NICE Health Technology Appraisal

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

Pfizer response to documents received 29th October 2008

26th November 2008

Key points

Pfizer would like to acknowledge the open stance adopted by NICE to the receipt of key clinical data that has been developed during the course of the submission. We share the Committee's concerns that responding to it has added delay to the process.

Overall survival (OS) analyses

- The Appraisal Committee continues to express concerns regarding the validity of the No Post Study Treatment (NPST) analysis, although it is noted that the Committee accepts the applicability of the analysis in relation to interferon alpha efficacy for patients receiving treatment in England and Wales.
  Pfizer understands the reluctance of the Committee to accept the NPST analysis for patients initially treated with sunitinib, based on the median duration of OS in relation to the Intention to Treat (ITT) analysis but still believe that it is a closer approximation to the 'true' efficacy of sunitinib in relation to the treatment of patients in England and Wales.

Progression Free Survival (PFS) analyses

- AG-PenTAG initially dismissed the use of PFS data from the unplanned updated analysis in Pfizer's original submission rationalising that the data was contaminated by cross-over that occurred subsequent to the second interim analysis.
  The Committee has subsequently dismissed the PFS from the NPST analysis because *"..participants would generally receive further therapy after the transit from the progression free state to progressive disease.".* This indicates a failure to understand the NPST analysis. As patients who received further therapies at any time during the study were excluded, therefore, it is inappropriate to apply the ITT PFS to the NPST group. The only PFS analysis that can be reasonably used is the one derived from the NPST group.

Utility values

- Pfizer has challenged the validity of the utility values used in all modelling approaches throughout the course of this submission. There appears to be an ongoing failure to understand the deficiencies in the approaches to measuring utilities in this area. We maintain that the approach taken by Pfizer in assessing utility for the progressed state (measured at point where progression noted to have commenced and then (inappropriately) applied to the duration of time in progressed state through to death) should be corrected.
  Correcting for this not only gives a more accurate reflection of what occurs in practice but also significantly modifies all Incremental Cost Effectiveness Ratios (ICERs) derived from both the AG-PenTAG and Pfizer models.

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

In the additional comments section of this document, PenTAG suggested NICE explore the following areas further:

1) **Approach to modelling:** it is "not specifically clear on the approach taken by Pfizer, and suggest (it appears) that they are (may be) using the OS data with HR for modelling sunitinib OS, and using PFS empirical data for IFN and sunitinib to model Weibull curves for each."
2) **Methods for modelling PFS and data source:** "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)"
3) **Differences in survival curves between Pfizer submission 2 and 3:** "empirical survival curves for PFS from the 'no post study treatment' group appear to be different"
4) **Differences in PFS data between IA2 and ITT analysis**: "PenTAG note that in Pfizer submission 2 (and subsequent) that the differences in empirical survival curves s not explained…why are the curves so different?"

Approach to modelling:
PenTAG are correct in their assumptions for modelling OS and PFS. When analysing the 'no post study treatment' group we initially used the same approach as in the original submission. A baseline IFN model (Weibull curve/model from Kaplan Meier data) and the use of the HR for sunitinib to derive the sunitinib curves.
As can be seen in Figure 4 submission 3, the sunitinib curve from month 9 onwards shows considerable lack of fit to the empirical data and consequently overestimates the sunitinib efficacy. When the sunitinib data was fitted independently, the modelled curve gives a better fit to the data and therefore a more accurate estimate of sunitinib PFS benefit.

As shown in Figure 3 submission 3, modelling the sunitinib curve independently produces a curve that does not fit the empirical data by overestimating the earlier portion of the data. The sunitinib curve modelled using the HR although still overestimating the benefit when compared to empirical data provides the closer fit of the two options explored.

Methods for modelling PFS and data source:
Although PenTAG acknowledge that they did not explore the problems using the sunitinib HR to derive sunitinib PFS curves; they rationalise that the problems we encountered using the sunitinib HR to derive PFS within the NPST analysis would not occur if the ITT analysis was used.
Pfizer believe this assumption cannot be determined without further investigation, as the ITT analysis presented in Fig 3 (Pfizer submission 2) contains modelled curves that have not been adjusted. Therefore, neither the HR derived nor the independently estimated sunitinib curve fits the empirical data.
The IFN-a curve as presented displays considerable lack of fit from month 10 onwards. If the fit of this curve was improved it is unknown where the application of the sunitinib HR would lead to a reliable estimate of PFS; it is plausible that the curve could lead to an overestimate of sunitinib PFS as in the NPST analysis.

