in collaboration with:

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Single Technology Appraisal:

Axitinib for the treatment of advanced renal cell carcinoma after failure of prior systemic treatment

Addendum to Evidence Review Group's Report following Pfizer's response to the ACD and revised patient access scheme of 11 January 2013

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam and Maastricht University

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1. Introduction

The Evidence Review Group (ERG) was requested by NICE to provide commentary and validity checks on the revised patient access scheme and additional information as part of the manufacturer's response to the ACD. It should be recognised that the work undertaken by the ERG does not constitute a full critique of the manufacturer's comments and new evidence and does not accord with the procedures and templates applied to the original submission due to the limited time available to review the additional submission. However, a number of detailed checks were undertaken to ensure the validity of the manufacturer's revised analyses based on the information provided by the manufacturer as part of its response to the ACD.

2. Factual information relating to manufacturer's response

In section 2.1.3 of the manufacturer's response to the ACD (page 14), a meta-analysis of 28 trials is cited that studied the relationship between PFS and OS. The publication cited is an abstract published in 2009. It should be noted that in 2012, the same authors have published their meta-analysis as a full paper, including a larger number of studies.
During the AC meeting a reference was made to the everolimus assessment in which NICE accepted a 1.4 month gain in OS for each month gain in PFS. We have explored the source of this relationship, and this appears to be the conference abstract by Delea et al. from 2009. In the conference abstract a 1.4 month gain in OS for each month gain in PFS was estimated for the subgroup of studies with patients with prior treatment. In the 2012 paper, the reported relationship (for the same subgroup, ie with prior treatment) is 1.04 (95% CI 0.14-1.94).
Similarly, in the manufacturer submission of everolimus the relationship in subgroup of studies with correction for cross-over was reported as 1.61 (based on the 2009 abstract). In the recent publication, this is now 1.29 (95% CI 0.47- 2.11) (Delea et al. 2012).

3. Simulated treatment comparison and measures of uncertainty

The manufacturer has provided estimates of the standard errors (SE) for the adjustment factors used in the SRC and details of their methods in section 1.1. Estimates of the SE of the log median OS and PFS were obtained from the RECORD-1 trial and from publications of additional analyses of this trial that used statistical methods to adjust for the high proportion of placebo patients crossing over to everolimus. The delta method has been used to estimate the SE for the adjustment factors to enable the calculation of a 95% confidence interval. This is an accepted method for SE estimation and its use seems appropriate in this setting. Two confidence intervals are reported one including and one excluding the uncertainty around the estimated median for BSC. For PFS the two confidence intervals are similar, but for OS the CI which accounts for the uncertainty in the BSC median is considerably wider. The SE estimate for median OS for BSC uses the results of the analysis which adjusted for treatment crossover (RPSFT method) which was stated to be "considered appropriate by both the manufacturer and the ERG". Therefore the calculation of the SE based on this method should be used as it reflects the more appropriate analysis. As the calculation of the adjustment factor involves estimates of survival for both the axitinib and BSC populations, the estimate of the SE should include the uncertainty of the estimates from both these populations. We recommend that the CI considering both sources of uncertainty should be used (the first ones reported in tables A1 and A2 of the manufacturer's additional information, see also below).

Table A1: Adjustment factor for Progression-Free Survival for Axitinib-like Best Supportive Care Patients

Distribution	Adjustment factor (95% CI)	HR
Lognormal	–1.12 (–1.295; –0.955) or (–1.29; –0.959) when uncertainty around median PFS for BSC was not considered in the calculation of 95% CI for the comparison factor	TR=0.33*
Weibull	–1.25 (–1.418; –1.1079) or (–1.414; –1.084) when uncertainty around median PFS for BSC was not considered in the calculation of 95% CI for the comparison factor	HR=4.1 for BSC versus axitinib

Abbreviations: BSC, best supportive care; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; TR, time ratio.

