Health Technology Appraisal
Bevacizumab, sorafenib, sunitinib and temsirolimus for renal cell carcinoma
Pfizer response to the Technology Assessment Report

Pfizer is pleased that the Assessment Group (p.49) acknowledge the clinical benefit of Sutent:

"We conclude that there is evidence to suggest that treatment with bevacizumab plus IFN and sunitinib has clinically relevant and statistically significant advantages over treatment with IFN alone in patients with metastatic RCC." (pg 206)

"In the comparison of sunitinib versus bevacizumab plus IFN, sunitinib presents with additional benefits at lower cost, dominating bevacizumab plus IFN" (pg155)

And also the questions raised about the position of IFN- α for the treatment of patients with metastatic RCC:
"It is unrealistic and perhaps unethical to expect that further randomised clinical trials would be performed using IFN or best supportive care as a comparator in these interventions that are now widely used in Europe and the US". (p.11)

Pfizer believe that although the approach taken overall by the Assessment Group appears reasonably objective, aspects of that approach and a number of the assumptions they have made serve to diminish the potential value that sunitinib can bring to improving both the quality of life and survival of patients with metastatic renal cell carcinoma, as well as seriously distort the cost-effectiveness of sunitinib.

The main concerns with the report produced by the Technology Assessment Group (TAG) are:

- The exclusion of all forms of clinical data other than that derived from Randomised Controlled Trials.
- The use of base line IFN-α Progression Free Survival (PFS) data from a trial comparing bevacizumab plus interferon-alpha versus interferon-alpha to model the effectiveness of sunitinib.
- The failure to adjust the IFN-α base line Overal Survival (OS) data from the Escudier study to reflect the impact of use of targeted therapies on patients progressing.
- The approach taken to utility values for disease states.
- The exclusion of the first free cycle from the base case.
- The assumption that Best Supportive Care (BSC) after disease has progressed carries only minimal Primary Care based costs.
- The exclusion of the cost of end-of-life care associated with death from the base case.

The exclusion of all forms of clinical data other than that derived from Randomised Controlled Trials (RCT)

The Assessment Group committed within the protocol to examine other forms of evidence other than RCTs:

> *"Types of study to be included*
> *Systematic reviews of RCTs and single RCTs will be included. These study design criteria may be relaxed to include other controlled and uncontrolled study designs depending on the availability of more methodologically robust evidence."(p.7)*

By choosing to restrict themselves to evidence from RCTs, the Assessment Group has excluded all of the evidence supporting the use of sunitinib for second line treatment of patients with mRCC, comprising two single arm studies, as well as the ongoing extended access programme (EAP) that has now enrolled over 4,000 patients with sunitinib being used either as first or second line treatment. As with a number of other cancers, the method of generating evidence segued rapidly from an RCT that allowed cross-over based on differential efficacy, to single arm designs because of the combination of the proof of efficacy provided in the pivotal study (A6181034) and because of concerns regarding continuing use of older more ineffective treatments.

The use of base line IFN- α Progression Free Survival data from a trial comparing bevacizumab plus IFN- α versus IFN- α to model the effectiveness of sunitinib, when sunitinib trial data was available.

The PenTAG base case assumes that IFN-α is given for a maximum of 12 months to all patients. This is reflected in their use of the Escudier AVOREN trial data where IFN-α stopped after 12 months regardless of outcome.

A group of eight Renal Oncologists sampled from a wide geographical spread over the UK, was consulted on June 1 2008. They were clear that the above assumption is not standard practice in the management of patients with metastatic RCC. 80% of the clinicians would treat to progression with a planned review at 12 months to determine response and toxicity. In practice, although many patients would receive less than 12 months, there is a small proportion with a durable response who would receive the drug for longer. The longest reported responder reported from the group was Progression Free at six years.

Pfizer questioned the applicability of the results of an indirect comparison between sunitinib and bevacizumab plus IFN-α to guiding clinical practice, based on IFN-α forming part of the intervention being compared with IFN- α in the AVOREN study in our original submission. It is believed that this is still a valid criticism.

The last and very significant concern is that PFS within the Escudier study was assessed solely by the investigators. The absence of an independent assessment severely compromises the use of the study as it is known that the findings between investigator and independent assessment can vary by as much as 40 per cent (Thiesse et al, 1997)

Given the above, the Phase III Motzer trial data, used by the Assessment Group to undertake a sensitivity analysis, should in fact have been part of the base case. It is also arguably more relevant for bevacizumab plus IFN-α to be reviewed with the Motzer IFN- α data as baseline as this more accurately reflects UK clinical practice.

The failure to adjust the IFN-α base line Overall Survival (OS) data from the Escudier study to reflect the impact of use of targeted therapies on patients progressing.