Differences in survival curves between Pfizer submission 2 and 3:
The difference in the empirical curves between submission 2 and 3 were explained within submission 3. Here it was noted that, when our statistical team conducted further analysis to answer the questions raised by submission 2 they uncovered an error in the statistical read-

out used to develop the results in submission 2. Our submission 3 was based upon the corrected results.

Differences in PFS data between second interim analysis and ITT analysis:
The differences in the empirical progression-free survival data between the second interim analysis and the ITT analysis are driven by the number of patients censored between the two analysis. Although median survival was reached at the time of the second interim analysis, many patients were still censored (ie had not progressed). By the time of ITT less patients were censored, leading to more accuracy in the reported results and slight change in the empirical survival curve.

Pfizer comments on document 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*

Modelling progression free survival
In the this report the Appraisal Committee discuss the data used to inform PFS and conclude that estimates for PFS for people receiving either sunitinib or IFN-a should be based on the overall ITT population. The Committee believe that estimates of PFS from the ITT analysis should be similar to estimates of PFS derived from the NPST group.
If only the median PFS values for the two treatments are compared across the two analysis, then the logic of this assumption would be true. However, the empirical data curves for each therapy differ by analysis and this would lead to different values of mean PFS.

The Committee conclude that PFS estimates derived from the ITT analysis are preferable to using *"estimates taken from an analysis that did not contain half the trial participants"*. However, in dismissing the NPST analysis the Committee do not address the potential limitations inherent in the ITT analysis. While it is correct to assume that "…participants would generally receive further therapy after the transit from the progression-free state to progressive disease." It is possible that patients in the ITT analysis switched therapies prior to disease progression because after the results from the Second Interim Analysis were disclosed patients were able to switch therapies.
In our original submission we included an economic analysis that used PFS data from an unplanned analysis because the data was more mature than that from the second interim analysis. PenTAG cautioned against using this data because patients were able to cross over leading to a confounding of the HR estimate. Pfizer suggest that the ITT result will also be confounded by cross over and maintain that PFS should be estimated from data where it is known that patients only received the allocated therapy until progression.

Finally, Pfizer believe that to use different data sources for each survival endpoint introduces structural uncertainties into the model which are unnecessary given that survival data is available for both PFS and OS from the same data source.

Modelling overall survival
Pfizer are disappointed that despite the fact that the Committee accepts the plausibility of using the NPST analysis to model OS for IFN-a, they have concluded that this analysis is inappropriate for estimating survival in the sunitinib group.

Pfizer acknowledge there are limitations in using the NPST analysis because the analysis was not pre-specified and only contains half of the trial population. However, these limitations would affect the estimates of both treatments. It would seem to be using double standards to adopt the analysis for IFN-a and yet dismiss its value for sunitinib.

The Committee also reject the use of the NPST analysis for sunitinib because they believe the modelled overall survival is overestimated. This assumption rests firstly; on the belief that it is implausible for OS in people who only received sunitinib to be higher than for those who have received sunitinib as well as other therapies, and secondly; that the model curve fitting techniques in the Pfizer model are inappropriate.

While on first consideration, the NPST results could be considered implausible the modelled results reflect the clinical trial results. Median OS for the sunitinib group was shown to be higher in the NPST analysis when compared to the ITT analysis, 28.1 month compared to 26.4 months respectively. Although these median results do not suggest a large difference in OS, the empirical data for NPST is highly censored with 49% of the patients in this analysis censored beyond 36 months, therefore modelling this group to gain mean values will produce a large survival estimate.

The Committee suggest that the modelling techniques used within the Pfizer model have inflated the sunitinib overall survival curve. The modelling approach to use the sunitinib hazard ratio to derive a curve from the IFN-a curve is consistent with the modelling approach used by PenTAG throughout this appraisal. We acknowledge that the sunitinib curve does not fit the empirical data but also note that the IFN-a modelled curve does not give a good fit to the empirical data either. Pfizer believe that other modelling approaches could have been employed to derive sunitinib benefit, for instance modelling the two curves independently, before dismissing the use of this analysis.