**The lognormal distribution is not a proportional hazard model and, therefore, the HRs cannot be provided in this case. A HR cannot be calculated when a lognormal distribution is assumed; however, the comparison measure δ derived from a lognormal model can be expressed as the ratio of mean (progression-free or overall) survival times, TR, of comparator versus axitinib and calculated as TR=exp(δ).*

Table A2: Adjustment Factors for Overall Survival for Axitinib-like Patients – RECORD-1 Intention-to-Treat Best Supportive Care

Distribution	Adjustment factor (95% CI)	HR
Lognormal	–0.59 (–2.01; 0.82) or (–0.76; –0.43) when uncertainty around median OS for BSC was not considered in the calculation of 95% CI for the comparison factor	TR=0.55
Weibull	–0.68 (–2.10; 0.73) or (–0.85; –0.51) when uncertainty around median OS for BSC was not considered in the calculation of 95% CI for the comparison factor	HR=2.46 for BSC versus axitinib

Abbreviations: BSC, best supportive care; CI, confidence interval; HR, hazard ratio; OS, overall survival; TR, time ratio.

More detail of the methods and results of the STC have been provided. These are clear and provide a more concise summary than those in the original submission. Results have now been provided for the ratios of PFS to OS which were not presented previously. However there are some discrepancies between the reporting of the STC results in this response and the original submission. In the original submission the median PFS and OS were reported together with the difference in mean values between axitinib and BSC. 95% CI for the difference in mean values were not reported, and have still not been provided. In the new evidence the median OS and PFS are still reported but the gain is calculated as the difference in medians, not the means as was previously reported. Again no CIs are provided. The use of means and medians for survival estimates should be consistent, particularly if PFS/OS ratios are being calculated as these would be different depending on whether the gain was based on the mean or median values.

In summary, the ERG thinks that although the STC appears to have been well-conducted, it involves some major assumptions, namely the comparability of patients between the trials and the assumption that the results of one trial would apply in the setting of the other. In addition, it is a fairly recent analysis method and we have been unable to find any published examples of its use or any evaluation by independent statisticians. Until there is further research into this method its robustness and reliability remains unclear.

4. Updated base case and revised patient access scheme

First it may be helpful to recapitulate that in the original ERG report, the ERG base case was the same as the manufacturer's base case; the ERG changes to the model only related to the uncertainty around various parameters and thus the uncertainty around the ICERs.

Following the critique of the manufacturer's model by the ERG, various (minor) changes were made by the manufacturer to the HE model. In addition, the parameter variation of the adjustment factors (see section 3 of this addendum) was included in the PSA and a revised patient access scheme was applied. Unfortunately, no updated electronic model was made available to the ERG.

The minor changes made by the manufacturer to the model relate to parameters for which standard deviations (SD) were used instead of SE in the PSA. In addition, the uncertainty around the cost of death was applied. Furthermore, the percentage of people with hypertension was set to 0%, a 15 year time horizon was applied and finally, subgroup specific utility values and relative dose intensity (RDI) rates were used rather than the estimates for the intention-to-treat (ITT) population.

Additionally, during the preparation of their response, the manufacturer identified a transcription error that involved the timescale of the STC analyses and the OS data analysis. This error was corrected and the estimated mean costs and QALYs were reduced in all cases for both arms. However, the error had only a marginal impact on ICERs for both the prior sunitinib and prior cytokine populations.

In addition to the changes in the base case described above, a revised PAS has been submitted to the Department of Health. [redacted]

Base line results

Table A4 of the manufacturer's additional information presents the results as they also appeared in the original MS and ERG report. These results are without PAS. In table A5, the model changes are implemented, while still presenting the results without PAS. When we compare the 2 tables, we see that the impact of all the changes is [redacted].

Table A6 presents the results of the initial analysis combined with the new PAS, and by comparing table A4 and A6, we see that the PAS decreases the ICER [redacted]. Finally, table A7 presents the results of all previously mentioned changes. The ICER for prior sunitinib patients is £33,538 and for prior cytokine £55,284.

Note that these are all deterministic results; the ERG has used the original version of the manufacturer's electronic model to calculate probabilistic ICERs, and we found [redacted] with the deterministic results in table A4.

