Sorafenib for Advanced Hepatocellular Carcinoma

ERG Comparison of the Patient Access Scheme as described to the Department of Health (DoH PAS) and the manufacturer's modelling of the PAS.

It is clear that the manufacturer has not modelled the DoH PAS.

The DoH PAS differs from the modelled PAS in two ways:

1. Consumption of sorafenib is 800mg/per day (recommended dose) rather than the 710.5mg/day (average trial dose) modelled. This difference will increase the cost of the sorafenib arm from that modelled.

2. Free packs are made available every fourth 28 days rather than every fourth month/cycle (30.4 days) as modelled. This more frequent provision of free packs will increase the savings accrued from free packs over the 14 year time horizon compared to the model.

It is not possible to readily adjust the model to a cycle of 28 days to assess the PAS as described to the DoH. However the ERG believe it is possible to derive an estimate of the likely base case ICER for the DoH PAS.

As a result of the increase in sorafenib consumption (see (1) above) the cost of the sorafenib arm in the DoH PAS is increased to £30,960 (from £28,359 in the modelled PAS) over the 14 year base case time horizon. This value was obtained from the model by use of a user selected option for altering consumption per day and/or sorafenib costs.

The increase in savings due to greater frequency of free packs (see (2) above) is approximated on a *pro rata* basis from the ERG's previous estimate that decreased free pack frequency (free pack every fourth 31.5 days instead of every fourth 30.4 days) reduces savings by £160. Thus:
extra savings = (30.4 – 28)/(31.5 – 30.4) * £160 = £358[*]

These extra savings offset the cost of the sorafenib arm which is now £30,960 - £358 = £30,602.

It is assumed that the cost of the best supportive care arm remains as modelled at £9,739 and thus the incremental cost for the DoH PAS = £30,602 – £9,739 = £20,863.

The incremental QALYs (unchanged) = 0.3588; therefore the estimate for the base case ICER is:
£20,863/0.3588 = £58,147/QALY (compared to £51,899/QALY modelled)

It is worth noting:

1. The DoH PAS may not reflect reality since the evidence available indicates that the consumption of sorafenib would on average be less than 800mg/day in practice (patients interrupt treatment/take treatment holidays for various reasons; mainly side effects).
2. [redacted]The base case ICERs above (modelled and DoH PAS) both invoke the assumption of sorafenib treatment ceasing on progression. [redacted].

[*] Calculated using non-rounded values

Evidence Review Group Report commissioned by the NHS R&D HTA Programme on behalf of NICE

Sorafenib for advanced hepatocellular carcinoma

Assessment of manufacturer's proposal for a Patient Access Scheme entitled: "*one pack free for responders every 4 months*"

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1 SUMMARY

1.1 Scope

Assessment of the impact upon the cost-effectiveness of sorafenib for advanced HCC of a patient access scheme (PAS) proposed by the manufacturer.

1.2 Summary of submitted PAS

The PAS proposed that every fourth pack of sorafenib is free for each patient. Two changes were made to the original model:

[1] "Patients who remain on treatment after every three packs of sorafenib receive the fourth pack free".

The PAS was slightly confusingly titled "*one pack free for responders every 4 months*" since one pack (as modelled) lasts 31.5 days rather than one month. In short, "one pack free every fourth month" is not quite the same as "every fourth pack free".

[2] "Consistent with UK clinical practice all patients stop treatment at the point of progression".

This change modifies one of the assumptions underlying the original base case analysis; it may therefore be viewed as independent of a PAS and as an additional modification to the cost-effectiveness analysis.

The changes in the model are only related to costs in the sorafenib arm.

As modelled these changes give a PAS base case ICER for sorafenib compared to Best Supportive Care (BSC) of £51,899/QALY (a reduction from £64,754/QALY in the original submission). When Weibull fits to survival data were substituted for lognormal fits the PAS ICER was £[redacted]/QALY (a reduction from £[redacted]/QALY in the original submission).

Analysis by the ERG using modified model inputs for the costs associated with sorafenib treatment, generated ICERs marginally higher than those presented in the submission for lognormal and Weibull analyses.

1.3 Commentary on the robustness of submitted evidence

1.3.1 Strengths

The submitted model was functional and generated the ICERs reported in the submission. The model allowed user-selection of several model inputs including log-normal and Weibull fits to survival analysis for deterministic analysis of the ICER for sorafenib v. BSC

1.3.2 Weaknesses

The PAS analysis did not estimate or appear to take into account any costs to the NHS of PAS administration.

The elimination of the cost of post-progression treatment represents a change to model assumptions that was not fully justified. Therefore more than the effect of a PAS is being estimated in the revised model base case relative to the original model base case.

The Markov model cycle duration and the duration of a pack of sorafenib for an average patient were slightly incongruous and the implementation of the PAS in the model could not be easily modified to adjust this.

The PAS modelling suffers from the same potential weaknesses that were identified by the ERG for the original model. The most important of these being: the uncertainty associated with utility values used and the algorithm employed in their generation; the submission does not include cost-effectiveness estimates using the independent assessment of time to disease progression (TTP); the economic evaluation relies heavily on the use of expert opinion for estimating resource use for the treatments in the model.

1.4 Analyses undertaken by the ERG

The ERG undertook:

1. To check the validity and consistency of the submitted PAS model the ERG tested its functionality and its ability to generate the ICERs presented in the PAS submission

2. An analysis of the PAS-generated savings that was independent of the model and under the assumptions that (i) one free pack was made available every fourth month and (ii) one free pack was made available every fourth pack.

3. To examine the validity of the curves (lognormal and Weibull) fitted to the trial data by comparing these to published information for survival of European patients with advanced HCC.

4. Re-calculation of the cost per cycle for sorafenib and conducted cost-effectiveness estimates using this value.

1.5 Key issues

The proposed scheme is complex in that the model allows a free pack every fourth month, whereas, based on the trial data, the average patient would consume less than 3 packs (in fact 2.89 packs) in the previous 3 months. This asynchrony between model and probable sorafenib usage becomes greater as the time horizon extends. Although this represents a difference between the model and practice it has a minor influence on estimated ICERs relative to the issue of selection of curves fitted to overall survival and time to progression.

The PAS ICERs are very sensitive to the type of parametric fit used for survival data. The committee previously considered that both lognormal and Weibull fits to survival data were plausible. Independent survival data for advanced HCC patients (BCLC class C) tend to support this view. A key issue is then: does the range of ICERs generated by modelling these fits provide a plausible range within which lies the cost-effectiveness of sorafenib for advanced HCC?

Implementation of the PAS scheme may involve additional administration costs which appear not to have been considered in the model. A rationale for the complexity of the PAS over simpler options is not provided in the submission.

2 INTRODUCTION

The manufacturer submitted a revised economic model (PAS model) that generates lower base case ICERs of £/LYG and £/QALY than those produced by their original model. Two changes were made to model parameters, these were:

From the submission

- Patients who remain on treatment after every three packs of sorafenib receive the fourth pack free.
- Consistent with UK clinical practice all patients stop treatment at the point of progression (Ref: Personal communication). Progression was defined as determined according to investigator assessment, as in the SHARP trial.
  All other model assumptions remained the same.

In consequence of these changes the new ICERs are £51,899/QALY and £36,469/LYG and the cost generated for the sorafenib arm in the base case is reduced from £32,971 to £28,359 (a reduction of £4,612). The original and PAS base case ICER values and their differences are summarised Table 1.

Table 1 Base case ICER values; new and original models (deterministic analyses)

	PAS§	**ORIGINAL**§	***Difference***
QALY SORAFENIB	1.08	1.08	*ZERO*
QALY BSC	0.72	0.72	*ZERO*
COST SORAFENIB (£)	28,359	32,971	*-4,612*
COST BSC (£)	9,739	9,739	*ZERO*
ICER Cost/QALY (£)	**51,899**	**64,754**	***-12,855***
LYG SORAFENIB	1.54	1.54	*ZERO*
LYG BSC	1.03	1.03	*ZERO*
COST SORAFENIB (£)	28,359	32,971	*-4,612*
COST BSC (£)	9,739	9,739	*ZERO*
ICER Cost/LYG (£)	**36,469**	**45,502**	*-9,033*

§ In the base case the original model included post-progression treatment with sorafenib whereas the PAS model did not include post-progression treatment with sorafenib

Probabilistic sensitivity analysis of the PAS base case was reported and the CEACs for willingness to pay/QALY according to new and original models are shown below in Figure 1.

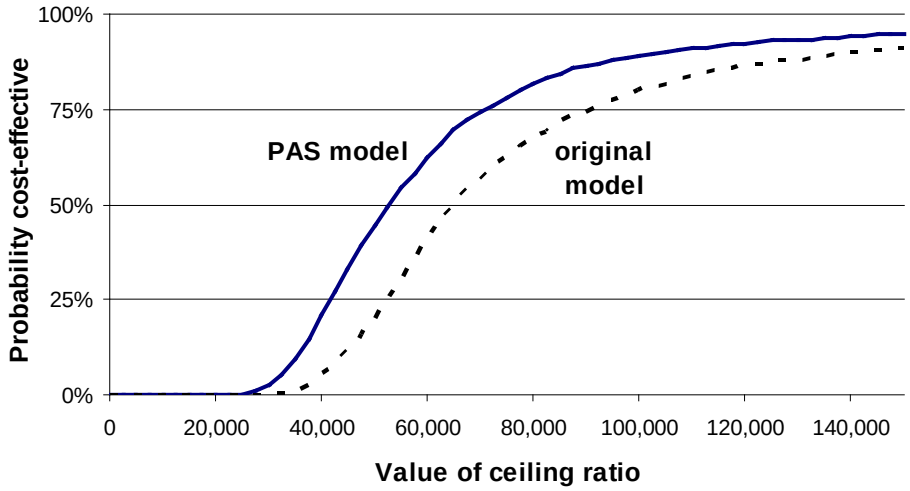


Figure 1 CEAC for Sorafenib vs. BSC, Cost per QALY (base case PAS & original models)
The ERG created this figure from data in the respective models. Appropriate data columns were used from the models to redraw the CEAC curves.

