NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

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

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal. Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

Current practice

- Does the Committee think a prior-cytokine population is appropriate, given that cytokines are rarely used in current clinical practice because most people with advanced disease start treatment with either sunitinib or pazopanib?
- What is the Committee's view on the exclusion of the prior-pazopanib population, and how this will affect the choice of first-line therapy in clinical practice given that a large proportion of people are usually treated with pazopanib? Does the Committee consider that the exclusion of this population will result in a large group of patients being untreated after progression, even though they may be as eligible as the prior-sunitinib population to receive axitinib?

Clinical effectiveness

- What is the Committee's view on the possible effect of the differing dosing strategies for axitinib and sorafenib employed in the AXIS trial?

- What is the Committee's view on the robustness of the evidence presented for the indirect comparison in the prior-cytokine population, given that:
  1. Patients from the placebo arm of TARGET were allowed to cross over to receive sorafenib upon disease progression.
  2. The manufacturer and the ERG stated that the method used to adjust for crossover in TARGET was not appropriate and may lead to bias.
  3. Patient characteristics were not presented separately for the prior-cytokine group, so the comparison between the AXIS trial and TARGET was based on the intention-to-treat (ITT) group.

- What is the Committee's view on the robustness of the evidence presented for the comparison of axitinib with best supportive care in the prior-sunitinib group, given that:
  1. Patients from the placebo arm of RECORD-1 were allowed to cross over to receive everolimus.
  2. 14% of patients in RECORD-1 discontinued previous therapy because of intolerance rather than disease progression.
  3. Patients in RECORD-1 could have received more than 1 previous treatment, and so may be a less fit population, unlike the AXIS trial where patients had only received 1 previous treatment.
  4. 43 patients in the everolimus arm of RECORD-1 had sunitinib as their only previous therapy, compared with 194 patients in AXIS. Moreover, the manufacturer was unaware of how many of these 43 patients entered the RECORD-1 trial because of disease progression and not intolerance.
  5. The overall survival data from the placebo arm of RECORD-1 used in the simulated treatment comparison (STC) were based on the ITT group because data for the prior-sunitinib group were not presented.
  6. The ERG stated that the outcomes of the STC could potentially be biased because it was based on a comparison of 2 single treatment arms and not on randomised treatment allocations.

7. The ERG stated that the RENCOMP analysis could also be biased because it is an observational study and patients were not randomly allocated to second-line treatments.

- What is the Committee's view on the validity and reliability of an STC for estimating the clinical effectiveness of axitinib compared with best supportive care in the prior-sunitinib group, in particular given the absence of any quantification of uncertainty in the derived estimates?

Cost effectiveness

- What is the Committee's view on the uncertainty around the benefit of axitinib on overall survival in the prior-cytokine group, given that the incremental cost-effectiveness ratio (ICER) increased to approximately £400,000 per quality-adjusted life year (QALY) gained in the ERG's univariate analysis?
- The ERG indicated that no measures of uncertainty were provided in the STC for the best supportive care arm, so the uncertainty around the ICER estimate for the prior-sunitinib group was not estimated. Does the Committee consider the results for the prior-sunitinib group to be robust?
- Does the Committee consider the modelled QALYs gained post progression for the prior-sunitinib group to be clinically plausible, given those modelled for the prior-cytokine group?
- Does the Committee consider the results of the economic analysis presented to be generalisable to the UK population, given that the estimation of the utilities was based on US valuations?
- Does the Committee accept the ERG's exploratory analyses, and which ICER does it consider the most plausible?

Other considerations

- Does the Committee consider that axitinib has met all the end-of-life criteria required for end-of-life considerations and that the estimates are robust?

- Potential equality issues were raised by patient experts, patient organisations and NHS organisations:
  1. Older patients with additional health issues may find the adverse effects more difficult to tolerate.
  2. People with rare cancers such as kidney cancer have inequity of access to NHS-funded treatments.
  3. The scope does not consider axitinib for people who are unsuitable for first-line immunotherapy.

What is the Committee's view on these equality issues?

- What is the Committee's view on the innovative aspects of axitinib raised by the manufacturer and patient organisations, given that the availability of axitinib was expected to offer a step-change in the second-line management of advanced renal cell carcinoma by improving survival beyond what is expected with best supportive care, while maintaining health-related quality of life?