Table A4 Base-case incremental results – with initial analysis without PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Prior Cytokine							
Axitinib	[redacted]	[redacted]	[redacted]				
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior Sunitinib							
Axitinib	[redacted]	[redacted]	[redacted]				
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio

Table A5 Base-case incremental results – with updated analysis without PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Prior Cytokine							
Axitinib	[redacted]	[redacted]	[redacted]				
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior Sunitinib							
Axitinib	[redacted]	[redacted]	[redacted]				
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table A6 Base-case incremental results – with initial analysis and revised PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Prior Cytokine							
Axitinib	[redacted]	[redacted]	[redacted]				
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior Sunitinib							
Axitinib	[redacted]	[redacted]	[redacted]				
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table A7 Base-case incremental results – with updated analysis and revised PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Prior Cytokine							
Axitinib	[redacted]	[redacted]	[redacted]				
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£55,284
Prior Sunitinib							
Axitinib	[redacted]	[redacted]	[redacted]				
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,538

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Deterministic univariate sensitivity analysis

Univariate sensitivity analyses were conducted by the manufacturer to test the sensitivity of the results (ICER) to plausible variation of input parameters. The response document provided by the manufacturer shows the full tornado diagrams; here we show only the parameters that have the largest impact on the outcome.

In figure A1, presenting the results for the prior cytokine population, we see that, as in the original submission, the outcomes most sensitive to changes in the OS hazard ratio. Unlike in the ERG base case, that was part of the earlier ERG report, now the utility post progression also has a large impact, which is most likely due to the fact that in the revised model subgroup specific utilities have been used, which have a wider confidence interval. The relative importance of the parameters of the parametric curves for PFS and OS is similar to what was observed in the original submission.

In figure A2, presenting the results for the prior sunitinib population, we see that the parameters of the parametric curves for PFS and OS now have more impact on the ICER. The ERG assumes that this is a direct consequence of incorporating the statistical uncertainty associated with the STC procedure. We also observe that for all parameters, the maximum ICER is below £50,000 per QALY gained.

Figure A1: Cytokine refractory tornado diagram – With revised PAS

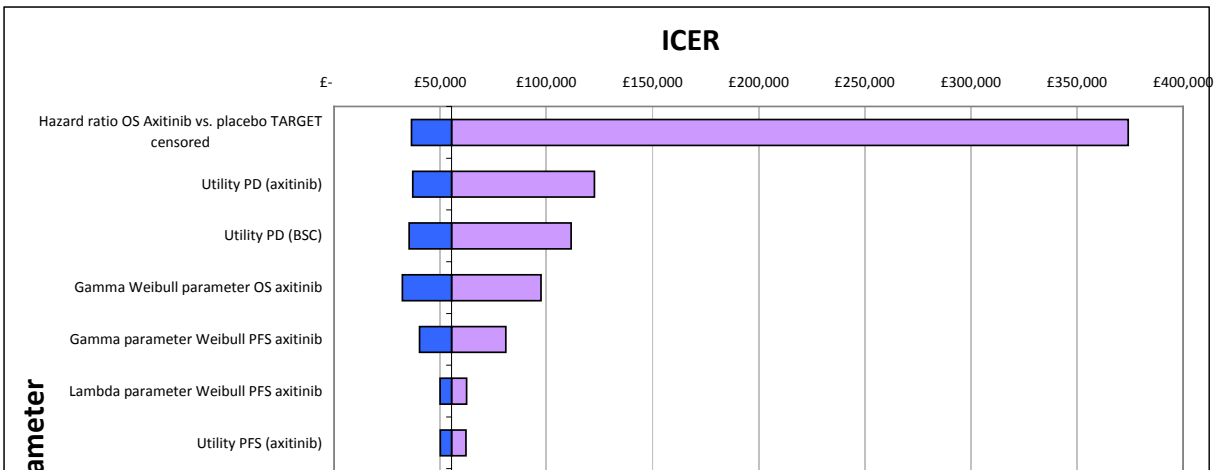
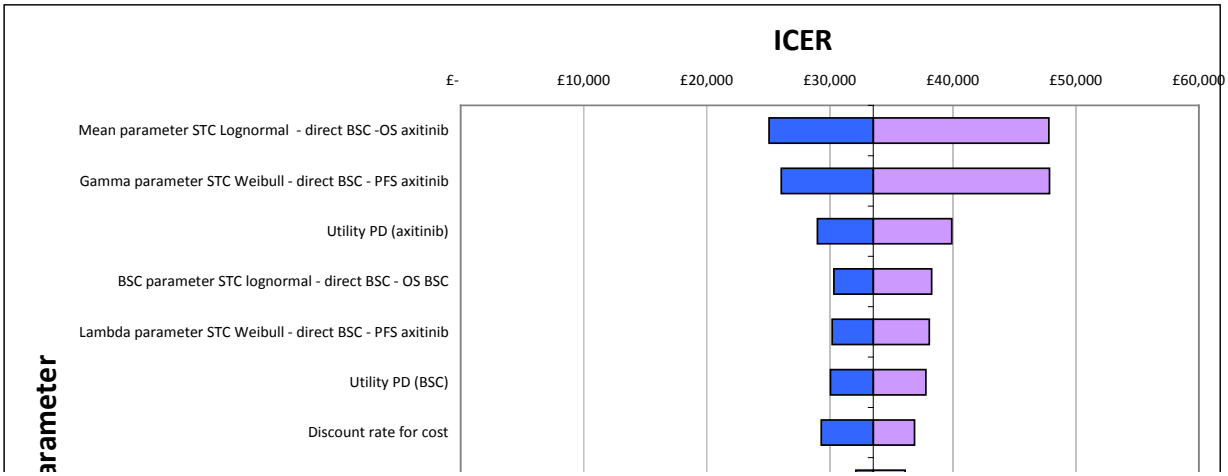