Pfizer acknowledges that PenTAG was restricted to the use of the data as presented within the clinical trials evaluated. For the trials evaluated for first line use versus IFN- α this is problematic as both allowed cross-over from the control group after interim analyses and/or the use of other TKIs temsirolimus and immunotherapy.

The impact of this has significant potential to overestimate the survival benefit of IFN-α. Escudier and his co-workers acknowledged that this was an issue within their study:

> *"We anticipated that the primary objective (overall survival) would be confounded by patients in the control group who progressed subsequently receiving these new second-line options or crossing over to receive bevacizumab, even though this scenario was not envisaged in the protocol. Therefore, an agreement with regulatory agencies was reached that presentation of the results of the pre-planned final analysis of progression-free survival before data for the primary endpoint were mature would be acceptable as the basis of the study to support regulatory submissions" (Escudier et al, 2007, p.2105)*

The effect of this within the Escudier study is to increase the benefit of IFN-α thus invalidating the PenTAG analyses of both sunitinib and bevacizumab plus IFN-α that are based on this.

The final results for the A6181034 study were presented at ASCO last month. Pfizer has undertaken to provide the National Institute for Health and Clinical Excellence with these results as they became available. The results presented at ASCO are more comprehensive than those given to NICE at the beginning of May and will be forwarded to NICE as stated in the Pfizer submission. A copy of the presented results is also attached here (Figlin et al, 2008).
Three main analyses of OS were presented to enable a fuller understanding of the clinical benefit of sunitinib for this population. The intention to treat (ITT) analysis showed a median OS of 26.4 months for the sunitinib group versus 21.8 months for the IFN-α group. The second analysis censored for crossovers from the IFN-α group after the second interim analysis, this showed a median OS of 26.4 months for the sunitinib group versus 20.0 months for the IFN-α group. The third analysis was focussed on patients who did not receive any post study treatment. This analysis was undertaken in order to demonstrate the 'true' Overall Survival of patients as would have been shown in the original study if conducted as per original protocol. In this analysis the median OS for the sunitinib group was 28.1 months versus 14.1 months for the IFN-α group. The median survival time of 14.1 months for IFN- α, is more consistent with other IFN-α survival evidence (Coppin et al, 2005).

The approach taken to utility values for disease states.

The Assessment Group, in the absence of utility data relating to patients with metastatic RCC, used values from two of the manufacturer submissions (Pfizer, Wyeth) as the basis for the values within their model.

The Assessment Group acknowledge the weakness of this approach (p.142):

> *"We acknowledge limitations in the utility data available to populate the model, and we explore the impact of assumptions on health state values in sensitivity analyses." (p.142)*

This approach is problematic as the values derived from the Motzer study for the 1st line modelling of sunitinib and bevacizumab plus Interferon-alpha 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.

A significant concern is that 'progressed' values within the trial were taken at the point where the patients entered the progressed state. A review of the literature for utilities associated with advanced and/or metastatic cancers provides a range of values that supports the lack of research in this area (table 1).

It should also be noted that the values from the Motzer study apply to either sunitinib or IFN-α and therefore should not be applied to bevacizumab when used in conjunction with IFN-α .

Table 1. Summary of stable and progressed utility values for advance/metastatic cancers

	Stable	Progressed	Difference
PenTAG sunitinib & IFN[1]	0.78	0.70	0.08
PenTAG temsirolimus[1]	0.60	0.45	0.15
Advanced colorectal[2]	0.72 - 0.80	-	
Metastatic colorectal[3]	0.80	0.50	0.30
Advanced ovarian[4]	0.63	0.34	0.29
Unresectable/metastatic GIST[5]	0.935	0.875	0.06

[1]Pentag Assessment Report. [2]Health Technology Assessment 2008; v12: No. 15. [3]Health Technology Assessment 2007; v11: No. 12. [4]Health Technology Assessment 2006; v10: No.9.
[5]Health Technology Assessment 2005; v9: No. 25.

It is likely that the true figure for the utility value difference, moving from progression free to progressed lies somewhere within the range of 6% and 30%. Within the PenTAG sensitivity analyses the difference between the upper CI limit for progression free and the lower CI for progressed is 14%. This value still appears low but the likely impact of this, if adopted as part of a revised PenTAG base case, is to strongly suggest that further analyses should be conducted with a wider range of values to better inform the discussion at the Appraisal Committee meeting.

Our advisory board also informed us that there is a between utility difference between sunitinib and IFN- α favouring sunitinib also reflected by spontaneous clinical reports from both patients and clinicians. We are unable to attribute a value to this in the absence of formal evaluations. This fits with the concerns we have that the QALY is only a function of overall survival within the PenTAG analysis.

