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

DECISION SUPPORT UNIT

Steve Palmer, Keith Abrams, Allan Wailoo

Draft report
08 January 2009

1. INTRODUCTION

Following consultation on additional analyses during November 2008, the manufacturer of sorafenib (Bayer) provided an updated analysis for sorafenib as a second-line treatment and suggested a pricing scheme (Nexavar patient access scheme) that requires further investigation.

The manufacturer of sorafenib (Bayer) has also highlighted that in the key (TARGET) trial, 83% of participants received sorafenib explicitly as a second-line therapy and specifically after failure of immunotherapy. In the original assessment report, PenTAG did not consider this subgroup separately and modelled sorafenib as a second-line treatment using data from the whole trial population. Bayer argues that the group of participants that received sorafenib specifically as a second-line treatment after immunotherapy failure should be considered separately.

Bayer has also proposed a pricing scheme and have accounted for this in their updated economic modelling. This scheme has not yet been formalised by the Department of Health although discussions are ongoing. The impact of the scheme in the Assessment Group's economic model requires exploration. The manufacturer also suggests a price rise in the context of PPRS 2009. Again, although this has not been confirmed with the Department of Health, a sensitivity analysis including this price rise is considered appropriate.

To consider these issues the NICE Decision Support Unit (DSU) was requested:

1) To establish a cost effectiveness estimate for sorafenib, as a second-line therapy after failure of immunotherapy, compared with BSC using the PenTAG economic model with and without the proposed pricing scheme
2) To explore the impact of the proposed price increase on the cost effectiveness estimates of sorafenib compared with BSC.
3) To comment on the appropriateness of the subgroup analysis (second-line, failed immunotherapy) suggested by Bayer.

2. OVERVIEW OF ISSUES

There are 3 main issues considered within the updated analysis presented by Bayer:

(i) The Nexavar (sorafenib) patient access scheme and the proposed price increase during the implementation of the 2009 PPRS
(ii) The approach to modelling progression-free and overall survival (PFS and OS)
(iii) The subgroup analysis of patients who received prior cytokine therapy (second-line, failed immunotherapy)

These issues are further considered by the DSU using the original version of Assessment Group model provided by PenTAG. In addition, new data and analyses were also provided by PenTAG to the DSU to evaluate the impact of employing an alternative approach to survival curve fitting applying independent Weibull survival curves to sorafenib and best supportive care (BSC) within the PenTAG model. The cost-effectiveness of sorefanib compared to BSC was considered in relation to each of these issues.

3. PATIENT ACCESS SCHEME + PROPOSED PRICE INCREASE

The Nexavar (sorefanib) patient access scheme proposed by Bayer to the Department of Health provides the first pack of sorefanib (112 tables, 200mg) free of charge to each patient commencing treatment of renal cell carcinoma. The equivalent value of the first pack free of charge is £2504.60. There is also an additional pricing issue since Bayer proposes to raise the price of sorefanib during the implementation of the 2009 PPRS from £2504.60 to £2980.47 per pack.

The results of the base-case analysis and the impact of these scenarios on the ICER estimates are shown in Table 1 using the original PENTAG model.

Table 1: Impact of proposed patient access scheme using the original PENTAG model – DSU analysis

Scenario	Inc Costs	Inc QALYs	ICER
Base-case analysis	*£24,001*	*0.23*	*£102,498*
Incorporating the patient access scheme	£21,496	0.23	£91,802
Incorporating the patient access scheme with proposed increase in price	£25,401	0.23	£108,479

4. THE APPROACH TO MODELLING SURVIVAL

The second issue concerns the alternative approaches to modeling survival reported by Bayer and the Assessment Group. The Assessment Group, in their original model, fitted Weibull survival curves to model PFS and OS for BSC. The corresponding survival estimates for sorefanib were subsequently estimated by applying a relative measure of treatment effect (hazard ratio) to the survival curves estimated for BSC. This contrasted with the approach originally employed by Bayer which estimated survival independently for both sorefanib and BSC as opposed to applying relative measures of treatment effect to a baseline survival estimate. The Bayer approach employed trial data (Kaplan Meier) for PFS in both sorefanib and BSC, while for OS data the trial data were extrapolated using an exponential function over time.

As part of the new analysis Bayer state that the use of hazard ratios does not necessarily provide an accurate fit to the actual survival data observed in the TARGET trial. Furthermore, Bayer report that the assumption of proportional hazards, required for the approach employing hazard ratios, is not valid. This issue is a potentially important driver of the subsequent ICER estimates since the approach of combining baseline survival estimates with hazard ratios appears likely to over-estimate survival gains associated with the progression-free period for sorefanib (see Figure 5 of the revised analysis provided by Bayer). This, in turn, will potentially over-estimate the difference in subsequent drug costs since patients are assumed to be treated with sorefanib until disease progression. Consequently, the estimates of the ICER employing the hazard ratio may over-estimate the ICER for sorefanib compared to BSC.