Figure A2: Prior sunitinib tornado diagram - With revised PAS



Probabilistic sensitivity analysis

Cytokine refractory analysis

Figure A3 and A4 present the PSA results for the prior cytokine population in a CEAC and scatter plot. At a willingness-to-pay of £50,000/QALY, axitinib demonstrated a 42% likelihood of being cost effective.

Figure A3: Cytokine refractory scatter plot – With revised PAS

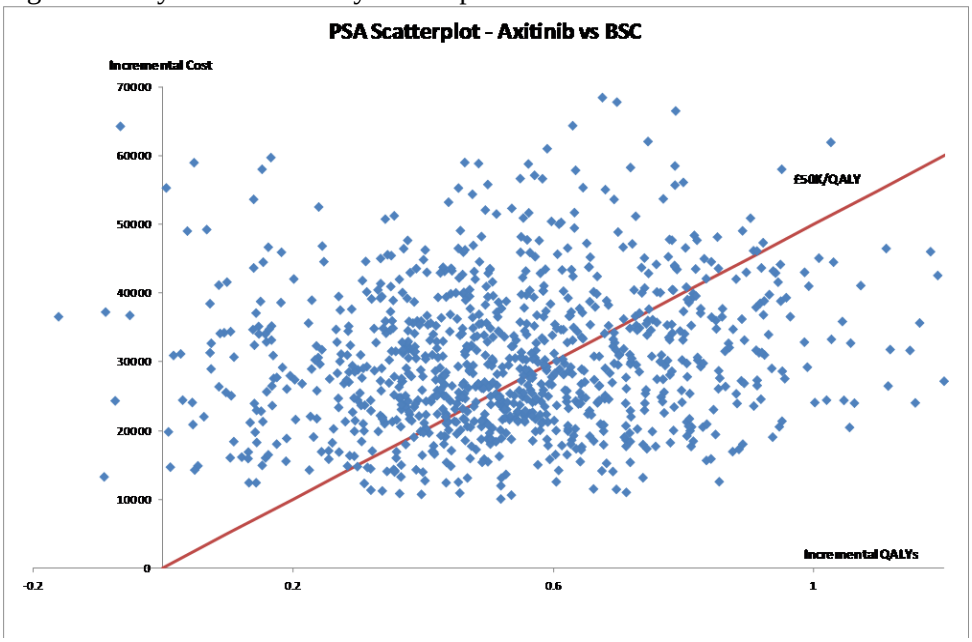
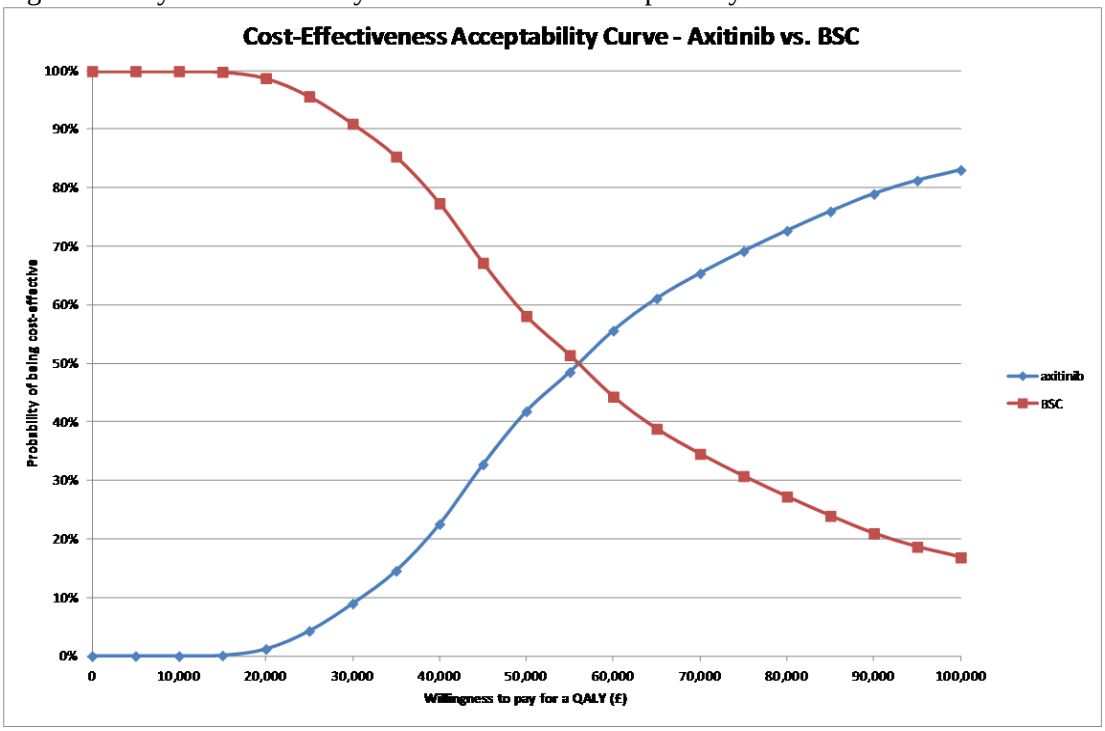