The new submission also reported numerous deterministic subgroup and sensitivity analyses using the PAS model (see Appendix 1). In view of the committee's previous deliberations it is clear that the most relevant of these is the substitution of Weibull for lognormal fits to overall survival and disease progression data. In Table 2 the ICERs produced in this PAS sensitivity analysis are compared to the PAS base case (lognormal) values and with the original model. It can be seen that with Weibull fits the PAS ICERs delivered are substantially greater than the base case, as also occurred in the original submission. The PAS "Weibull" ICERs are £[redacted]/QALY and £[redacted]/LYG (compared to £[redacted]/QALY and £[redacted]/LYG in the original submission). The cost generated for the sorafenib arm in this analysis is now reduced from the original model value of £[redacted] to £[redacted] (a reduction of £[redacted]; see Appendix 2).

Table 2 PAS and original sensitivity analyses: lognormal and Weibull fits

	PAS § *lognormal*	**PAS § Weibull**	***Difference lognormal-Weibull***	**ORIGINAL§ *lognormal***	**ORIGINAL§ Weibull**	***Difference lognormal-Weibull***
QALY SORAFENIB	*1.08*	[redacted]	[redacted]	*1.08*	[redacted]	[redacted]
QALY BSC	*0.72*	[redacted]	[redacted]	*0.72*	[redacted]	[redacted]
COST SORAFENIB (£)	*28,359*	[redacted]	[redacted]	*32,971*	[redacted]	[redacted]
COST BSC (£)	*9,739*	[redacted]	[redacted]	*9,739*	[redacted]	[redacted]
ICER Cost/QALY	***51,899***	[redacted]	[redacted]	***64,754***	[redacted]	[redacted]
LYG SORAFENIB	*1.54*	[redacted]	[redacted]	*1.54*	[redacted]	[redacted]
LYG BSC	*1.03*	[redacted]	[redacted]	*1.03*	[redacted]	[redacted]
COST SORAFENIB (£)	*28,359*	[redacted]	[redacted]	*32,971*	[redacted]	[redacted]
COST BSC (£)	*9,739*	[redacted]	[redacted]	*9,739*	[redacted]	[redacted]
ICER Cost/LYG (£)	***36,469***	[redacted]	[redacted]	***45,502***	[redacted]	[redacted]

§ In the base case the original model included post-progression treatment with sorafenib whereas the PAS model did not include post-progression treatment with sorafenib
* Incremental gain in QALY = [redacted] ** Incremental cost = [redacted] *** Incremental gain in life years = [redacted]

3 Assessment of the proposed PAS

The PAS model was found to be executable to the same extent as the originally submitted model but in addition allowed user-selection of analysis with Weibull fits to overall survival and to disease progression survival data. As was the case for the original, the new model was not set up for user-selection of the independent assessment of TTP.

3.1 Changes to the original model

The manufacturer has introduced two changes to the original model.

One change allows a proportion of the cost of sorafenib to be foregone; thus one pack of sorafenib is free every fourth month for responders (1 month = 1 cycle = 30.4 days). This may legitimately be considered part of a PAS.

The second change concerns an assumption in the original model. The original model base case assumed that a small proportion of patients continue on sorafenib for a short time after disease progression; this proportion has been reduced to zero in the PAS model. This modification is essentially a retrospective adjustment to an underlying assumption in the original model. It may be questioned whether this

change can be considered a legitimate part of the analysis of the PAS. The manufacturer's justification for this change was:

From the submission

- Consistent with UK clinical practice all patients stop treatment at the point of progression (Ref: Personal communication). Progression was defined as determined according to investigator assessment, as in the SHARP trial.

The "personal communication" was not referenced in the PAS submission received by ERG.

The effect on the ICER of eliminating post-progression costs is the same as making post-progression sorafenib free of charge. However it appears that if the PAS was implemented then any patient that received post-progression sorafenib would incur cost to the NHS (unless the sorafenib came from a fourth pack), that is not accounted for in the PAS base case.

Eliminating the cost of post-progression sorafenib treatment reduces the cost of the sorafenib arm by £937 (see ERG calculation Appendix 3). Thus the reduction in cost that derives solely from a free supply of one free pack every fourth month (cycle) is less than the difference between the base case for the PAS and original models. The actual reduction due to one free pack every fourth month can be calculated by subtracting the cost of post progression sorafenib treatment from the difference between the cost of the sorafenib arm in the PAS base case (£28,359) and that in the original base case (£32,971). This is: £4,612 - £937 = £3,675. An ICER calculated only on this latter reduction generates a base case PAS ICER of £54,509/QALY (Table 4 of PAS submission) which could be considered a valid ICER for the PAS for comparison to the ICER in the original model.

3.2 Model validation

3.2.1 Replication of reported results

The ERG confirmed that the PAS model could be used to replicate the deterministic and probabilistic base case results submitted. Within the limits of user manipulation the ERG considered the model was internally valid. The results generated in sensitivity analyses again could be replicated.

The ERG identified two issues, (i) related to the cost per cycle of sorafenib and (ii) ambiguity in the definition of the PAS as either one free pack every fourth month or one free pack every fourth pack .

3.2.2 Cost of sorafenib per model cycle

The cost of sorafenib used in the PAS model was £2,836.1 per cycle. This was based on a pack content of 112 tablets of 200mg, a pack cost of £2890.47 and an average daily consumption of 710.5mg per day for 30 days (see Appendix 4). However, the cycle length in the model is 30.4 days; this would actually give a cost per cycle of £2,877.5. When this value is used in the PAS model, the base case cost per QALY becomes £52,641 (compared to the submitted value of £51,899). If in addition post progression treatment is not excluded then the PAS ICER becomes £55,290/QALY.

3.2.3 Difference between Markov cycle and pack duration

The description of the PAS model states that after three packs the fourth pack is free. However the PAS model was actually modified so that one free pack was received every fourth month (not every fourth pack), consistent with the submission's title "*one pack free for responders every 4 months*". For the average patient, one pack lasts longer than one cycle, so one pack free every fourth month does not coincide with the consumption of the fourth pack of sorafenib. The submission states:

From the submission

> ..a small proportion the fourth pack will be used in the subsequent month. However, for discounting purposes, in the model the cost of the fourth pack is assumed to be realized in the fourth month only.

As one pack of sorafenib contains 112x200mg tablets, at the recommended dose of 800mg/day the pack lasts 28 days. However, in the SHARP trial(Llovet et al. 378-90) the average consumption was 710.5mg/day and this value was used in modelling. At this rate of consumption a pack lasts 31.5271 days. Yet the Markov model cycle-length was 1 month; defined as 365.25/12 days (30.4375 days).

As duration of treatment progresses, the discrepancy between cycle length and pack duration becomes greater; e.g. the 20th pack consumed by a patient taking the average dose is started on day 599, however the 20th month (representing receipt of the fifth free pack as modelled) starts on day 578 (about ⅔ of a cycle earlier).

The model is set up so that a free pack can be implemented only at every fourth month (cycle). It was insufficiently flexible to allow a cost-effectiveness analysis in which every fourth pack was free. Because of this issue the ERG conducted an analysis of the expected savings that was independent of the model. This was done as an assurance that savings had been appropriately accounted for in the submission.

3.2.4 The ERG analysis of savings generated.

Since the PAS proposal involved only changes in cost of sorafenib (no changes to effectiveness inputs or to comparator inputs) the reduced cost in the sorafenib arm claimed in the PAS base case could be tested independently of the model itself.

This was done using the fitted survival for patients in the non-progressed state (lognormal parameters). To calculate accrued savings the proportion of patients not progressed at the mid-time in each fourth cycle was multiplied by the cost of a pack of sorafenib (£4,890.47). Each fourth cycle result was discounted at the rate presented in the model and the results summed across 168 cycles (the time horizon of the model). The results are summarised in Appendix 5 . Savings came to £3,675. This value corresponds to that in the submission once the cost of post-progression treatment is accounted for (see section 3.1).

Every fourth month (cycle) does not correspond to the consumption of every fourth pack by the average patient. Figure 2 illustrates the asynchrony between fourth cycle and fourth pack under the assumption that tablets are not discarded and each finished pack is followed with a new one.

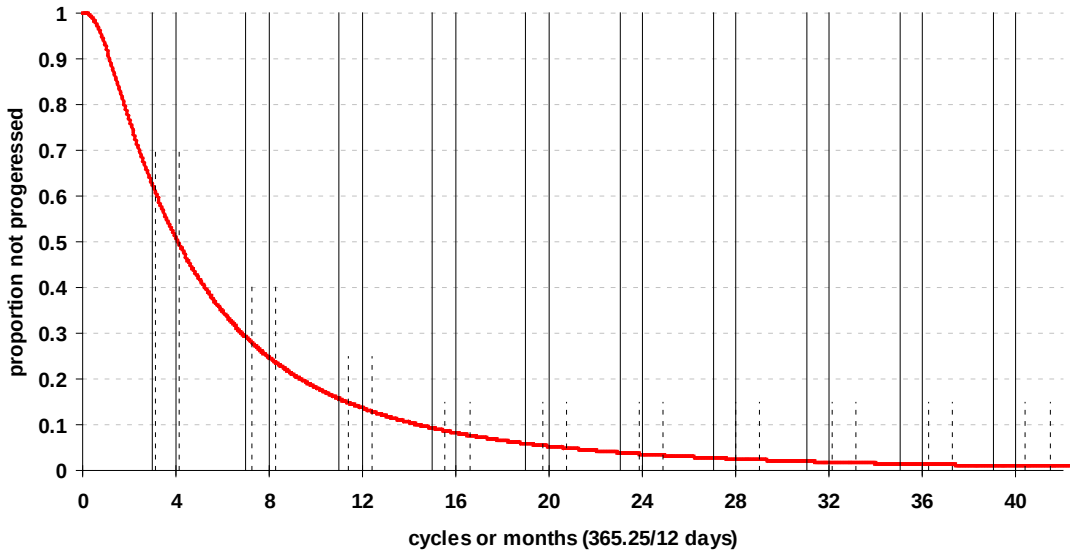


Figure 2 Asynchrony of fourth cycles and fourth packs consumed by average patient.
Each fourth cycle is indicated by solid vertical lines and each fourth pack by dashed vertical lines.