1 Background: clinical need and practice

1.1 Renal cell carcinoma is the collective name for a group of cancers that originate in the lining of the kidney tubules. It is the most common type of kidney cancer, accounting for around 3% of male cancers and 2% of female cancers. Renal cell carcinoma is commonly staged using the American Joint Cancer Committee (AJCC) Tumour Node Metastasis (TNM) staging system. Advanced renal cell carcinoma falls within stages III and IV. Stage III is disease that is locally advanced and/or has spread to regional lymph nodes, and stage IV is disease with distant metastases. The most common sites of metastasis include the lungs and bones. Renal cell carcinoma is usually asymptomatic until it is advanced. The most common presenting symptoms of the disease are blood in the urine (haematuria), a palpable mass in the flank or abdomen,

and abdominal pain. Other non-specific symptoms include fever, night sweats, malaise and weight loss. The health-related quality of life of people with advanced renal cell carcinoma declines as the disease progresses.

1.2 In 2009 8163 new kidney cancers were diagnosed (of which an estimated 90% were renal cell carcinoma), and there were 3328 registered deaths from kidney cancer in England and Wales. Approximately 27% and 14% of people are expected to have stage III and IV disease respectively, and 33% of former stage I–II cancers are expected to recur as stage III–IV cancers. The 5-year survival rate for advanced renal cell carcinoma is approximately 10%. The risk of renal cell carcinoma increases with age; it is rare under the age of 50 and approximately two thirds of newly diagnosed cases are in people over the age of 65. The average age of diagnosis in the UK is 64 years. Other risk factors include smoking, overweight or obesity, hypertension, family history and certain genetic mutations.

1.3 The primary aims of medical intervention are to extend life, prevent worsening of disease, relieve physical symptoms and maintain function. Advanced renal cell carcinoma is largely resistant to chemotherapy, radiotherapy and hormonal therapy. 'Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma' (NICE technology appraisal 169) recommends sunitinib as a first-line treatment for people with advanced and/or metastatic renal cell carcinoma for whom immunotherapy is suitable and who have an Eastern Cooperative Oncology Group (ECOG) status of 0 or 1. 'Pazopanib for the first-line treatment of advanced renal cell carcinoma' (NICE technology appraisal 215) recommends pazopanib as a first-line treatment for people with advanced renal cell carcinoma who have an ECOG status of 0 or 1. An alternative

treatment option for advanced renal cell carcinoma is cytokine-based immunotherapy, including interleukin-2 (sometimes called aldesleukin) or interferon-alfa 2a. NICE does not currently recommend any interventional therapies for advanced renal cell carcinoma after failure of initial systemic therapy. Therefore, it is expected that patients would subsequently receive best supportive care.

2 The technology

2.1 Axitinib (Inlyta, Pfizer) is an oral multi-targeted kinase inhibitor with anti-tumour activity. Axitinib selectively inhibits vascular endothelial growth factor receptors (VEGFR) 1, 2 and 3, platelet-derived growth factor receptor (PDGFR), and c-kit, which may inhibit angiogenesis in tumours. Axitinib is indicated for the treatment of adult patients with advanced renal cell carcinoma after failure of prior treatment with sunitinib or a cytokine.

2.2 The summary of product characteristics lists the following adverse reactions for axitinib: diarrhoea, hypertension, fatigue, dysphonia, nausea, decreased appetite, palmar–plantar erythrodysaesthesia (hand–foot syndrome), hypothyroidism, headache, dysgeusia, haemorrhage, vomiting, stomatitis, constipation, rash, dry skin, proteinuria, asthaenia and mucosal inflammation. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Axitinib is available in 1 mg and 5 mg film-coated tablets at net prices of £703.40 and £3517 per 56-tablet pack respectively (excluding VAT). Axitinib is administered orally at a recommended starting dose of 5 mg twice daily. This dose may be increased to 7 mg and then up to 10 mg, or decreased to 3 mg and then down to 2 mg, depending on individual safety and tolerability. The

manufacturer of axitinib has agreed a patient access scheme with the Department of Health. The patient access scheme will be applied at the point of purchase at a simple discount of [redacted] below the UK NHS list price for each presentation of axitinib, and this is conditional upon the size of the discount remaining confidential from the public. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of axitinib within its licensed indication for the treatment of advanced renal cell carcinoma after failure of prior systemic treatment.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	Adults with advanced renal cell carcinoma who have received prior systemic treatment	Adult patients with advanced renal cell carcinoma after failure of prior treatment with sunitinib or a cytokine

The manufacturer's submission was based on the subgroups of patients who received prior cytokine treatments and prior sunitinib treatments in line with the marketing authorisation for axitinib. The Evidence Review Group (ERG) considered the restriction of the population in the manufacturer's submission to the licensed population to be appropriate.

	Final scope issued by NICE	Decision problem addressed in the submission
Intervention	Axitinib	
Comparators	Best supportive care	
Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	
Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of quality-adjusted life years. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and personal social services perspective.	

