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

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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

1. 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.

1.1. 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).

1.2. 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.

2. 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.

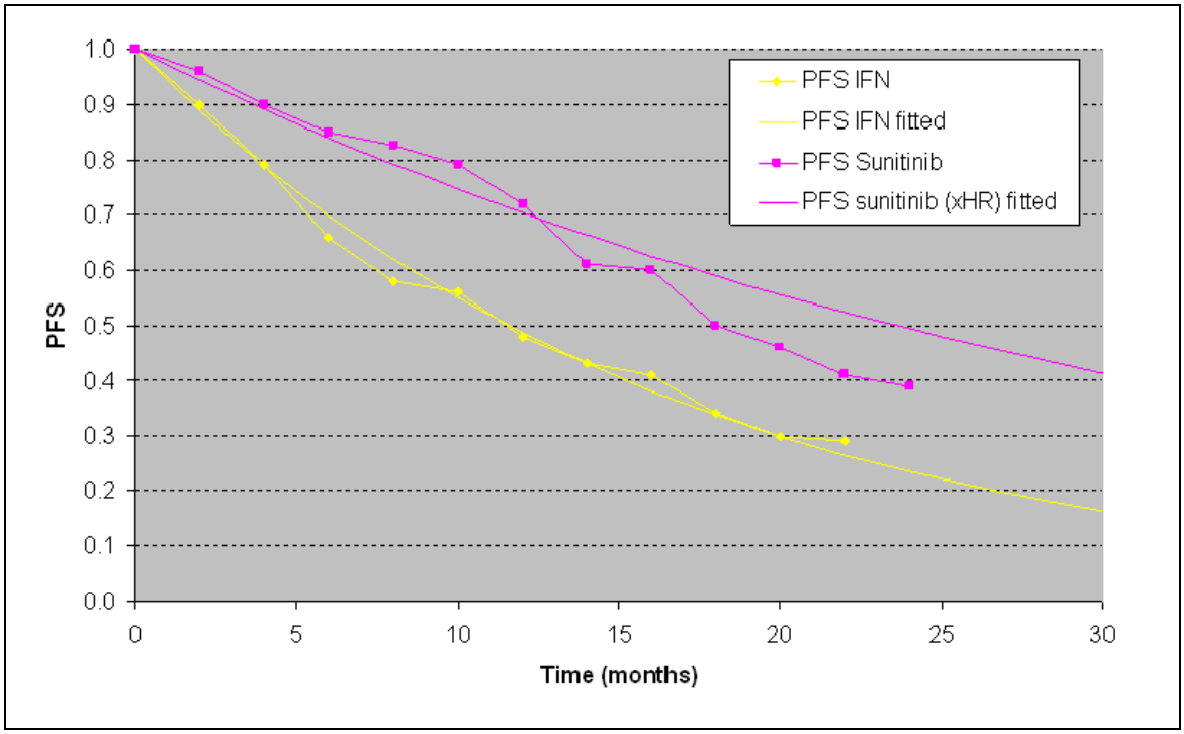
2.1. Question 1: Provide further explanation as to why the PFS estimates for IFN differ between PenTAG (16.44 months or 1.37 years) and Pfizer (12.72 months or 1/06 years) when both come from the same data source (Pfizer submission 2).

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

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.

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.

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.

Table 3: 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 (Figure 2) derived for use in the PenTAG model, based on the NICE Appraisal Committee preferred assumptions (Table 3).

2.3.1. 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).

2.3.2. 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,

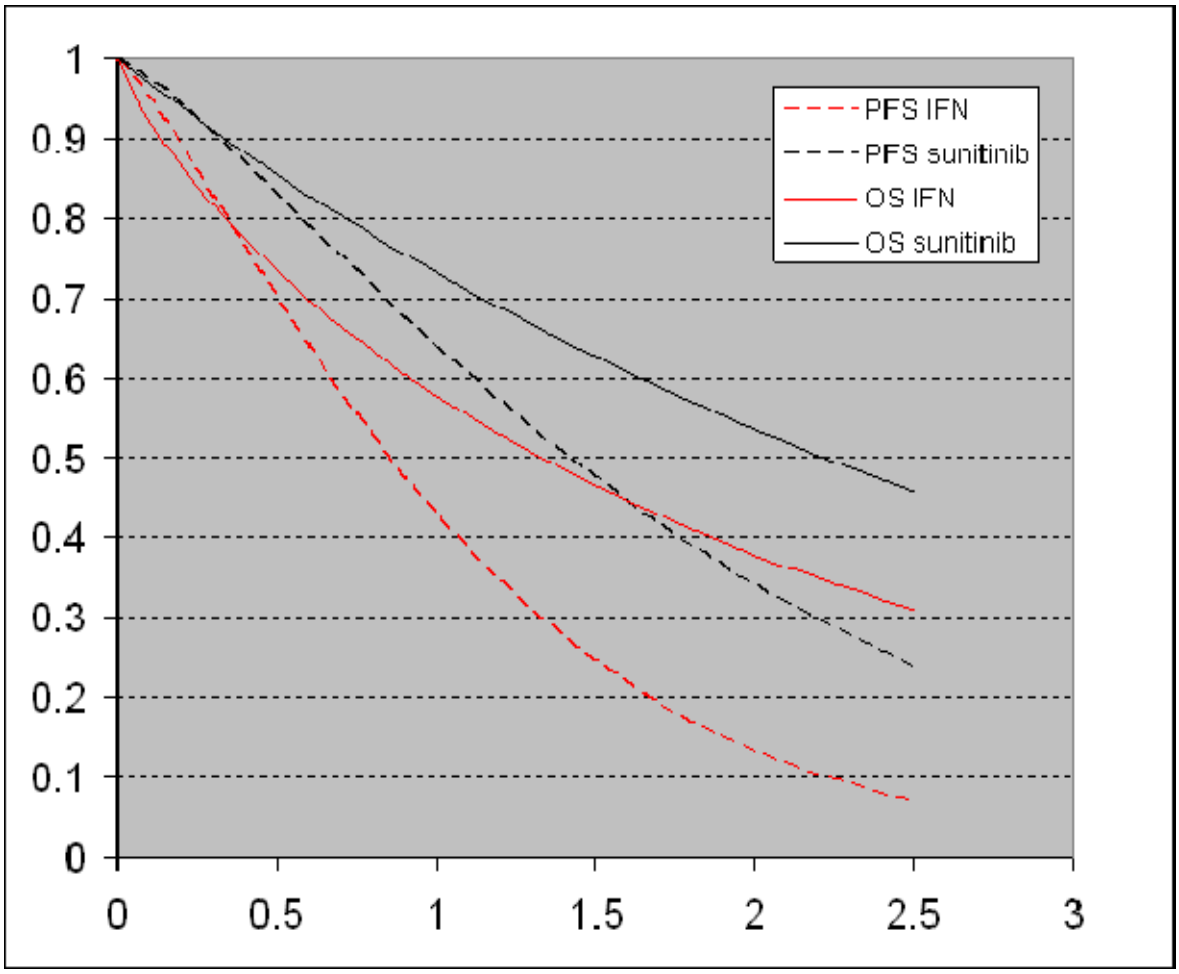
where they measure time in years, not months. These values correspond to gamma = 0.83, lambda = 0.070, where time is measured in months, which is the framework used for the PenTAG model.

2.3.3. 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.

2.4. Requested PenTAG cost effectiveness analysis

Table 4: 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 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)

	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.