The ERG calculated the accrued savings should the PAS be implemented as “every fourth pack free” (as would be supposed according to the description of the model change presented in the submission).

Again this was done using the fitted survival for patients in the non-progressed state (lognormal parameters), and the starting and ending times of every fourth sorafenib pack using the model assumption of 710.5mg/day and corresponding pack duration

of 31.5 days (22400/710.5). The cost saved was derived by multiplying the proportion of non-progressed patients mid-time in the fourth pack by the cost of one pack (£2,980.47). This was discounted using the cycle discount rate (from the model) for the cycle that corresponded to the start of the free pack. The results are summarised in Appendix 6.

Savings calculated in this way came to £3,515 (over 168 cycles) compared to £3,675 generated by the PAS base case model, that is £160 less than PAS implemented as one free pack every fourth month. This would act to raise the ICERs.

It should be emphasised that these differences are dwarfed by the effects of selecting Weibull rather than lognormal fits to survival data (see section 3.4).

3.3 Critique of approach used

The PAS proposed is a complex method of achieving the simple outcome of a lower ICER of around £51,899/QALY (or £54,509/QALY if post-progression treatment is not excluded from the PAS model). This applies both to modelling the scheme and to its implementation in clinical practice. A simpler approach is to reduce the cost of a pack of sorafenib. To achieve an ICER of £51,899/QALY (base case PAS value) using the original model requires the drug cost/cycle to be reduced from £2,836 to £2,155; the model's deterministic output is then £51,900/QALY. Given a cycle of 30.4 days the cost/day is £70.8. At a daily dose of 710.5 mg this equates to a pack cost of £2,232 (for 22400mg). The original cost of a pack is £2,980.47 so the new price represents a reduction of 25.1%, which is rather similar to making every fourth pack free.

The PAS proposed may carry an administrative burden for the NHS. The cost of this burden has not been estimated or taken into account in the PAS submission. In discussion with commissioners the ERG has learnt that the scheme would probably require registering each HCC patient, tracking their individual use of packs (consumption will vary between patients), collating information for the group of patients under the responsibility of commissioners and auditing costs in a satisfactory way for transaction so that appropriate rebate can be obtained. With increasing numbers of PASs under adoption, the administrative load of the schemes may become a serious issue.

3.4 Plausible ICER values (£/QALY)

The ICERs (£/QALY) for the PAS are very different depending on the choice of parametric fit to survival data: "lognormal" ICER £51,899/QALY, "Weibull" ICER £[redacted]/QALY. Both lognormal and Weibull distributions provide plausible fits to the trial data (Appendix 7) and produce similar goodness-of-fit Akaike Information Criteria scores. It is evident that the difference in the extrapolations beyond trial data is the major contributor to the marked disparity between ICERs.

To explore this issue further the ERG looked for published information on survival of advanced HCC patients (i.e. HCC BCLC stage C disease). As prognosis is distinctly different for Asian patients (hepatitis B regions) the ERG only sought European studies. The most relevant information came from the study by Camma et al 2008(Camma et al. 62-75) who reported the survival of 406 consecutive HCC patients classified according to BCLC criteria. The results for BCLC class C patients (n=77) are shown in Figure 3. As sorafenib was not listed as a treatment for patients in this study, this data is compared to the lognormal and Weibull fits for survival of best supportive care patients in the SHARP trial(Llovet et al. 378-90) in the figure.

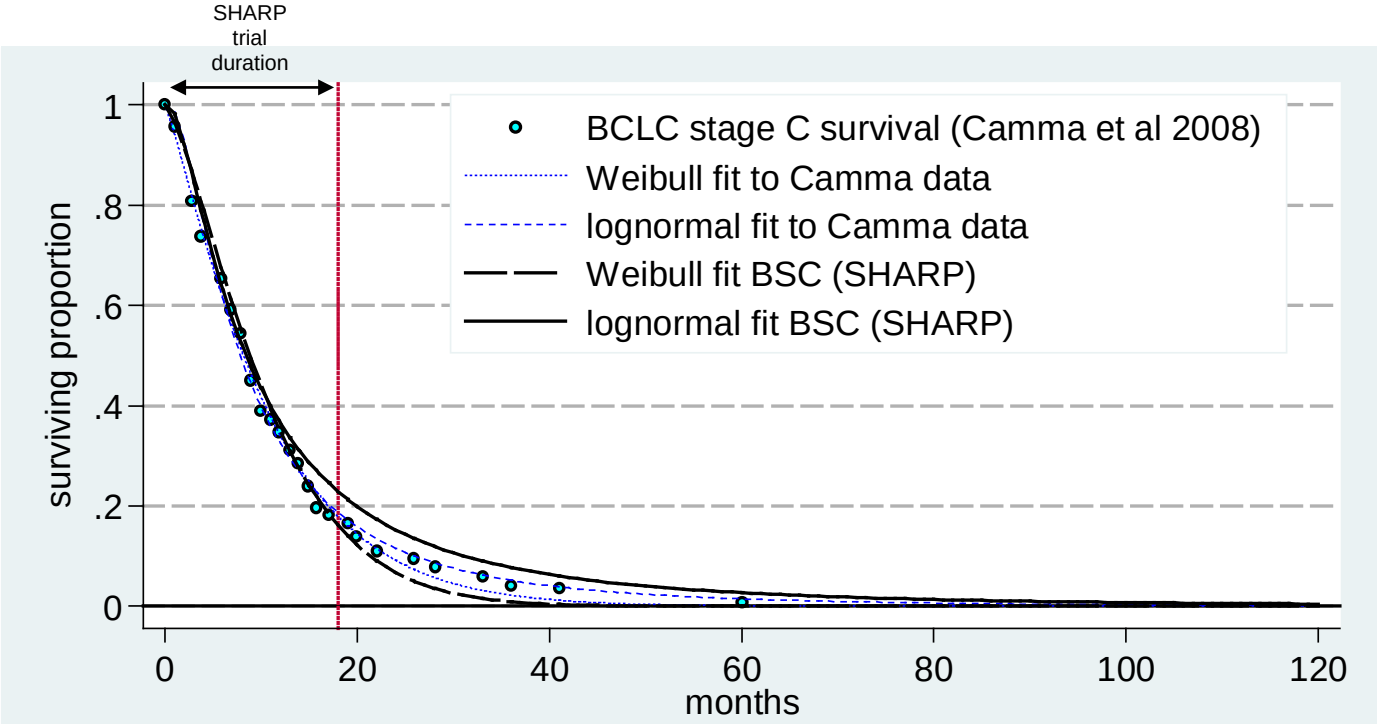


Figure 3 Survival in BCLC class C HCC and extrapolations for best supportive care group

Both Weibull and lognormal distributions provide good fits to the Camma data with the latter arguably superior. The Camma population is more likely to reflect the HCC population defined by the decision problem than that in SHARP(Llovet et al. 378-90); SHARP included 17% BCLC stage B patients (better prognosis than "advanced"

HCC) and a disproportionately large number (95%) of Child-Pugh class A patients who would have relatively good prognosis within the BCLC stage C patient group.

The SHARP trial(Llovet et al. 378-90) and Camma et al data(Camma et al. 62-75) are remarkably similar for the duration of the SHARP trial, thereafter the observed survival from Camma lies between the two (lognormal and Weibull) extrapolated SHARP curves. Since the Camma population is more like the target population, and bearing in mind the uncertainty associated with these data, this observation tends to support the proposition that the two modelled extrapolations may represent a plausible range for survival of the target population. Consequently the range of ICERs generated by modelling these fits may provide a plausible range within which lies the estimated cost-effectiveness of sorafenib for advanced HCC.

A smaller UK series of BCLC stage C HCC patients (n=30) has been published by Kung et al(Kung et al. 188-94) and reports similar results to Camma et al (median survival 10.5 and 9.2 months respectively).

Subsequent to the guidance ACD issued by NICE (7th May 2009) the manufacturer submitted a document arguing that in general lognormal distributions were better suited to describe HCC survival data than were Weibull distributions. Greten et al 2005(Greten et al. 1862-68) reported on the survival of 389 German patients with HCC. The ERG extracted the data and fitted lognormal and Weibull distributions (Figure 4). There appears very little difference between fits, lognormal being closer to observed data at early times but less satisfactory than Weibull at longest times.

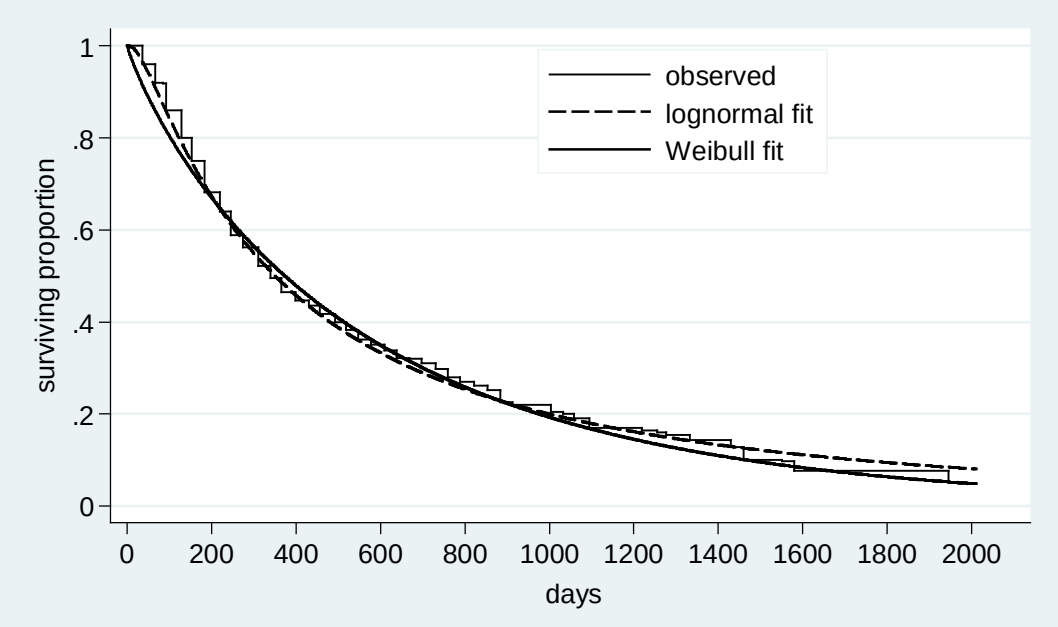


Figure 4 Survival of HCC patients (Greten et al 2005) with lognormal and Weibull fits

4 DISCUSSION

The PAS model delivers lower £/QALY ICERs than the original model. The most relevant ICER values in the original and PAS submissions are summarised in Table 3 together with values delivered when a per-cycle sorafenib cost of £2,877.5 rather than £2,836.1 is used (see Appendix 4).