The ERG was concerned that the lifetime time horizon of 10 years used in the base-case model may not be long enough considering real life expectancy and a lifetime time horizon assumption. Nevertheless, it considered the time horizon to be acceptable because the sensitivity analysis performed by the manufacturer showed that increasing the time horizon to 15 years had minimal impact on the base-case results.

3.2 Axitinib is proposed as a second-line treatment after failure of sunitinib or a cytokine (interferon-alfa 2a, interleukin-2).

4 Clinical-effectiveness evidence

4.1 The manufacturer conducted a systematic literature search and identified 1 randomised controlled trial (AXIS) that assessed axitinib for the second-line treatment of people with advanced renal cell carcinoma. AXIS was a phase III, international, multicentre, randomised, open-label, active-controlled trial comparing axitinib with sorafenib for the treatment of advanced or metastatic renal cell carcinoma after failure of prior first-line systemic therapy. The study was undertaken in 175 centres in 22 countries and lasted for 3 years. The clinical-effectiveness evidence presented in the

manufacturer's submission was based mainly on this trial, but because this trial had no best supportive care comparator as defined in the scope, additional studies were used for an indirect comparison of axitinib with best supportive care.

4.2 Patients were eligible to enter the AXIS trial if they had measurable and progressive disease according to the Response Evaluation Criteria in Solid Tumours (RECIST) at least 2 weeks after 1 systemic first-line treatment with sunitinib, temsirolimus, cytokine(s) or at least 4 weeks or more with bevacizumab plus interferon-alfa 2a. 723 patients were randomised in a 1:1 ratio to receive either axitinib 5 mg twice daily or sorafenib 400 mg twice daily. The dose for axitinib was either maintained, increased to 7 mg and then up to 10 mg twice daily, or reduced to 3 mg and then down to 2 mg twice daily, depending on individual safety and tolerability and at the discretion of the treating physician. The dose for sorafenib was reduced to 400 mg once daily and then to 400 mg every other day if there were sorafenib-related adverse reactions. No other chemotherapy or experimental anti-cancer medications were permitted during the on-study period. Palliative care was allowed for pain control only, for bone disease present at baseline and for disease-related symptoms. Baseline patient characteristics were balanced between the 2 treatment groups (see table 1). The mean age was approximately 60 years (66% of the participants were less than 65 years), 72% were male and 76% were white. The previous systemic therapies used were also similar between the 2 groups (in both groups, 54% of patients had received sunitinib, 35% had received cytokines, 8% had received bevacizumab and 3% had received temsirolimus). There were no notable differences between the treatment groups in terms of disease history.

Table 1 Patient demographics and baseline characteristics: AXIS

Characteristic		Axitinib (n=361)	Sorafenib (n=362)
Age, years	Mean (SD)	59.7 (10.5)	60.0 (10.1)
	Median	61.0	61.0
	Min, max	20, 82	22, 80
Age (years)	<65	238 (65.9)	238 (65.7)
	≥65	123 (34.1)	124 (34.3)
Sex	Male	265 (73.4)	258 (71.3)
	Female	96 (26.6)	104 (28.7)
Race	White	278 (77.0)	269 (74.3)
	Black	1 (0.3)	4 (1.1)
	Asian	77 (21.3)	81 (22.4)
	Other	5 (1.4)	8 (2.2)
Geographic region	North America	88 (24.4)	98 (27.1)
	Europe	187 (51.8)	170 (47.0)
	Asia	73 (20.2)	79 (21.8)
	Other	13 (3.6)	15 (4.1)
ECOG performance status[a]	0	195 (54.0)	200 (55.2)
	1	162 (44.9)	160 (44.2)
	>1	1 (0.3)	0
MSKCC risk group[b]	Favourable	100 (27.7)	101 (27.9)
	Intermediate	134 (37.1)	130 (35.9)
	Poor	118 (32.7)	120 (33.1)
	Not applicable	9 (2.5)	11 (3.0)
Previous systemic therapy	Sunitinib	194 (53.7)	195 (53.9)
	Cytokines	126 (34.9)	125 (34.5)
	Bevacizumab	29 (8.0)	30 (8.3)
	Temsirolimus	12 (3.3)	12 (3.3)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; kg, kilogram; mg, milligram; MSKCC, Memorial Sloan-Kettering Cancer Centre; SD, standard deviation.

[a] ECOG performance status was taken from case report forms and was the last measure obtained before dosing.

[b] MSKCC risk groups were calculated based on the criteria for previously treated renal cell carcinoma patients.