The exclusion of the first free cycle from the base case
The first free cycle for sunitinib has been available in the UK since May 2007 and failure to incorporate this into the base case overestimates the costs associated with the use of sunitinib.

It is part of Pfizer's ongoing commitment to ensure the widest possible access to clinically effective drugs. Irrespective of the outcome of the decision of this review, the availability of the first free cycle will continue.

On this basis the first free cycle should be incorporated into a revised base case for consideration by the Appraisal Committee.

The assumption that Best Supportive Care after disease has progressed carries only minimal Primary Care based costs.
In the Pfizer submission model, the costs of BSC following disease progression were assumed to be similar to costs for BSC identified within a study of stage IV breast cancer. The Assessment Group, while acknowledging this approach to be reasonable (pg113), assumed that BSC would be delivered solely from a primary care setting at a relatively low cost.

Pfizer have understood best supportive care to be the best palliative care available, as judged appropriate by the investigator, and could include antibiotics, analgesics, radiation therapy for pain control (limited to bone metastases), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy as clinically indicated. We would suggest that this care would be similar following disease progression regardless of tumour type; thus a patient with metastatic/stage IV breast cancer would receive the similar BSC as a patient with metastatic RCC.
In Remak and Brazil's study of stage IV breast cancer they found that when patients progressed the emphasis of their care shifted to treatments aimed at alleviating pain and other symptoms; the number of blood transfusions and other special interventions increased; and there was an increase in hospitalisations, hospice stays and outpatient visits. This study would suggest that BSC is not carried out solely in primary care and therefore Pfizer contends that the Assessment Group assumption underestimates the cost of the Progressed Disease (PD) health state within their base case analysis.

An advisory board of eight Renal Oncologists sampled from a wide geographical spread over the UK, was consulted on June 1 2008 specifically about the above points. Only 10% of clinicians discharged patients back to Primary Care immediately on progression. 80% followed up every 8-12 weeks in a hospital outpatient setting until patient had reached terminal phase (within 6 weeks of death). They would then discharge patient to Palliative Care services rather than Primary care with either Hospice follow up or admission with far greater intensity than assumed in the Base Case although the exact costs are not quantified. 10% of clinicians followed patients up to death.

Given the difference in clinical opinion between clinicians advising Pfizer and the Assessment Group and the Assessment Groups own comment re the source of costs of BSC used within the Bayer model:

> *"we urge caution when using the data from such surveys in small samples, and such caution applies to the estimates used in the PenTAG analysis".(p.129)*

Pfizer contend that costs associated with BSC should be derived from the literature source provided within our submission.

As shown in the sensitivity analysis provided by the Assessment Group using this alternative value for BSC reduces the cost per QALY of Sutent vs IFN from £71,462 to £64,601.

The exclusion of the cost of end-of-life care associated with death from the base case.

All submitted models and that developed by the Assessment Group included three health states of which death was one. The Assessment Group noted that the industry submissions all included a cost associated with this state death but did not include these costs in their base case analysis. Although the Assessment Group conduct sensitivity analysis using a cost associated with death that demonstrates a slight reduction in their base case ICER (shown for all therapies), we believe this cost should be included as part of the base case analysis. Omitting this cost from the base case analysis, implies that costs associated with death are not applicable to the NHS, this is an unreasonable assumption when it has been shown that 50% of cancer deaths occur within NHS hospitals (Office for National Statistics, 2005).

Results of cumulative analysis

Modifying each of the points above has an impact on the base case ICER as demonstrated in Table 2.

Table 2: Individual sensitivity analyses from PenTAG modelling

Assumption	Impact on PenTAG base case ICER of £71,462
Use of Motzer 2007 data	-£9,594
Revision of Progressed Disease costs	-£4,632
1st cycle sunitinib free	-£6,100
Inclusion of end of life/death costs	-£168
Utility estimates	-value unknown

All of these significantly modify the ICER for sunitinib vs. IFN- α. It has been possible to look at the cumulative impact of four of these within the read only version of the model supplied by NICE (Table 3). It has not been possible to examine the impact of modifying the last of the assumptions but it is believed that it would have a further significant impact on any revised base case.

Table 3: Cumulative impact of modifying assumptions

Base case analysis	£71,462
Revised base case analysis	£52,242

Were all of the above assumptions to be adopted within a revised base case, we believe that it would prove a more accurate reflection of the cost-effectiveness of sunitinib for the use of improving the quality of life and survival of patients with metastatic RCC.

References:

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Thiesse P, Ollivier L, Di Stefano-Louineau D, et al. Response rate accuracy in oncology trials: reasons for interobserver variability. *J Clin Oncol* 1997; **15:** 3507-3514.

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[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
A copy of the results has therefore been appended.]