Table 3 Comparison of PAS and original model ICER values.

Analysis description	PAS model £/QALY	Original model £/QALY	Comment / source
BASE CASE	51,899	64,754	Manufacturers submissions
Post progression sorafenib treatment as original model	54,509	64,754	Manufacturers submissions
Per cycle cost of sorafenib £2,877.5	52,641	65,535	ERG user selected model input
Per cycle cost of sorafenib £2,877.5 and post progression sorafenib treatment as original model	55,290	65,535	ERG user selected model input
Weibull fits to survival data	[redacted]	[redacted]	Manufacturers submissions
Weibull fits & Post progression treatment with sorafenib as original model	[redacted]	Option not available	ERG user selected model inputs
Weibull fits to survival data & per cycle cost of sorafenib £2,877.5	[redacted]	Option not available	ERG User selected model inputs
Weibull fits & Post progression treatment with sorafenib as original model & per cycle cost of sorafenib £2,877.5	[redacted]	Option not available	ERG user selected model inputs
BCLC stage C (“advanced” HCC)	60,681	76,592	Manufacturers submissions

It is clear that the key driver of the ICER value is the choice of curve fitted to the survival data. The reference population for the decision problem is patients with “advanced” HCC (BCLC stage C).(Llovet et al. 698-711;Ryder) The SHARP trial population consisted of 82.4% BCLC stage C and 17.5% BCLC stage B patients. Published data for survival of BCLC stage C patients(Camma et al. 62-75) from a European population are similar to the observed survival for BSC patients in the SHARP trial (Figure 3). Comparison of the observed survival for BCLC stage C

patients with the Weibull and lognormal extrapolations for survival in SHARP indicates that these extrapolations may represent a reasonable range within which survival of the reference population might lie. On this basis a plausible range for the ICER of sorafenib relative to BSC under the assumptions of the PAS may be between about £52k and £[redacted]k/QALY; or £52k to £[redacted]k/QALY when adjustments itemised in this assessment are introduced.

APPENDICES

Appendix 1 Subgroup and sensitivity analyses presented in the PAS submission

The following tables are taken from the PAS submission (Table 3 subgroup analyses and Table 4 sensitivity analyses).

Results from Subgroup Analyses

	Incremental LYG	Incremental QALYs	Incremental cost (£)	Cost/ LYG(£)	Cost/ QALY(£)
Total Population (base case)	0.51	0.36	18,620	**36,469**	**51,899**
Age =>65	0.78	0.55	22,669	**28,939**	**41,086**
Child Pugh A	0.47	0.33	17,903	**37,889**	**53,924**
TNM I-III	1.32	0.94	27,516	**20,779**	**29,372**
BCLC Stage C	0.43	0.30	18,085	**42,425**	**60,681**
BCLC Stage B	1.26	0.89	25,122	**19,971**	**28,105**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Changing the utility values, the drug costs and the time horizon has a significant effect on the results, while the modification of the management costs and the disutilities have a limited influence on the results (TABLE BELOW)

Scenario Analysis Discounted Results

Analyses description	Incremental LYG	Incremental QALYs	Incremental cost (£)	Cost/ LYG (£)	Cost/QALY (£)
Base Case	0.51	0.36	18,620	**36,469**	**51,899**
Discount rates					
Discount rate: costs 0%, benefits 0%;	0.58	0.41	19,666	**33,759**	**47,995**
Discount rate: costs 6%, benefits 0%;	0.58	0.41	17,991	**30,883**	**43,907**
Discount rate: costs 0%, benefits 6%	0.47	0.33	19,666	**41,946**	**59,732**
Cost data					
Zero drug costs	0.51	0.36	4,029	**7,891**	**11,230**

Same patient management costs	0.51	0.36	19,145	**37,496**	**53,361**
Management costs taken from the RCC assessment report^	0.51	0.36	16,545	**32,404**	**46,113**
Inclusion of PSS costs	0.51	0.36	19,749	**38,679**	**55,044**
Cost of death included *(£3,923)	0.51	0.36	18,534	**36,301**	**51,660**
Alternative utility assessment					
a) Separate Sorafenib and BSC**	0.51	0.36	18,620	**36,469**	**51,100**
b) AEs disutility 0.05	0.51	0.36	18,620	**36,469**	**52,042**
c) AEs disutility 0.2	0.51	0.36	18,620	**36,469**	**52,413**
d) Utility of 0.41 for all health states	0.51	0.21	18,620	**36,469**	**88,886**
e) No AE disutility	0.51	0.36	18,620	**36,469**	**51,920**
f) Utilities from RCC assessment report~~	0.51	0.36	18,620	**36,469**	**51,288**
Length of sorafenib treatment after progression					
4.3 months	0.51	0.36	19,557	**38,303**	**54,509**
3 months	0.51	0.36	19,274	**37,749**	**53,720**
Time horizon					
2 years	0.19	0.13	14,527	**75,520**	**109,024**
5 years	0.38	0.27	17,206	**44,900**	**64,128**
10 years	0.48	0.34	18,336	**37,895**	**53,962**
Outcomes assessment					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Additional scenarios					
Management costs^ and utilities~~ taken from the RCC assessment report	0.51	0.36	16,545	**32,404**	**45,570**
Management costs taken from the RCC assessment report^ and general population utilities*** for all health states, with no disutilities for AEs		0.40	16,545	**32,404**	**41,543**

LYG= life-years gained, TTSP: time to symptomatic progression

*Assumed a cost of £3,923, taken from Coyle et al (1999), averaged over hospital and hospice stays = £2,701, revalued to 2007/8

**Using the following mapped utilities: First line – no progression with sorafenib: [redacted], First-line treatment continued – post progression with sorafenib: [redacted], First line – no progression with BSC: [redacted], BSC - post progression: [redacted] (see Appendix 12)

Assumed a 6-weekly cost of £81 and £223 for BSC and drug treatment before progression respectively, and £435 for progressive disease independent of the treatment (table 41 in the Renal Cell Carcinoma NICE Assessment Report).

Utilities for Sorafenib and BSC Before progression equated to 0.76 and utilities after progression equated to 0.68 (table 37 in the Renal Cell Carcinoma NICE Assessment Report)

***Using general population utility of 0.78 (appropriate for age group 65-74) as mean age at enrollment of the SHARP trial was 65.6 (Table A in Kind et al 1999)

~ Assumes for discounting purposes, that the cost of every fourth pack is realized within one month

Appendix 2 ERG calculation of reduced cost in sorafenib arm ("Weibull" analysis)

The cost of the sorafenib arm in the original model's sensitivity analysis using Weibull fits was not reported (see response to ERG requests for clarification). Therefore the cost reduction in the sorafenib arm that is generated by introducing the PAS model was calculated indirectly as follows:

With default settings "continued sorafenib treatment post-progression" for BOTH MODELS:

Original model (Weibull) Incremental cost (sorafenib - BSC) = £[redacted] (manufacturers clarification response Table 2)

PAS model OUTPUT (Weibull distributions, continued post-progression sorafenib)
Marginal costs: sorafenib = £[redacted] BSC = £[redacted]
Incremental cost £[redacted] - £[redacted] = £[redacted]

Since the marginal cost for the BSC arm remains unchanged between models
Original model Marginal cost sorafenib = £[redacted] + £[redacted] = £[redacted]

Difference in marginal cost (original - PAS) = £[redacted] - £[redacted] = £[redacted] Difference in incremental cost (original – PAS) = £[redacted] – £[redacted] = £[redacted]

If post-progression treatment with sorafenib is eliminated in the PAS model (Weibull fits) but remains in the original model Weibull fit the difference in cost of the sorafenib arm between the models becomes £[redacted] + £937 = £[redacted]

Appendix 3 ERG calculation of cost of post-progression sorafenib treatment

A value of £937 is saved by eliminating post-progression treatment with sorafenib from the model.

This can be calculated as follows:

A] Using the original submission: by subtracting the sensitivity analysis (0% receive post-progression sorafenib) incremental cost of £[redacted] (table 51 section 7.2.15.1, original submission) from the base case incremental cost of £23,232 (table 51 section 7.2.15.1, original submission). £23,232 – £[redacted] = £[redacted]

Or

B] Using the PAS submission: by subtracting base case incremental cost of £18,620 (table 4 PSA submission) from the sensitivity analysis for "4.3 months post-progression sorafenib" incremental cost of £19,557 (table 4 PSA submission).

. £19,557 – £18,620 = £937

Appendix 4 ERG calculation of cost per cycle used in PAS model

The cost per cycle used in the model (£2,836) was based on 30 days consumption of sorafenib at an average daily dose of 710.5mg and at a cost of £2980.47 for 22,400mg sorafenib. However, the cycle length in the model was 30.4375 (365.25/12) days; with this cycle length the cost/cycle becomes £2877.5 (Table 4).

