curve to fewer data points (one per month). We have adopted this approach to improve the fit of the IFN-α curve shown in figure 2 and generated the survival curves for IFN-α and sunitinib as shown in figure 4. While adjusting 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**[iii]

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

[iii] 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.

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 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

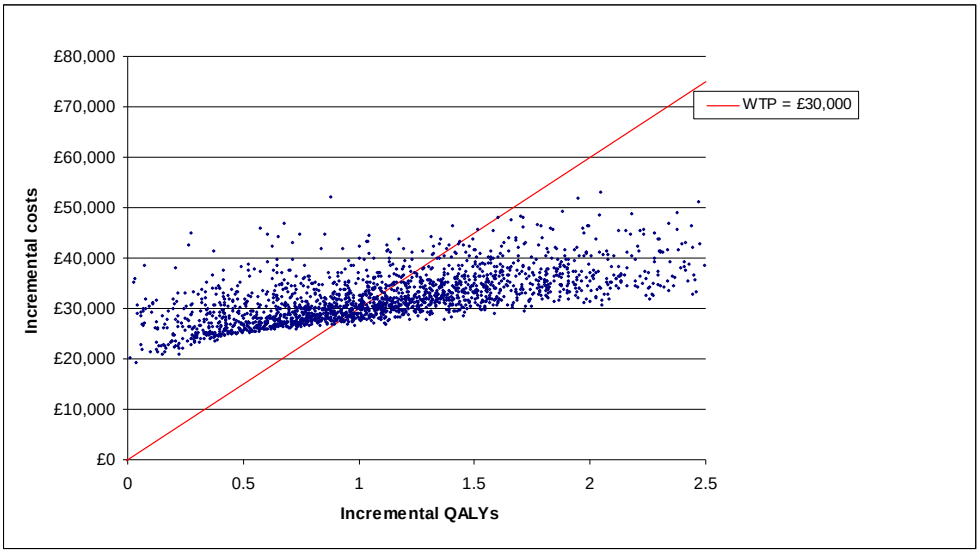
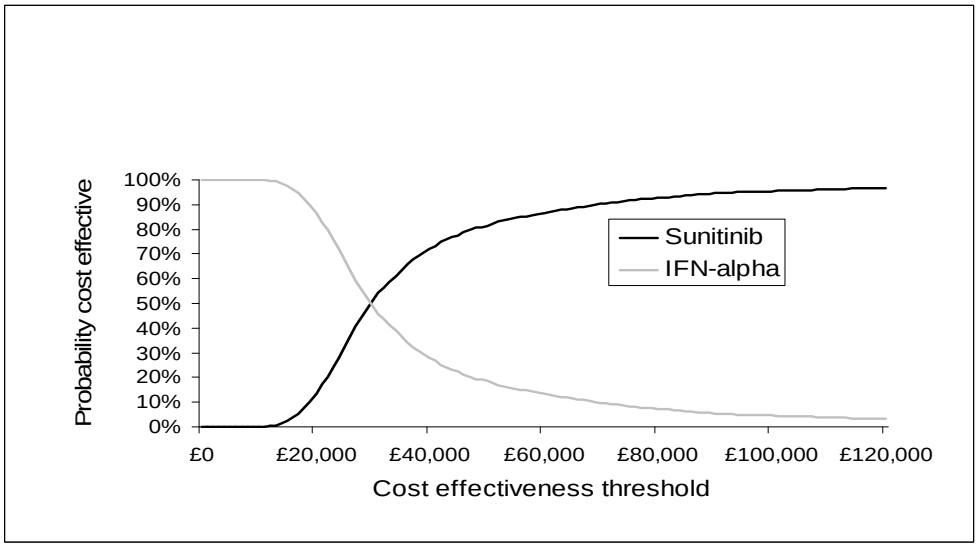


Figure 7: Cost effectiveness acceptability curve



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.