Pfizer comments on document 6: *DSU report on Pfizer's costs effectiveness model for sunitinib in the subgroup with no systemic post study treatment incorporating the Committee's preferred assumptions*

Validity of the DSU's revised cost-effectiveness estimates for sunitinib using final HRs and PenTAG model.
We note that, Pfizer have not been provided with the excel model (data) used by the DSU to generate the analysis presented in Table 1 of this document. In addition, given the importance of fitting the model curves to the empirical data, from the information provided in this report it is not possible to establish how well the sunitinib curves, used by the DSU, fit the empirical data.

In the detailed cost-effectiveness analysis (table 2), the IFN-a estimate of PFS is written as 0.62 years. Does this refer to a capped treatment duration as in PenTAG's original analysis or the total PFS time? This distinction is important as the table could be considered misleading if this time is actually the treatment duration.
Assuming the labels in Table 2 are accurate, the clinical logic of the estimates should be questioned. These results infer that a longer duration of treatment to progression results in a shorter post progression survival time, conversely longer post progression survival time is being associated with a shorter duration of treatment. The estimate of time spent with progressed disease for sunitinib is 0.73 years compared to 1.01 years for IFN-a.

DSU's cautions relating to the analysis focused upon patients who did not receive a second line therapy.
The DSU argue that "*…the use of second line therapies in the UK NHS must be considered in order to identify the appropriate subgroups of patients."* Ordinarily, Pfizer would agree with this statement, however in the current context this position is problematic.

Firstly, the research question set out within this appraisal is concerned with the comparison of sunitinib and IFN-a in the first line setting and not the sequencing of treatments. Using clinical data that is known to contain multiple sequences of treatments does little to inform the assessment of sunitinib benefit within the first line setting compared to IFN-a.
Secondly, as a consequence of access issues, current UK clinical practice is characterised by the absence of second line therapies. The analysis excluding patients who received second line therapies provides a close approximation of the current clinical situation.
Finally, using data from the patients who did not receive a second line therapy does not preclude further analysis to identify appropriate subgroups of patients. Clearly, further exploration of the clinical trial could identify patients who have a greater capacity to benefit from sunitinib.

In challenging the use of the NPST analysis, the DSU also argue that excluding patients who receive a second line therapy will *"almost certainly produce inappropriate results since their*

reason for exclusion is inextricably linked to outcome i.e. death." The validity of the NPST analysis could be questioned if the sub-group was not representative of the ITT population. However, a comparison of the demographics and patient characteristics between the NPST and ITT analysis has shown no systemic difference between the two analysis groups. In addition, the empirical PFS curves for the NPST analysis is comparable to the empirical PFS curves for the ITT population.

Cost effectiveness analysis resulting in ICER of £49,304
In their report the DSU present a cost effectiveness analysis based on the Committee's preferred assumptions using the Pfizer model and resulted in a cost per QALY of £49,304. The DSU regarded this result to be an underestimate of the ICER since the mean overall survival estimate used for sunitinib was based on the results from the overall ITT population.

The certainty with which this estimate is presented must be challenged. The DSU are using in their analysis a value of 2.29 years for IFN-a extracted from a modelled curve of the NPST analysis. When this curve is used to derive an estimate for sunitinib with in the Pfizer model, this data is challenged by the DSU for its 'lack of fit' to the empirical data. It would therefore appear to be adopting significant double standards to use without question the IFN-a curve in deriving the 'definitive' estimate of cost-effectiveness.

Pfizer response on 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.*

Modelling approach to fitting survival curves
In no part of this document, do PenTAG acknowledge that there is a possibility that their own modelling of the sunitinib survival curves may also not be ideal. They do concede the possible value of approach taken with the Pfizer model but dismiss this without a clear and definitive justification. There is much discussion as to the appropriate approach to modelling within oncology, in the circumstance where there is yet to be a single agreed approach it cannot be justified to rule out any of the alternative possibilities.

Validity of presented cost effectiveness results
The executable version of the economic model provided to Pfizer on (13th November), does not contain the analysis referenced within this document. As such, it is impossible to validate the results as presented [Pfizer will follow-up in a separate communication regarding this].

Overall if it conceded that the modelling approach taken by Pfizer has validity, it is not possible to support any of the estimates of cost effectiveness presented; the 'true' valuation may still be considerably less.

At a minimum this analysis should have been subject to sensitivity analysis to determine the upper and lower boundaries of cost-effectiveness.

Other comments:
PenTAG raise concerns with the approach requested by NICE. In using the different data to model sunitinib the committee have moved away from the research question considered by PenTAG that is the comparison of sunitinib, bevacizumab + IFN, and IFN alone. Therefore, their rationale to use HR methodology to model is no longer supportable.