Table 4 Cost of sorafenib per cycle

	Cost parameter	**Value**	**Information source**	from submission
a	1 cycle; defined as 365.25/12 days	30.4375	model sheet	
b	1 pack costs (£)	2980.47	submission section 7.2.9.6	Section 7.2.6.1 presents the monthly cost of sorafenib based on the mean daily dosage. In accordance with the SHARP trial report, the mean daily dose is 710.5 mg/day which includes dose reductions and interruptions (section 7.2.1.1). This is equivalent to a monthly cost of £2,836. The mean cost per month of sorafenib is calculated using the cost of £2,980.47 for 112, 200 mg tablets. The price per mg (calculated by dividing £2,980.47 by the number of tablets, 112, and dose, 200 mg) is multiplied by the average daily dosage, 710.5 mg, and the average number of days in a month, 30 days.
c	1 pack contains (mg) sorafenib	22400	submission	
d	cost of 1 mg sorafenib	0.1330567	calculated [b / c]	
e	average sorafenib consumed / day (mg)	710.50	submission 7.2.9.6	
f	cost of sorafenib / day (£)	94.5367828	calculated [e * d]	
g	cost of sorafenib / cycle (£)	2877.4633269	calculated [f * a]	
h	cost of sorafenib / cycle (£), if cycle = 30 days	2836.103484	Calculated [f * 30]	
i	default cost / cycle used in model (£)	[redacted]	from model and submission section 7.2.9.6	Section 7.2.6.1 presents the monthly cost of sorafenib based on the mean daily dosage. In accordance with the SHARP trial(28) report, the mean daily dose is 710.5 mg/day which includes dose reductions and interruptions (section 7.2.1.1). This is equivalent to a monthly cost of £2,836.

Appendix 5 Results of ERG analysis of savings; one pack free every month

cycle number	day 4th cycle started	day 4th cycle finished	cycle that 4th cycle occurs in	discount factor	proportion not progressed	proportion not progressed mid 4th cycle	£ saved not discounted	£ saved discounted
3	91.313		4	0.98860	0.62281742			
4		121.75			0.50801927	0.565418347	1685.2124	1665.998
7	213.06		8	0.97733	0.29135115		0	0.000
8		243.5			0.24656398	0.268957566	801.61996	783.445
11	334.81		12	0.96618	0.15638039		0	0.000
12		365.25			0.136102	0.146241195	435.86749	421.128
15	456.56		16	0.95517	0.09256838		0	0.000
16		487			0.08214498	0.087356679	260.36396	248.691
19	578.31		20	0.94428	0.05871102		0	0.000
20		608.75			0.05284317	0.055777096	166.24196	156.978
23	700.06		24	0.93351	0.03919277		0	0.000
24		730.5			0.03565909	0.037425929	111.54686	104.130
27	821.81		28	0.92287	0.02722001		0	0.000
28		852.25			0.02497852	0.026099263	77.788071	71.788
31	943.56		33	0.90973	0.01951264		0	0.000
32		974			0.0180308	0.018771719	55.948546	50.898
35	1065.3		37	0.89936	0.01435542		0	0.000
36		1095.75			0.01334216	0.013848788	41.275898	37.122
39	1187.1		41	0.88911	0.0107932		0	0.000
40		1217.5			0.01008059	0.010436894	31.106851	27.657
43	1308.8		45	0.87897	0.00826635		0	0.000
44		1339.25			0.00775309	0.008009718	23.872724	20.983
47	1430.6		49	0.86895	0.00643287		0	0.000
48		1461			0.00605554	0.006244206	18.61067	16.172
51	1552.3		53	0.85904	0.00507625		0	0.000
52		1582.75			0.00479387	0.00493506	14.708797	12.635
55	1674.1		57	0.84925	0.00405521		0	0.000
56		1704.5			0.00384053	0.00394787	11.766509	9.993
59	1795.8		62	0.83716	0.00327509		0	0.000
60		1826.25			0.00310961	0.003192349	9.5147001	7.965
63	1917.6		66	0.82761	0.00267103		0	0.000
64		1948			0.00254189	0.002606458	7.7684707	6.429
67	2039.3		70	0.81818	0.00219768		0	0.000
68		2069.75			0.00209575	0.002146716	6.3982229	5.235
71	2161.1		74	0.80885	0.00182273		0	0.000
72		2191.5			0.00174147	0.001782099	5.3114937	4.296
75	2282.8		78	0.79963	0.00152281		0	0.000
76		2313.25			0.00145743	0.00149012	4.4412569	3.551
79	2404.6		82	0.79278	0.00128076		0	0.000
80		2435			0.00122772	0.001254239	3.7382223	2.964
83	2526.3		86	0.78150	0.00108382		0	0.000
84		2556.75			0.00104045	0.001062137	3.1656677	2.474
87	2648.1		91	0.77038	0.00092238		0	0.000
88		2678.5			0.00088667	0.000904524	2.695907	2.077
91	2769.8		95	0.76159	0.00078912		0	0.000
92		2800.25			0.00075952	0.00077432	2.3078389	1.758
95	2891.6		99	0.75291	0.00067842		0	0.000
96		2922			0.00065373	0.000666076	1.9852185	1.495

cycle number	day 4th cycle started	day 4th cycle finished	cycle that 4th cycle occurs in	discount factor	proportion not progressed	proportion not progressed mid 4th cycle	£ saved not discounted	£ saved discounted
99	3013.3		103	0.74432	0.00058591		0	0.000
100		3043.75			0.0005652	0.000575555	1.7154239	1.277
103	3135.1		107	0.73584	0.00050817		0	0.000
104		3165.5			0.00049071	0.000499439	1.4885638	1.095
107	3256.8		111	0.72745	0.0004425		0	0.000
108		3287.25			0.00042771	0.000435108	1.2968251	0.943
111	3378.6		115	0.71915	0.00038677		0	0.000
112		3409			0.00037418	0.000380474	1.1339902	0.816
115	3500.3		120	0.70892	0.00033925		0	0.000
116		3530.75			0.00032848	0.000333866	0.9950771	0.705
119	3622.1		124	0.70084	0.00029856		0	0.000
120		3652.5			0.00028931	0.000293936	0.8760674	0.614
123	3743.8		128	0.69285	0.00026357		0	0.000
124		3774.25			0.00025561	0.00025959	0.7737008	0.536
127	3865.6		132	0.68495	0.00023338		0	0.000
128		3896			0.00022649	0.000229936	0.6853166	0.469
131	3987.3		136	0.67714	0.00020723		0	0.000
132		4017.75			0.00020125	0.00020424	0.6087314	0.412
135	4109.1		140	0.66942	0.0001845		0	0.000
136		4139.5			0.00017929	0.000181899	0.542145	0.363
139	4230.8		144	0.66178	0.00016469		0	0.000
140		4261.25			0.00016014	0.000162412	0.4840655	0.320
143	4352.6		149	0.65237	0.00014736		0	0.000
144		4383			0.00014337	0.000145363	0.4332508	0.283
147	4474.3		153	0.64493	0.00013216		0	0.000
148		4504.75			0.00012865	0.000130403	0.3886626	0.251
151	4596.1		157	0.63757	0.00011878		0	0.000
152		4626.5			0.0001157	0.00011724	0.3494294	0.223
155	4717.8		161	0.63030	0.00010699		0	0.000
156		4748.25			0.00010426	0.000105626	0.3148164	0.198
159	4839.6		165	0.62312	9.6562E-05		0	0.000
160		4870			9.4147E-05	9.53548E-05	0.2842022	0.177
163	4961.3		169	0.61601	8.732E-05		0	0.000
164		4991.75			8.5176E-05	8.62479E-05	0.2570592	0.158
167	5083.1		173	0.60899	7.9109E-05		0	0.000
168		5113.5			7.7201E-05	7.81548E-05	0.2329379	0.142
							SUM	**3674.846**

Appendix 6 Results of ERG analysis of savings; every fourth pack free

The PAS model allowed one free pack every fourth month. According to the model the average patient consumes less than one pack per month. The savings accrued by making every fourth pack free of charge (rather than one pack free every fourth month) was calculated independently of the submitted model.

This was done using the fitted survival for patients in the non-progressed state (lognormal parameters), and the starting and ending times of every fourth sorafenib pack using the model assumption of 710.5mg/day and corresponding pack duration of 31.5 days (22400/710.5). The cost saved was derived by multiplying the proportion of non-progressed patients mid-time in the fourth pack by the cost of one pack (£2,980.47).

proportion non-progressed mid-time in 4th pack x *pack cost* (£2980.47).

This was discounted using the cycle discount rate (from the model) for the cycle that corresponded to the start of the free pack.

The survival curve for the first five years and the timing of each free fourth pack is shown in Figure 5 .

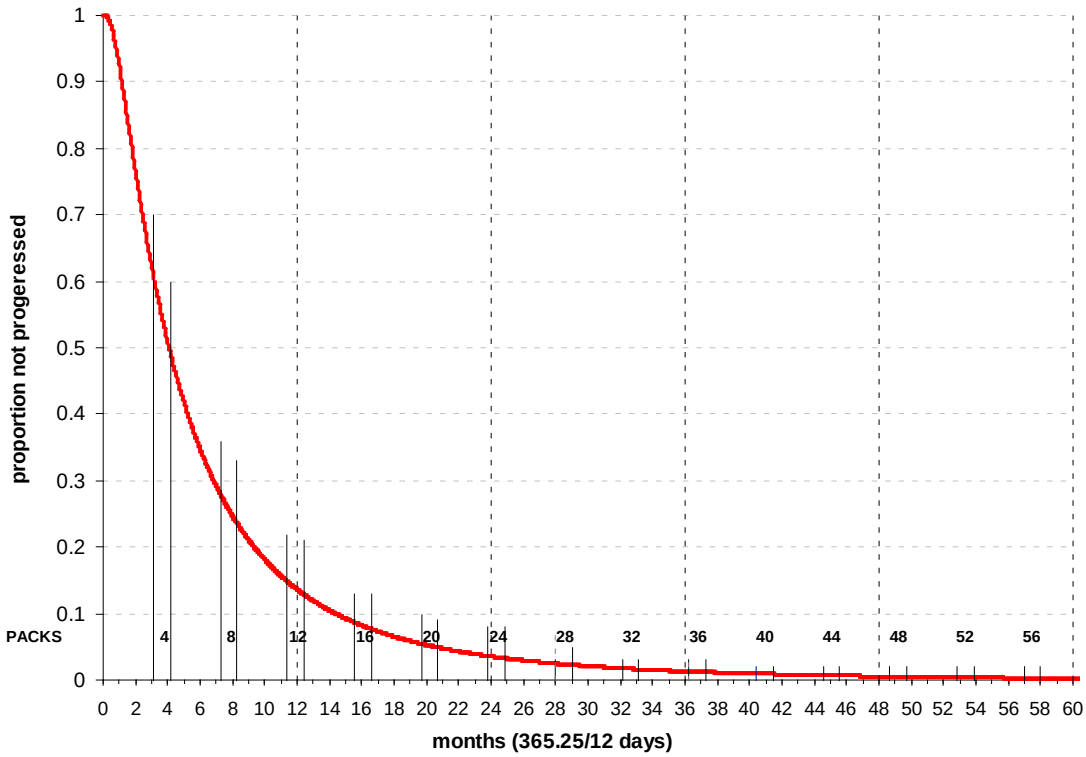


Figure 5 Occurrence of free packs relative to cycle number and proportion non-progressed
Vertical solid lines represent start and finish of every fourth pack on the basis of 31.5 days pack duration. The x axis is shown in model cycles (1 cycle equals 365.12/12 days). Note the lack of synchrony between each fourth pack and each fourth cycle. The dashed vertical lines represent ends of year.