Source: manufacturer's submission (table 8, page 51).

4.3 The primary outcome in the AXIS trial was progression-free survival as measured by the independent review committee (IRC), and this was defined as the time from randomisation to first disease progression or death from any cause (whichever occurred first). Secondary outcomes included progression-free survival as

assessed by the investigator; overall survival, defined as the time from randomisation to the date of death from any cause; objective response rate, defined as the number of patients with complete or partial response according to RECIST criteria; duration of response, defined as the time of the first tumour response to the time of disease progression or death from any cause (whichever occurred first); and patient-reported outcomes (quality of life). Quality of life was assessed using the 15-item Functional Assessment of Cancer Therapy Kidney Symptom Index (FKSI-15), which measures symptoms and quality of life in people with advanced kidney disease; and the FKSI Disease-Related Symptoms subscale (FKSI-DRS), which measures symptoms related to advanced kidney cancer disease. Symptoms measured include lack of energy, pain, weight loss, bone pain, fatigue, shortness of breath, coughing, fevers and haematuria. The EuroQol-5D (EQ-5D) was also used to assess generic health status.

4.4 Subgroup analyses of the primary and secondary endpoints were performed for the stratification factors based on ECOG performance score (0 and 1) and prior treatment regimen (sunitinib, cytokine, bevacizumab and temsirolimus). The evidence in the manufacturer's submission was based on the subgroup of patients who were previously treated with sunitinib and cytokines, in line with the marketing authorisation for axitinib. Subgroups were also predefined for the secondary endpoints based on baseline patient characteristics of age (less than 65 years, 65 years or more); sex (male, female); ethnic origin (white, non-white); geographical region (Asia, Europe, North America, other) and Memorial Sloan-Kettering Cancer Centre (MSKCC) risk groups (favourable, intermediate, poor).

4.5 In the main trial population, there was a statistically significant difference of 2 months in the IRC-assessed median progression-free survival, which was 6.7 months in the axitinib group compared with 4.7 months in the sorafenib group. The hazard ratio (HR) for progression was 0.67 (95% confidence interval [CI] 0.54 to 0.81, p<0.0001), adjusted for the stratification factors (ECOG performance score and prior systemic therapy). The secondary outcome of investigator-assessed progression-free survival also demonstrated a significant difference of 2.7 months (HR 0.66, 95% CI 0.54 to 0.79, p<0.0001). However, the improvement in overall survival was not statistically significant (HR 0.97, 95% CI 0.80 to 1.17, p=0.37).

4.6 Quality of life data were collected at day 1, every 4 weeks afterwards, at the end of study treatment or withdrawal, and on day 28 of the follow-up period. Higher FKSI-15, FKSI-DRS and EQ-5D scores indicate better quality of life. A repeated measures mixed-effects model was used to compare differences in quality of life between the 2 treatment groups. There were no statistically significant differences at follow-up between axitinib and sorafenib using the 3 health measures. The axitinib group had FKSI-DRS scores 0.12 higher than the sorafenib group, measured using the FKSI-DRS measure for the main trial population (95% CI –0.45 to 0.69, p=0.68). However, the manufacturer did not report the differences using the FKSI-15 and EQ-5D measures. The differences for the populations covered by the marketing authorisation are:

Prior cytokine

- EQ-5D: difference [redacted]
- FKSI-15: difference [redacted]

- FKSI-DRS: difference [redacted]

Prior sunitinib

- EQ-5D: difference [redacted]
- FKSI-15: difference [redacted]
- FKSI-DRS: difference [redacted]

4.7 The safety analysis was performed for all patients who received at least 1 dose of axitinib or sorafenib in the AXIS trial (n=714). Diarrhoea was the most common treatment-emergent adverse event, occurring proportionately in both treatment groups (54.9% in the axitinib group and 53.2% in the sorafenib group). The most common adverse events in the axitinib group were hypertension, dysphonia, nausea and hypothyroidism. Hand–foot syndrome, rash and alopecia were more common in the sorafenib group. The sorafenib group had a higher occurrence of grade 3 (51.3% versus 50.4%) and grade 4 (10.1% versus 5.8%) adverse events compared with axitinib. Serious adverse events resulting in death, inpatient hospitalisation or prolonged hospitalisation, significant disability and congenital abnormalities and/or birth defects in children of trial participants occurred equally in both treatment groups in the full trial population. The sorafenib group was associated with higher proportions of adverse events leading to dose reductions or interruptions (62% versus 55.4%) and permanent discontinuation of study medication (13% versus 9.2%).