References

Aass N, De Mulder PH, Mickisch GH, et al. Randomized phase II/III trial of interferon Alfa-2a with and without 13-cis-retinoic acid in patients with progressive metastatic renal cell carcinoma: The European Organisation for Research and Treatment of Cancer Genito-Urinary Tract Cancer Group (EORTC 30951). *Journal of Clinical Oncology* 2005;23:4172-4178.

Coppin C, Porzsolt F, Autenrieth M, Kumpf J, Coldman A, Wilt T. Immunotherapy for advanced renal cell cancer. *Cochrane Database of Systematic Reviews* 2004, Issue 3.

Creagan ET, Twito DI, Johansson SL, et al. A Randomized Prospective Assessment of Recombinant Leukocyte A Human Interferon With or Without Aspirin in Advanced Renal Adenocarcinoma. *Journal of Clinical Oncology* 1991;9:2104-2109.

Escudier B, Eisen T, Stadler WM, et al. Sorafenib in Advanced Clear-Cell Renal-Cell Carcinoma. *New England Journal of Medicine* 2007[1];356;125-134

Escudier B, Pluzanska A, Koralewski P, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. *Lancet* 2007[2];370:2103-2111.

European Medicines Agency. Guideline on the Evaluation of Anticancer Medicinal Products in Man. London; 2005 (CPMP/EWP/205/95/Rev.3/Corr.2).

Figlin RA, Hutson TE, Tomczak P, et al. Overall survival with sunitinib versus interferon (IFN)-alfa as first-line treatment of metastatic renal cell carcinoma (mRCC). *Journal of Clinical Oncology* 2008;26: 2008 (May 20 suppl; abstr 5024)
[Full results can only be accessed by subscribers at
http://www.asco.org/ASCO/Abstracts+%26+Virtual+Meeting/Abstracts?&vmview=abst_detail_view&confID=55&abstractID=32895

Flanigan RC, Salmon SE, Blumenstein BA, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. *New England Journal of Medicine* 2001;345:1655-1659.

Fossa SD, Martinelli G, Otto U, et al (1992). Recombinant interferon alfa-2a with or without vinblastine in metastatic renal cell carcinoma: Results of a European multi-center phase III study. *Annals of Oncology* 1992;3:301-305.

Hernán MA, Brumback B, Robins JM. Marginal Structural Models to Estimate the Causal Effect of Zidovudine on the Survival of HIV-Positive Men. Epidemiology 2000;11(5):561-570.

Medical Research Council Renal Cancer Collaborators: Interferon-alpha and survival in metastatic renal carcinoma. Early results of a randomised controlled trial. *Lancet* 1999;353:14-17.

Mickisch GH, Garin A, van Poppel H, et al. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: A randomised trial. *Lancet* 2001;358:966-970.

Minasian LM, Motzer RJ, Gluck L, et al. Interferon alfa-2a in advanced renal cell carcinoma: Treatment results and survival in 159 patients with longterm follow-up. *Journal of Clinical Oncology* 1993;11:1368-1375.

Motzer RJ, Murphy BA, Bacik J, et al. Phase III trial of interferon alfa-2a with or without 13-cisretinoic acid for patients with advanced renal cell carcinoma. *Journal of Clinical Oncology* 2000;18:2972-2980.

Motzer RJ, Michaelson MD, Redman BG, et al. Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. *Journal of Clinical Oncology* 2006;24 16-24.

Neidhart JA, Anderson SA, Harris JE, et al. Vinblastine fails to improve response of renal cancer to interferon alfa-n1: High response rate in patients with pulmonary metastases. *Journal of Clinical Oncology* 1991;9:832-836.

Wang, Y., Hong, S., and **Zhang, M.** (2008) Using marginal structural model to adjust for post-study treatment. (In Preparation) and: http://statgen.ncsu.edu/icsa2007/talks/Session%205A%20MSM%20for%20ICSA%202007%20Yanping%20Wang.ppt