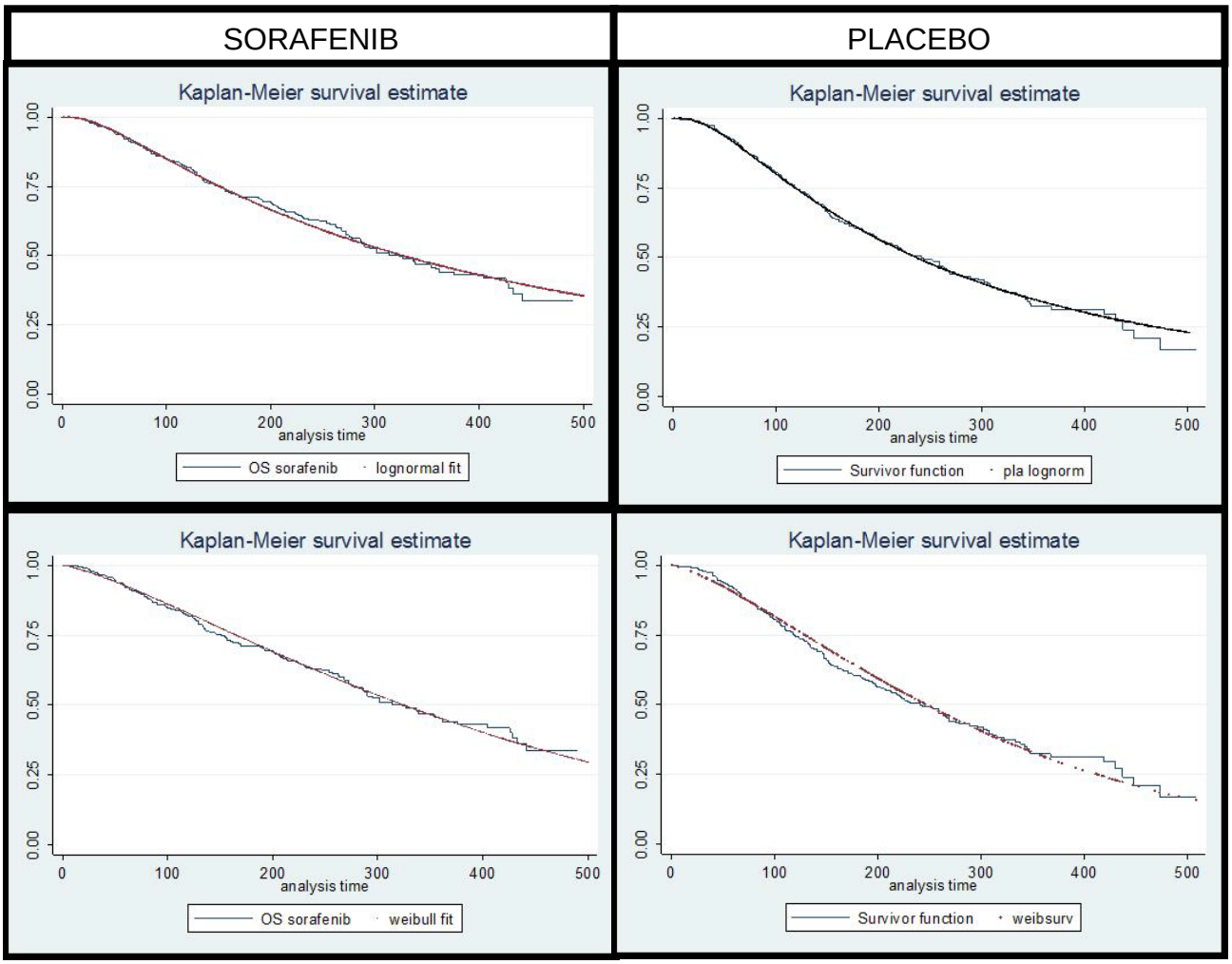
The results are summarised below.

pack number	day 4th pack started	day 4th pack finished	cycle completed at start of 4th pack	cycle that 4th pack starts in	discount factor	proportion not progressed	proportion not progressed mid 4th pack	£ saved not discounted	£ saved discounted
3	94.581		3.107393	4	0.98860	0.60914561			
4		126.108				0.49373957	0.551442587	1643.5581	1624.819
7	220.69		7.250584	8	0.97733	0.27919395		0	0.000
8		252.217				0.23541225	0.2573031	766.88417	749.496
11	346.8		11.39378	12	0.96618	0.14795559		0	0.000
12		378.325				0.12843985	0.138197717	411.89415	397.965
15	472.91		15.53697	16	0.95517	0.08677271		0	0.000
16		504.433				0.07685004	0.081811376	243.83635	232.905
19	599.01		19.68016	20	0.94428	0.05463506		0	0.000
20		630.542				0.04909569	0.051865377	154.5832	145.969
23	725.12		23.82335	24	0.93351	0.03625304		0	0.000
24		756.65				0.0329398	0.03459642	103.11359	96.258
27	851.23		27.96654	28	0.92287	0.02504968		0	0.000
28		882.759				0.02296002	0.024004846	71.545724	66.027
31	977.34		32.10973	33	0.90973	0.01787691		0	0.000
32		1008.87				0.01650227	0.017189589	51.233053	46.608
35	1103.4		36.25292	37	0.89936	0.01310014		0	0.000
36		1134.98				0.01216427	0.012632205	37.649909	33.861
39	1229.6		40.39611	41	0.88911	0.00981453		0	0.000
40		1261.08				0.0091589	0.009486718	28.274877	25.139
43	1355.7		44.5393	45	0.87897	0.00749264		0	0.000
44		1387.19				0.00702208	0.007257362	21.630351	19.012
47	1481.8		48.68249	49	0.86895	0.00581362		0	0.000
48		1513.3				0.00546879	0.005641203	16.813437	14.610
51	1607.9		52.82568	53	0.85904	0.00457515		0	0.000
52		1639.41				0.00431784	0.004446494	13.252642	11.385
55	1734		56.96888	57	0.84925	0.00364569		0	0.000
56		1765.52				0.00345062	0.003548157	10.575176	8.981
59	1860.1		61.11207	62	0.83716	0.00293744		0	0.000
60		1891.63				0.00278745	0.002862447	8.5314373	7.142
63	1986.2		65.25526	66	0.82761	0.00239039		0	0.000
64		2017.73				0.00227361	0.002331999	6.9504536	5.752
67	2112.3		69.39845	70	0.81818	0.0019627		0	0.000
68		2143.84				0.00187074	0.00191672	5.7127256	4.674
71	2238.4		73.54164	74	0.80885	0.00162466		0	0.000
72		2269.95				0.0015515	0.001588078	4.7332198	3.828
75	2364.5		77.68483	78	0.79963	0.00135482		0	0.000
76		2396.06				0.00129607	0.001325444	3.9504472	3.159
79	2490.6		81.82802	82	0.79278	0.00113747		0	0.000
80		2522.17				0.0010899	0.001113682	3.3192943	2.631
83	2616.7		85.97121	86	0.78150	0.00096095		0	0.000
84		2648.28				0.00092212	0.000941537	2.806224	2.193
87	2742.9		90.1144	91	0.77038	0.00081651		0	0.000
88		2774.38				0.00078459	0.000800546	2.3860037	1.838
91	2869		94.25759	95	0.76159	0.00069747		0	0.000
92		2900.49	0			0.00067106	0.000684268	2.0394394	1.553
95	2995.1		98.40078	99	0.75291	0.00059875		0	0.000
96		3026.6	0			0.00057676	0.000587754	1.7517825	1.319
99	3121.2		102.544	103	0.74432	0.00051638		0	0.000
100		3152.71	0			0.00049796	0.000507166	1.5115938	1.125

pack number	day 4th pack started	day 4th pack finished	cycle completed at start of 4th pack	cycle that 4th pack starts in	discount factor	proportion not progressed	proportion not progressed mid 4th pack	£ saved not discounted	£ saved discounted
103	3247.3		106.6872	107	0.73584	0.00044726		0	0.000
104		3278.82	0			0.00043175	0.000439503	1.3099243	0.964
107	3373.4		110.8304	111	0.72745	0.00038896		0	0.000
108		3404.93	0			0.00037583	0.000382395	1.1397165	0.829
111	3499.5		114.9735	115	0.71915	0.00033954		0	0.000
112		3531.03	0			0.00032838	0.000333962	0.9953629	0.716
115	3625.6		119.1167	120	0.70892	0.00029746		0	0.000
116		3657.14	0			0.00028794	0.000292698	0.8723769	0.618
119	3751.7		123.2599	124	0.70084	0.00026147		0	0.000
120		3783.25	0			0.00025331	0.000257391	0.7671455	0.538
123	3877.8		127.4031	128	0.69285	0.00023057		0	0.000
124		3909.36	0			0.00022354	0.000227058	0.6767407	0.469
127	4003.9		131.5463	132	0.68495	0.00020394		0	0.000
128		4035.47	0			0.00019786	0.0002009	0.5987764	0.410
131	4130		135.6895	136	0.67714	0.00018089		0	0.000
132		4161.58	0			0.00017563	0.00017826	0.5312976	0.360
135	4256.2		139.8327	140	0.66942	0.00016089		0	0.000
136		4287.68	0			0.00015631	0.000158597	0.4726936	0.316
139	4382.3		143.9759	144	0.66178	0.00014346		0	0.000
140		4413.79	0			0.00013947	0.000141465	0.4216316	0.279
143	4508.4		148.1191	149	0.65237	0.00012824		0	0.000
144		4539.9	0			0.00012474	0.000126491	0.3770034	0.246
147	4634.5		152.2623	153	0.64493	0.0001149		0	0.000
148		4666.01	0			0.00011183	0.000113366	0.3378834	0.218
151	4760.6		156.4055	157	0.63757	0.00010318		0	0.000
152		4792.12	0			0.00010048	0.000101828	0.3034957	0.194
155	4886.7		160.5486	161	0.63030	9.2852E-05		0	0.000
156		4918.23	0			9.0465E-05	9.1659E-05	0.2731868	0.172
159	5012.8		164.6918	165	0.62312	8.3729E-05		0	0.000
160		5044.33	0			8.1617E-05	8.2673E-05	0.2464045	0.154
163	5138.9		168.835	169	0.61601	7.565E-05		0	0.000
164		5170.44	0			7.3777E-05	7.47133E-05	0.2226806	0.137
167	5265		172.9782	173	0.60899	6.8478E-05		0	0.000
168		5296.55	0			6.6813E-05	6.76459E-05	0.2016167	0.123
								SUM	3514.994

Appendix 7 Parametric fits for overall survival and AIC scores

Lognormal and Weibull fits to overall survival in sorafenib and placebo groups of the SHARP trial; are shown in the figure below.