Figure A4: Cytokine refractory cost-effectiveness acceptability curve - With revised PAS



Sunitinib refractory analysis

Figure A5 and Figure A6 present the PSA results for the prior sunitinib population in a CEAC and scatter plot. At a willingness-to-pay of £50,000/QALY, axitinib demonstrated a 65% likelihood of being cost effective even when uncertainty around median crossover-adjusted OS for BSC was considered. When uncertainty around median crossover-adjusted OS for BSC was not considered due to the number of assumptions required to derive the SE of the median OS, axitinib demonstrated a 90% likelihood of being cost effective at a willingness-to-pay of £50,000/QALY (see Figures A7 and A8) which demonstrates that most of the cost-effectiveness uncertainty is due to uncertainty around the median crossover-adjusted (with RPSFT) OS for BSC in RECORD-1.

The ERG considers the analysis including the uncertainty around median crossover-adjusted OS for BSC the most valid. The fact that assumptions had to be made to derive the SE of the median OS is not a compelling reason to disregard it altogether (see also section 2 of this addendum).

Figure A5: Sunitinib refractory scatter plot – With revised PAS (With Uncertainty Around Median Crossover-Adjusted Overall Survival for Best Supportive Care)

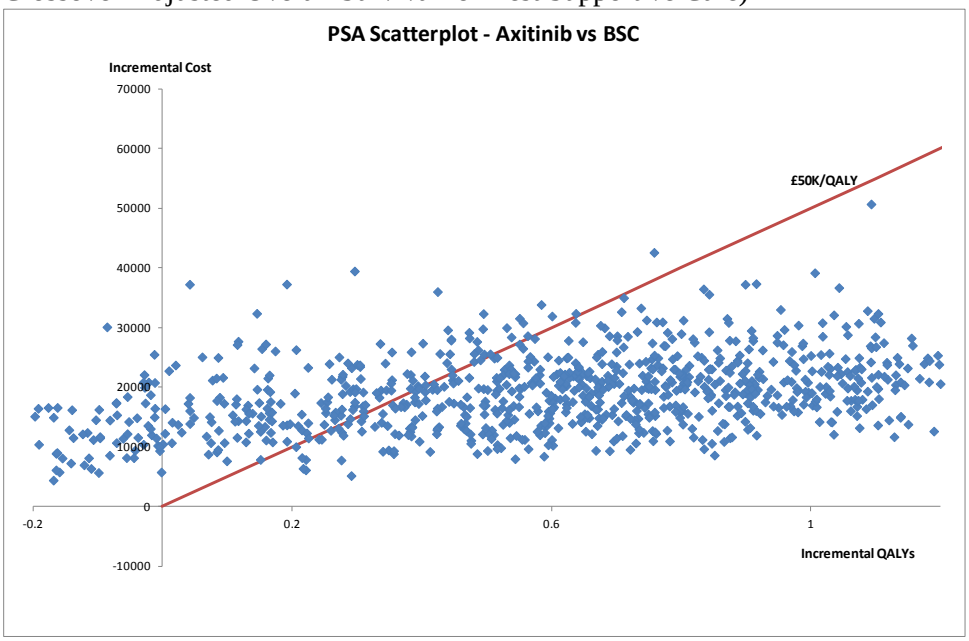


Figure A6: Sunitinib refractory cost-effectiveness acceptability curve - With revised PAS (With Uncertainty Around Median Crossover-Adjusted Overall Survival for Best Supportive Care)

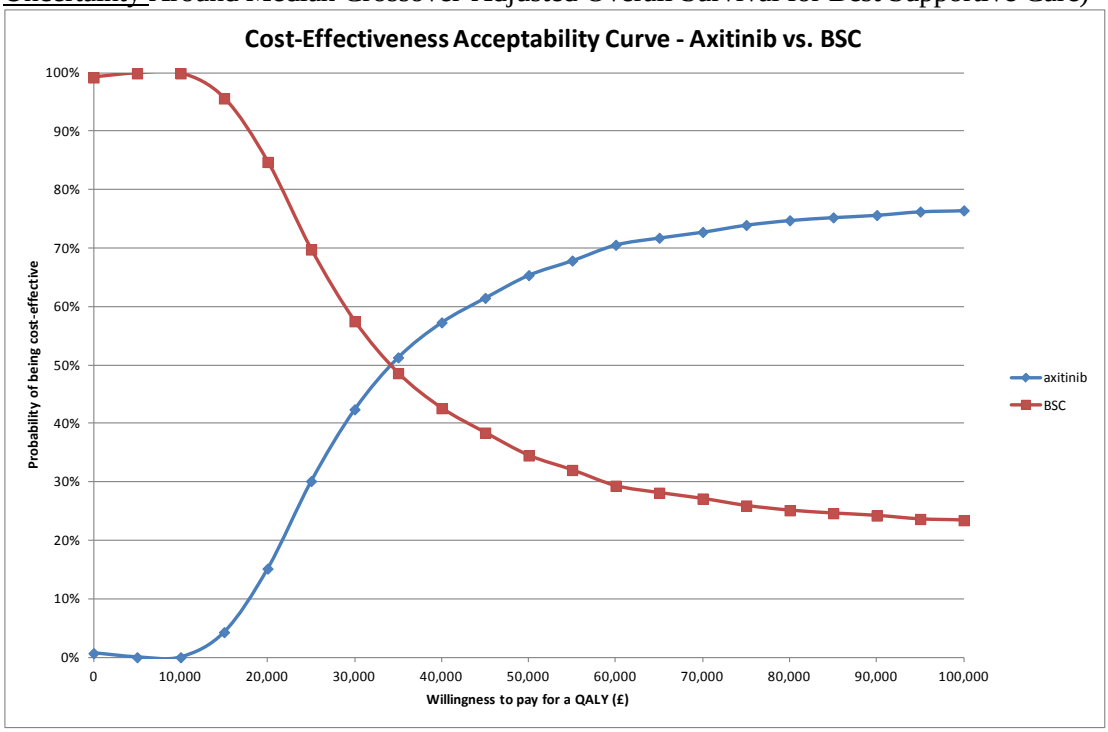


Figure A7: Sunitinib refractory scatter plot – With revised PAS (Without Uncertainty Around Median Crossover-Adjusted Overall Survival for Best Supportive Care)