As part of their new analysis Bayer presented results based on an alternative approach to modeling survival; fitting independent Weibull survival distributions for both PFS and OS to each of the separate treatments. The justification employed by Bayer for the different approach to their earlier submission was to be more consistent with the general approach used within the 'academic model'. Amendments to the cost and utility assumptions were also made to more closely reflect the assumptions employed within the original PenTAG model

The results of the revised analysis from Bayer are reported in Table 2. The combined impact of the alternative assumptions related to survival, costs and utilities results in a more favourable ICER estimate (£70,804) compared to their original submission (£90,630).

Table 2: Revised analysis (all patients) presented by Bayer

Scenario	**Inc Costs**	**Inc QALYs**	**ICER**
Original submission (all patients)	£23,849	0.26	£90,630
Revised analysis (all patients)	£19,797	0.28	£70,804
Revised analysis incorporating the patient access scheme (all patients)	£17,292	0.28	£61,846
Revised analysis incorporating the patient access scheme with proposed increase in price (all patients)	£20,283	0.28	£72,546

To explore the robustness of the revised results reported by Bayer, a similar approach to modeling survival was employed by PenTAG and the survival results were provided to the DSU on request. Separate Weibull survival cures were fitted by PenTAG independently to BSC and sorefanib (for both PFS and OS). The revised survival results were subsequently employed by the DSU to estimate the ICER estimates for the different scenarios within the PenTAG model. The results from the revised analysis are reported in Table 3.

Table 3: Revised analysis (all patients) using PENTAG model – DSU analysis

Scenario	Inc Costs	Inc QALYs	ICER
Original submission (all patients)	£24,001	0.23	£102,498
Revised analysis (all patients)	£19,490	0.27	£73,245
Revised analysis incorporating the patient access scheme (all patients)	£16,985	0.27	£63,832
Revised analysis incorporating the patient access scheme with proposed increase in price (all patients)	£19,934	0.27	£74,915

In general there appears close agreement between the results of the revised analysis reported by Bayer and those obtained using the revised survival approach employing the PenTAG model. The more favourable ICER estimate based on the alternative approach to modelling survival appears to be driven by the increase in overall QALYs gains estimated for sorefanib and the higher proportion of these gains achieved within the progressive disease period. This is illustrated in Table 4.

Table 4: Comparison of QALY gains based on alternative approaches to modeling survival using PENTAG model

Sorefenib vs BSC	All patients – original submission	All patients – revised analysis
QALY gains (Overall)	0.23	0.27
QALY gains (PFS)	0.27	0.15
QALY gains (PD)	-0.03	0.11

5. SUBGROUP ANALYSIS

The evaluation of sorefanib is based on the TARGET trial. This recruited patients who had received prior cytokine based immunotherapy (83%) and those who were considered unsuitable for such therapy (17%). The new submission from Bayer

presents a separate evaluation of the subgroup who received prior cytokine therapy, for whom, sorefanib is a second line treatment. The issue which needs to be addressed is whether this subgroup is considered appropriate and, if so, whether the subsequent approach to modeling survival presented in the latest submission by Bayer appears robust.

In their original submission, Bayer presented separate results for the entire group as well as sub-group analyses for those who received prior cytokine treatment and those considered unsuitable. The ICER results for the original Bayer submission are reported in Table 5.

Table 5: Original subgroup results from Bayer submission (reported in Table 76 of Assessment Group report)

Sorefenib vs BSC	**All patients**	**Prior cytokine**	**Cytokine unsuitable**
Increase in OS	0.46	[redacted]	[redacted]
Increase in PFS	0.19	[redacted]	[redacted]
Increase in QALYs	0.26	[redacted]	[redacted]
Increase in total costs	£23,849	[redacted]	[redacted]
Increase in drug costs	£19,601	[redacted]	[redacted]
Cost per QALY	*£90,630*	[redacted]	[redacted]

It should be noted that the ICER estimate for sorefanib for the subgroup of patients who received prior cytokine treatment was [redacted] than for the overall population (£90,630).

The revised results from the new Bayer analysis are reported in Table 6. The ICER for the subgroup who received prior cytokine treatment [redacted] appears to be more favourable (£60,892) than that reported for the overall population (£70,804). This appears primarily driven by [redacted] for the prior cytokine group compared to the previous analysis and also the [redacted]. The gains in OS are arising from [redacted] which, in turn, brings about [redacted] since patients are only treated until progression.