The corresponding AIC scores for fits to observed overall survival are taken from the original submission appendices document page 31 and summarised below.

OBSERVED GROUP	PARAMETRIC FIT	AIC SCORE
SORAFENIB	LOGNORMAL	[redacted]
SORAFENIB	WEIBULL	[redacted]
PLACEBO	LOGORMAL	[redacted]
PLACEBO	WEIBULL	[redacted]

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Greten, T. F., et al. "Survival rate in patients with hepatocellular carcinoma: a retrospective analysis of 389 patients." British Journal of Cancer 92.10 (2005): 1862-68.

Kung, J. W., et al. "Predicting survival in patients with hepatocellular carcinoma: a UK perspective." Eur.J Surg.Oncol. 33.2 (2007): 188-94.

Llovet, J. M., et al. "Design and Endpoints of Clinical Trials in Hepatocellular Carcinoma." Journal of National Cancer Institute 100 (2008): 698-711.

Llovet, J. M., et al. "Sorafenib in advanced hepatocellular carcinoma." N.Engl.J.Med. 359.4 (2008): 378-90.

Ryder, S. D. UK Guidelines for the management of suspected hepatocellular carcinoma (HCC) in adults (Revised guidelines, in draft, British Society of Gastroenterology). 2008.

Ref Type: Personal Communication

Patient Access Scheme: one pack free for responders every 4 months

Methods

An additional base case has been developed to assess the cost-effectiveness of sorafenib in advanced HCC in the UK incorporating the following patient access scheme:

- Patients who remain on treatment after every three packs of sorafenib receive the fourth pack free.
- Consistent with UK clinical practice all patients stop treatment at the point of progression (Ref: Personal communication). Progression was defined as determined according to investigator assessment, as in the SHARP trial.

This was incorporated in the model by extracting the cost of one pack of sorafenib every fourth month in the 14 year model time horizon for patients still receiving sorafenib. As the average monthly dose is slightly less than one pack of sorafenib (due to the incorporation of dose reductions and interruptions); a small proportion the fourth pack will be used in the subsequent month. However, for discounting purposes, in the model the cost of the fourth pack is assumed to be realized in the fourth month only. Patients do not continue treatment post progression. All other model assumptions remained the same.

The base case results and the sensitivity analyses are outlined in the following section.

Results

Base-case analysis

The base case analysis is presented in Table 1. The incremental difference in costs and QALYs results in an ICER of £36,469 per LYG and £51,899 per QALY. This compares more favourably with the base case model originally submitted, where the cost per LYG and cost per QALY was £45,502 and £64,754 respectively.

Table 1: Base Case Results

Per Patient	LYG	QALYs	Total Costs (£)	ICER	
				Cost/LYG (£)	Cost/QALY (£)
Sorafenib	1.54	1.08	28,359	**36,469**	**51,899**
BSC	1.03	0.72	9,739		

Costs and benefits discounted 3.5%

The proposed patient access scheme reduces the ICER to £51,899 per QALY from £64,754 presented in the original submission. Furthermore the inclusion of the management costs and utility values used in the appraisal of sorafenib in renal cell carcinoma (RCC), which were previously accepted by NICE, further reduces the cost per QALY to £45,570.

Figure 1: Cost Breakdown by Phase (Undiscounted Results)

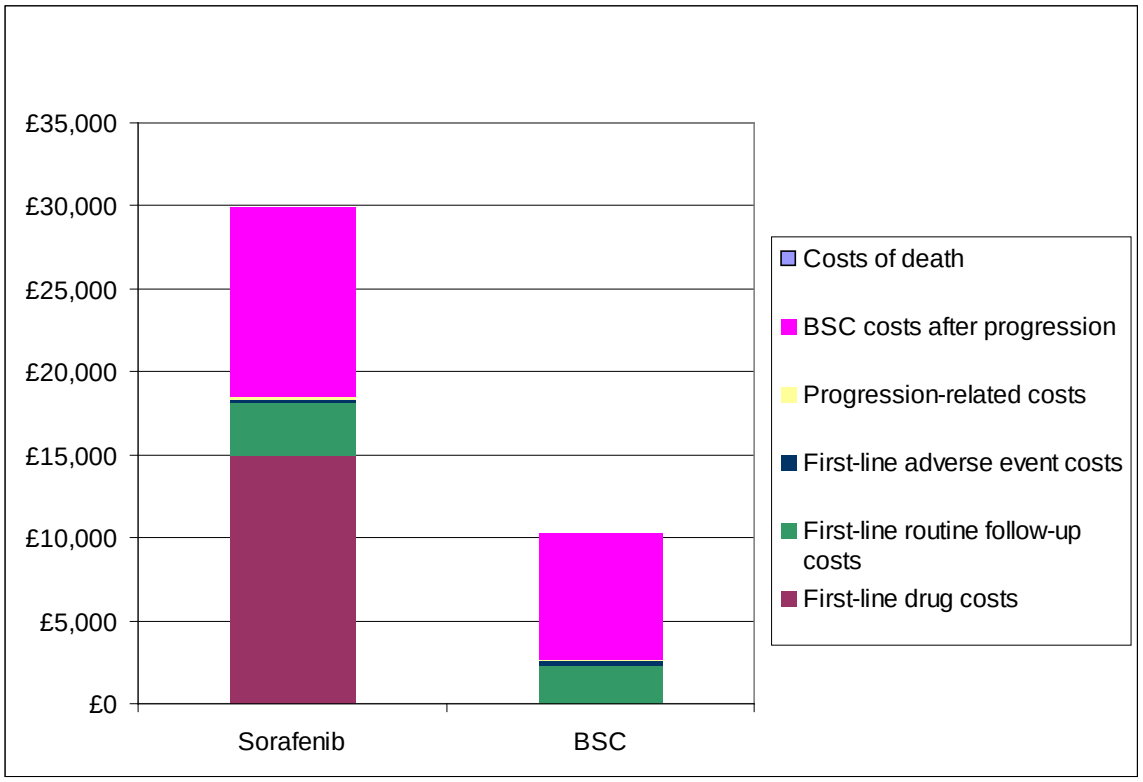

Table 2: Cost breakdown by phase

First-line treatment	Sorafenib	BSC
Total costs (discounted)	**£28,359**	**£9,739**
Total costs (undiscounted)	£29,928	£10,262
Break-down by phase (undiscounted)		
First-line drug costs	£14,938	£0
First-line routine follow-up costs	£3,171	£2,322
First-line adverse event costs	£216	£208
Progression-related costs	£144	£156
BSC costs after progression	£11,459	£7,576
Costs of death	£0	£0

Subgroup analysis

In addition to the base case analysis, a series of subgroups were considered. Using the lognormal distribution, TTP and OS for the various subgroups was predicted based on investigator assessment. The results from the subgroup analyses are tabulated below.

Table 3: Results from Subgroup Analyses

	Incremental LYG	Incremental QALYs	Incremental cost (£)	Cost/ LYG(£)	Cost/ QALY(£)
Total Population (base case)	0.51	0.36	18,620	**36,469**	**51,899**
Age =>65	0.78	0.55	22,669	**28,939**	**41,086**
Child Pugh A	0.47	0.33	17,903	**37,889**	**53,924**
TNM I-III	1.32	0.94	27,516	**20,779**	**29,372**
BCLC Stage C	0.43	0.30	18,085	**42,425**	**60,681**
BCLC Stage B	1.26	0.89	25,122	**19,971**	**28,105**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Sensitivity analyses

Changing the utility values, the drug costs and the time horizon has a significant effect on the results, while the modification of the management costs and the disutilities have a limited influence on the results (Table 4).