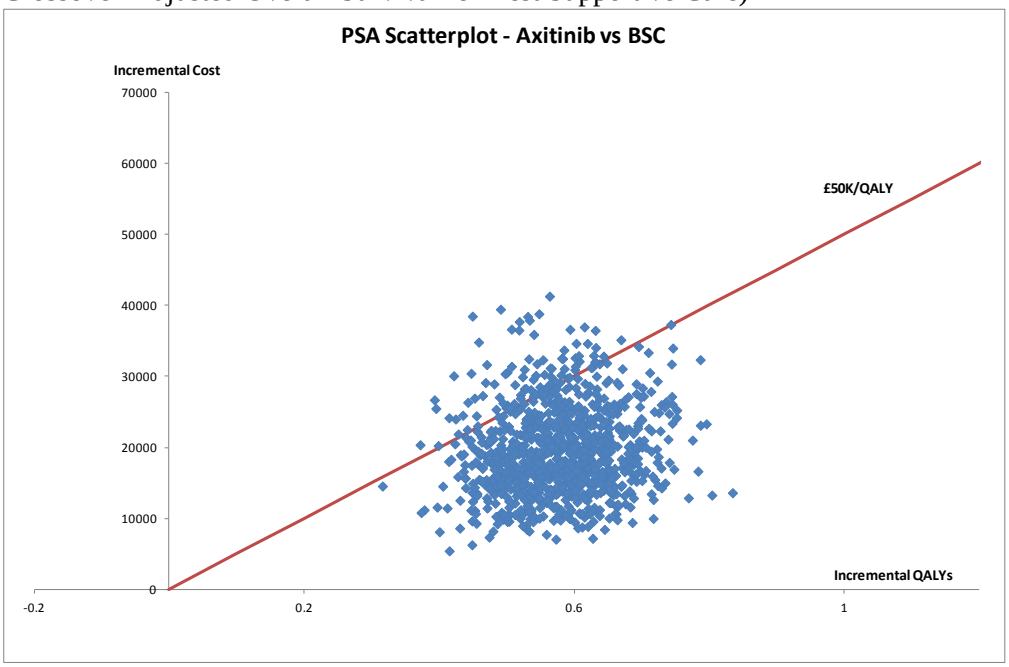
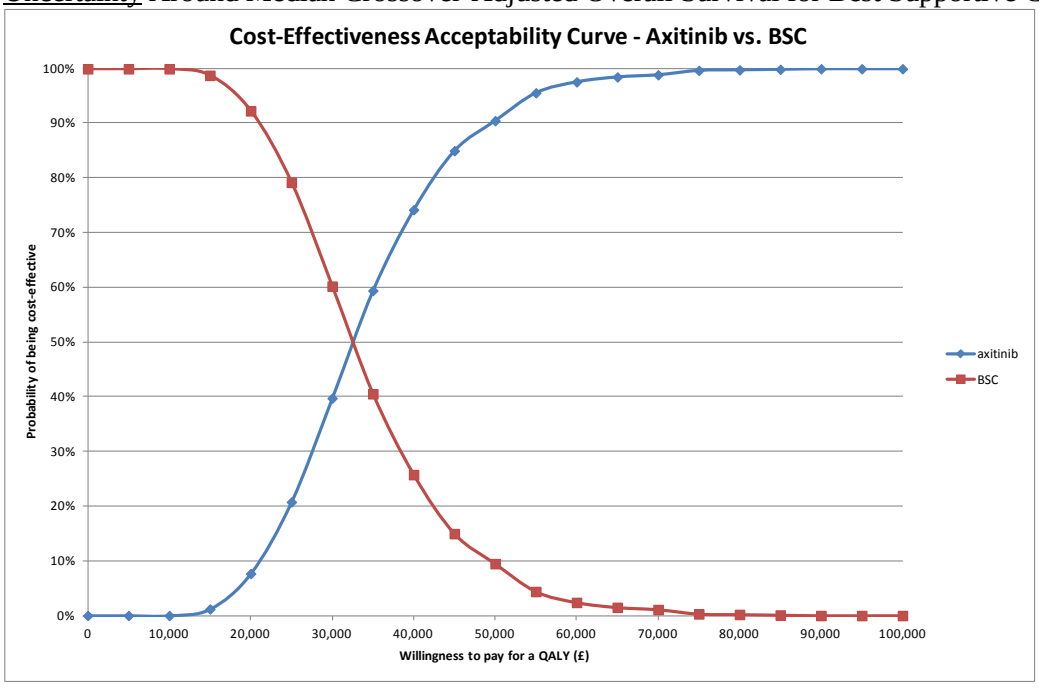