Table 6: Revised subgroup results from Bayer

Sorefenib vs BSC	**All patients**	**Prior cytokine**	**Cytokine unsuitable**
Increase in OS	0.421*	0.496*	NR
Increase in PFS	0.197*	[redacted]	NR
Increase in PD	0.224*	[redacted]	NR
Increase in QALYs	0.280	0.325	NR
Increase in total costs	£19,797 (£17,292)	£19,810 (£17,306)	NR
Increase in drug costs	£18,504*	£15,999*	NR
Cost per QALY*	*£70,804 (£61,486)*	*£60,892 (£53,193)*	NR

* Undiscounted

** Figures in brackets include proposed patient access scheme

The differences in results based on the earlier submission are due to an alternative approach to curve fitting as well as the alterations to cost and utility assumptions. In the original analysis, the results were based on survival curves fitted independently to the sorefanib and BSC arms based on trial data (Kaplan Meier) for PFS and extrapolation for OS assuming an exponential distribution. The revised analysis is now based on fitting independent Weibull survival distributions to both PFS and OS for each of the separate treatments. There is no discussion in the revised submission of why the Weibull approach leads to different results to the exponential applied originally by Bayer. Furthermore the justification employed by Bayer for the different approach is simply to be consistent with the 'academic model'. This is clearly an important issue since the different approaches appear to give quite different results – particularly for the prior cytokine group.

There are 3 main issues that need to be considered:

(i) the clinical appropriateness of the subgroup itself;
(ii) the difference between the original results and the revised results
(iii) the robustness of the revised estimates

In terms of the prior cytokine subgroup, PenTAG previously discussed this in their original report (page 85). They outlined several reasons why they did not consider this subgroup in more detail, choosing instead to focus on the overall population in the TARGET trial:

- The clinical basis underlying an expected difference in response to treatment in the two groups was not evident.
- It was unclear whether the subgroups were conceived a priori and the sample size calculations were based on the entire trial population.

In addition, there appear some important uncertainties concerning the revised Bayer results. In particular, there is no explanation provided by Bayer as to why the results for the subgroup who received prior cytokine therapy (compared to the overall TARGET population) differs so markedly between the original and revised analyses.

Furthermore, there is also a potential issue in relation to the modeling approach employed for overall survival by Bayer for sorefanib (both the earlier submission and the revised estimate). Figures 8 [redacted] of Bayer's revised submission illustrate that the length of follow-up for the sorefanib arm is much longer than that for BSC. This is because patients were allowed to cross-over from BSC to sorefanib after a particular point in time (after the initial positive findings for PFS were reported) and hence were censored for the comparison of OS. However, within the Bayer submission there is no discussion of whether patients initially receiving sorefanib went on to receive subsequent treatments or not. Consequently, OS data for sorefanib is not censored within the Bayer analyses.

Given the uncertainty surrounding whether patients randomised to sorefanib may have received subsequent treatments following disease progression it may have been more appropriate to censor both arms at a similar date and use this as the basis for extrapolation. Indeed, this approach appears to be how the comparison of OS data, adjusting for cross-over, is formally presented within the main trial paper reported in the NEJM. Consequently, it is possible that the Weibull extrapolation employed by Bayer may be over-estimating the longer term survival for the sorefanib arm.

In order to address this potential concern, a separate analysis was undertaken for the prior cytokine group by the DSU. This approach employed independent Weibull distributions for sorefanib and BSC. The estimates of OS for sorefanib were based on survival data for the prior cytokine group censored at the same follow-up duration as BSC. The results of this analysis are reported in Table 7.

Table 7: Revised analysis (prior cytokine) using PENTAG model - DSU analysis

Scenario	**Inc Costs**	**Inc QALYs**	**ICER**
Original submission (prior cytokine)	NR	NR	NR
Revised analysis (prior cytokine)	£19,708	0.31	£64,475
Revised analysis incorporating the patient access scheme (prior cytokine)	£17,204	0.31	£56,281
Revised analysis incorporating the patient access scheme with proposed increase in price (prior cytokine)	£20,153	0.31	£65,929

A comparison of the QALY gains and the distribution of these gains across the different periods of progression-free and progressive disease are reported in Table 8.

Table 8: Comparison of QALY gains based on PENTAG model

Sorefenib vs BSC	**All patients – original submission**	**All patients – revised analysis**	**Prior cytokine group – revised analysis**
QALY gains (Overall)	0.23	0.27	0.31
QALY gains (PFS)	0.27	0.15	0.15
QALY gains (PD)	-0.03	0.11	0.15

The revised analysis for the prior cytokine group, censoring patients in both arms for OS, results in marginally more favourable ICER results compared to those estimated for the overall population. This is primarily due to the higher overall QALY gains (0.31 vs 0.27) and also because these additional gains are predicted to be achieved in the progressive period (such that the overall drug costs for sorefanib do not

correspondingly increase with the higher survival estimates for the prior cytokine group). Compared to the results presented by Bayer, the ICER results appear slightly less favourable which appears to be explained by the distribution of survival gains predicted for this subgroup between the progression free and progressive disease period – with the Bayer model predicting a higher proportion of these gains being achieved in the PD period (which is associated with lower overall drug costs).