Table 4: Scenario Analysis Discounted Results

Analyses description	Incremental LYG	Incremental QALYs	Incremental cost (£)	Cost/ LYG (£)	Cost/QALY (£)
Base Case	0.51	0.36	18,620	**36,469**	**51,899**
Discount rates					
Discount rate: costs 0%, benefits 0%;	0.58	0.41	19,666	**33,759**	**47,995**
Discount rate: costs 6%, benefits 0%;	0.58	0.41	17,991	**30,883**	**43,907**
Discount rate: costs 0%, benefits 6%	0.47	0.33	19,666	**41,946**	**59,732**
Cost data					
Zero drug costs	0.51	0.36	4,029	**7,891**	**11,230**
Same patient management costs	0.51	0.36	19,145	**37,496**	**53,361**
Management costs taken from the RCC assessment report^	0.51	0.36	16,545	**32,404**	**46,113**
Inclusion of PSS costs	0.51	0.36	19,749	**38,679**	**55,044**
Cost of death included *(£3,923)	0.51	0.36	18,534	**36,301**	**51,660**
Alternative utility assessment					
a) Separate Sorafenib and BSC**	0.51	0.36	18,620	**36,469**	**51,100**
b) AEs disutility 0.05	0.51	0.36	18,620	**36,469**	**52,042**
c) AEs disutility 0.2	0.51	0.36	18,620	**36,469**	**52,413**
d) Utility of 0.41 for all health states	0.51	0.21	18,620	**36,469**	**88,886**
e) No AE disutility	0.51	0.36	18,620	**36,469**	**51,920**
f) Utilities from RCC assessment report~~	0.51	0.36	18,620	**36,469**	**51,288**
Length of sorafenib treatment after progression					
4.3 months	0.51	0.36	19,557	**38,303**	**54,509**
3 months	0.51	0.36	19,274	**37,749**	**53,720**
Time horizon					
2 years	0.19	0.13	14,527	**75,520**	**109,024**
5 years	0.38	0.27	17,206	**44,900**	**64,128**
10 years	0.48	0.34	18,336	**37,895**	**53,962**
Outcomes assessment					

Analyses description	Incremental LYG	Incremental QALYs	Incremental cost (£)	Cost/ LYG (£)	Cost/QALY (£)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Additional scenarios					
Management costs^ and utilities~~ taken from the RCC assessment report	0.51	0.36	16,545	**32,404**	**45,570**
Management costs taken from the RCC assessment report^ and general population utilities*** for all health states, with no disutilities for AEs		0.40	16,545	**32,404**	**41,543**

LYG= life-years gained, TTSP: time to symptomatic progression

*Assumed a cost of £3,923, taken from Coyle et al (1999), averaged over hospital and hospice stays = £2,701, revalued to 2007/8

**Using the following mapped utilities: First line – no progression with sorafenib: [redacted], First-line treatment continued – post progression with sorafenib: [redacted], First line – no progression with BSC: [redacted] BSC - post progression: [redacted] (see Appendix 12)

(81)^Assumed a 6-weekly cost of £81 and £223 for BSC and drug treatment before progression respectively, and £435 for progressive disease independent of the treatment (table 41 in the Renal Cell Carcinoma NICE Assessment Report).

~~(81) Utilities for Sorafenib and BSC Before progression equated to 0.76 and utilities after progression equated to 0.68 (table 37 in the Renal Cell Carcinoma NICE Assessment Report)

***Using general population utility of 0.78 (appropriate for age group 65-74) as mean age at enrollment of the SHARP trial was 65.6 (Table A in Kind et al 1999)

~ Assumes for discounting purposes, that the cost of every fourth pack is realized within one month

Probabilistic sensitivity analyses for sorafenib vs. BSC

Results of the probabilistic sensitivity analyses for sorafenib vs. BSC are presented in Table 5. The results on the cost-effectiveness plane and the cost-effectiveness acceptability curves are shown in Figures 2-5 respectively.

Table 5: Probabilistic Sensitivity Analysis for Sorafenib vs. BSC

First-line treatment		**Sorafenib**	**BSC**	**Incremental**
Total costs (discounted) (£)	Probabilistic Mean	**28,574**	**9,777**	18,796
	Standard Deviation	2,881	1,734	
	2.5% and 97.5% percentile	23,440 to 34,741	6,894 to 13,494	
LY gained	Probabilistic Mean	**1.55**	**1.03**	**0.52**
	Standard Deviation	0.17	0.10	
	2.5% and 97.5% percentile	1.23 to 1.89	0.86 to 1.22	
QALYs	Probabilistic Mean	**1.08**	**0.72**	**0.36**
	Standard Deviation	0.19	0.12	
	2.5% and 97.5% percentile	0.72 to 1.46	0.49 to 0.96	
Incremental cost (£) per LY gained				**36,486**
Incremental cost (£) per QALY				**52,136**

Figure 2: Probabilistic Analysis - Results on the Cost-Effectiveness Plane, BSC vs. Sorafenib, Cost per QALY

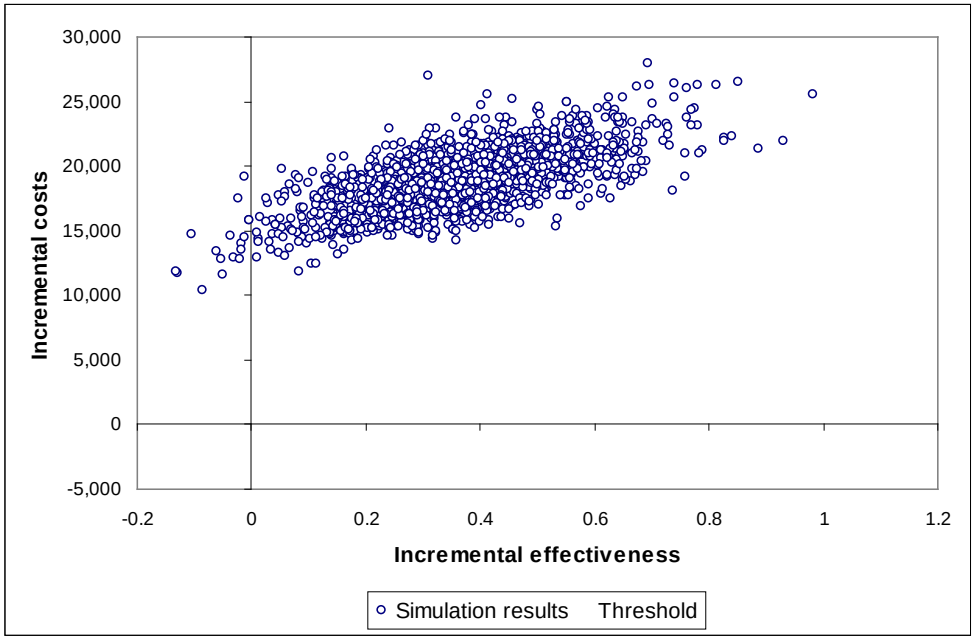

Figure 3: Probabilistic Analysis - Results on the Cost-Effectiveness Plane, BSC vs. Sorafenib, Cost per LY

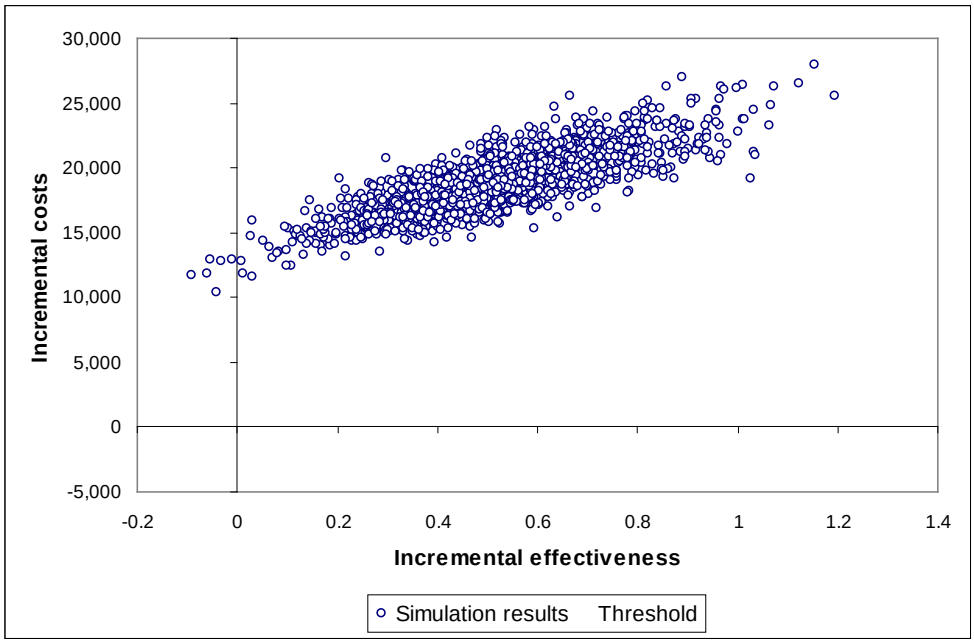

Figure 4: Probabilistic Analysis, CEAC for BSC vs. Sorafenib, Cost per QALY

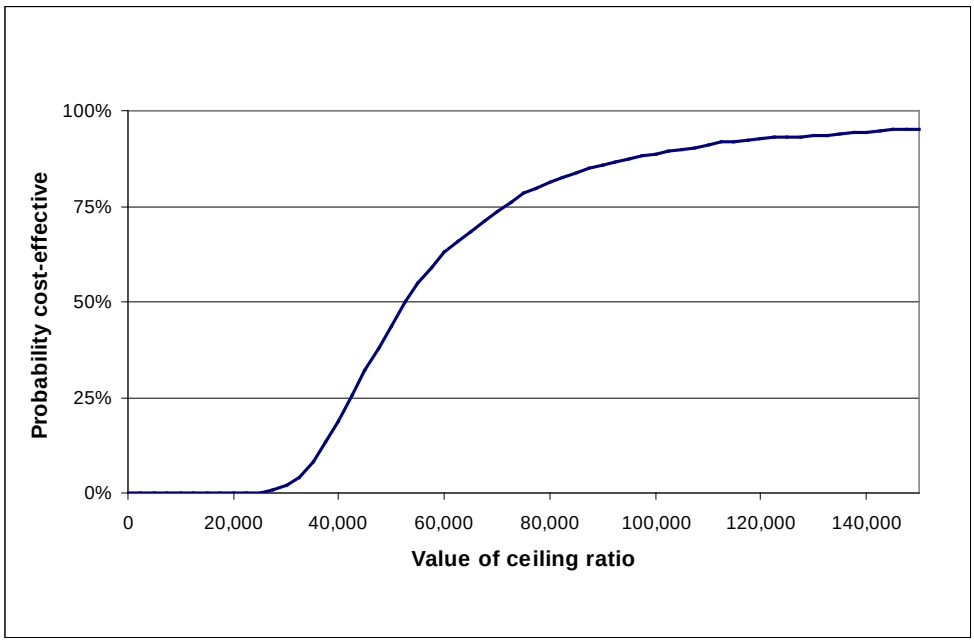

Figure 5: Probabilistic Analysis, CEAC for BSC vs. Sorafenib, Cost per LY gained