Figure A8: Sunitinib refractory cost-effectiveness acceptability curve - With revised PAS (Without Uncertainty Around Median Crossover-Adjusted Overall Survival for Best Supportive Care)



Scenario analysis

Using the updated version of the model, the manufacturer has again explored the impacts on model outcomes of a number of structural assumptions. The same scenarios as in the original MS were considered, i.e. assumptions were tested around the survival distribution chosen to extrapolate axitinib OS and PFS, the method of comparison to BSC, utility measurement, dosing intensity, and medical management (see Table A8 and A9).

In table A8 we observe that for the prior cytokine population, the outcome is quite sensitive to the method of extrapolation of OS, all other scenarios yield ICERs close to the base case.

Table A8: Scenario analysis results with revised PAS – Prior cytokine population

Parameter	Base case	Scenario analysis	ICER with PAS
Base case	–	–	£55,284
Method of PFS extrapolation	Weibull	Lognormal Gompertz	£60,443 £53,926
Method of OS extrapolation	Weibull	Loglogistic Gompertz	£21,959 £72,537
Axitinib and BSC utility estimates	AXIS study	2nd-line utilities (mRCC MTA and everolimus appraisal)	£52,461
Axitinib relative dosing intensity	AXIS study	Estimated real-world dosing intensity (Everolimus appraisal)	£42,577
Ongoing medical management in pre-progression state	GP Management	Oncologist Management	£56,322

Abbreviations: BSC, best supportive care; GP, general practitioner; ICER, incremental cost-effectiveness ratio; mRCC< metastatic renal cell carcinoma; MTA multiple technology appraisal; OS, overall survival; PFS, progression-free survival.

For all scenarios assessed in the prior sunitinib population, the ICERs with the revised PAS were below £50,000 per QALY (see Table A9).

Table A9: Scenario analysis results – Prior sunitinib population

Parameter	Base case	Scenario analysis		ICER with PAS
Base case	–	–		£33,538
Method of PFS comparison	STC Weibull via ITT RECORD-1 BSC population	STC lognormal via RECORD-1 BSC		£34,775
		STC Weibull via everolimus prior sunitinib – BSC PFS		£33,150
Method of OS comparison	STC lognormal via RECORD-1 ITT BSC population	STC Weibull via RECORD-1 BSC		£34,378
		STC Weibull via everolimus prior sunitinib – BSC RPSFT		£28,958
		RENCOMP	Weibull	£47,515
			Lognormal	£34,973
			Gompertz	£39,479
Axitinib and BSC utility estimates	AXIS study	2nd-line utilities (mRCC MTA and everolimus appraisal)		£29,369
Axitinib relative dosing intensity	AXIS study	Estimated real-world dosing intensity (Everolimus appraisal)		£27,324
Medical management pre-progression	GP Management	Oncologist Management		£34,722

Abbreviations: BSC, best supportive care; GP, general practitioner; ICER, incremental cost-effectiveness ratio; mRCC, metastatic renal cell carcinoma; MTA, multiple technology appraisal; OS, overall survival; PFS, progression-free survival; RPSFT, rank preserving structural time failure; STC, simulated treatment comparison.

Besides these scenarios, the manufacturer has also recalculated the exploratory analysis that was provided by the ERG in which no QALY/survival gain post progression was assumed. The manufacturer showed that the ICER in the updated analysis and the revised PAS for the prior sunitinib population was £52,850 per QALY gained.