Table 2 Summary of the most common grade 3 and 4 treatment-related adverse events

MedDRA preferred term	Axitinib n=359		Sorafenib n=355	
	Grade 3 n (%)	Grade 4 n (%)	Grade 3 n (%)	Grade 4 n (%)
Any AE	162 (45.1)	11 (3.1)	167 (47.0)	19 (5.4)
Diarrhoea	35 (9.7)	1 (0.3)	23 (6.5)	2 (0.6)
Hypertension	55 (15.3)	1 (0.3)	38 (10.7)	1 (0.3)
Fatigue	34 (9.5)	1 (0.3)	12 (3.4)	1 (0.3)
Palmar-plantar erythrodysaesthesia syndrome	18 (5.0)	0	57 (16.1)	0

Abbreviations: AE, adverse event; MEdDRA, Medical Dictionary for Regulatory Activities; SA, safety analysis.

Source: manufacturer's submission (table 32, page 120).

Prior-cytokine group

4.8 For the prior-cytokine group in AXIS, the axitinib group had a statistically significant IRC-assessed median progression-free survival of 5.6 months more than the sorafenib group (HR 0.46, 95% CI 0.32 to 0.68, p<0.0001). There was also a statistically significant 3.7-month higher investigator-assessed progression-free survival in the axitinib group (HR 0.64, 95% CI 0.45 to 0.90, p=0.0049). However, there was no statistically significant improvement in overall survival. The hazard ratio for overall survival was 0.81 (95% CI 0.56 to 1.19, p=0.14), based on 51 deaths (40.5%) in the axitinib group and 57 deaths (45.6%) in the sorafenib group.

4.9 For the prior-cytokine safety group (n=249) in AXIS, the treatment-emergent adverse events that occurred more frequently in the axitinib group than the sorafenib group were [redacted]. However, the following adverse events occurred

more frequently in the sorafenib group than the axitinib group: [redacted]. The proportion of people with any grade 3 or 4 treatment-related adverse events was [redacted].

Indirect treatment comparison

4.10 In a systematic review of the literature, the manufacturer identified 1 relevant trial, known as TARGET (Treatment Approaches in Renal Cancer Global Evaluation Trial), that was considered suitable for an indirect comparison of axitinib versus best supportive care. For the purpose of this appraisal, the manufacturer used placebo as a proxy for best supportive care. TARGET was a phase III, multicentre, randomised, double-blind, placebo-controlled trial comparing sorafenib with placebo for people with metastatic renal cell carcinoma who had received 1 prior systemic therapy. However, TARGET was made up mostly of patients that had received first-line cytokine therapy only, and had no prior-sunitinib group. Therefore, an indirect comparison of axitinib versus best supportive care was possible only for the cytokine-refractory subgroup. The patients in TARGET were similar to the patients in AXIS in terms of age, gender and previous nephrectomy (see table 3). However, only 2 metastatic sites (lung and liver) were reported in TARGET, while AXIS reported more than 8 sites. MSKCC risk scores and prior treatments also differed between the 2 trials, with TARGET patients having predominantly received prior cytokines.

Table 3 Patient characteristics in RCTs used for the indirect comparison

	AXIS		TARGET	
	Axitinib n=361	**Sorafenib n=362**	**Sorafenib n=451**	**Placebo n=452**
Age, median (range)	61 (20–82)	61 (22–80)	58 (19–86)	59 (29–84)
Male, n (%)	265 (73)	258 (71)	315 (70)	340 (75)
ECOG performance status, n (%)				
0	195 (54)	200 (55)	219 (49)	210 (46)
1	162 (45)	160 (44)	223 (49)	236 (52)
>1	1 (<1)	0	7 (2)	4 (1)
Missing data	0	0	2 (<1)	2 (<1)
MSKCC risk score, n (%)				
Favourable	100 (28)	101 (28)	233 (52)	228 (50)
Intermediate	134 (37)	130 (36)	218 (48)	223 (49)
Poor	118 (33)	120 (33)	0	0
Missing data	9 (2)	11 (3)	0	1 (<1)
Previous nephrectomy, n (%)	327 (91)	331 (91)	422 (94)	421 (93)
Previous systemic therapy, n (%)	361 (100)	362 (100)		
Sunitinib	194 (54)	195 (54)		
Cytokines	126 (35)	125 (35)	374 (83)	368 (81)
Bevacizumab	29 (8)	30 (8)		
Temsirolimus	12 (3)	12 (3)		
Common metastatic sites				
Lung	274 (75.9)	292 (80.7)	348 (77)	348 (77)
Liver	102 (28.3)	103 (28.5)	116 (26)	117 (26)
Bone	119 (33.0)	107 (29.6)	NR	NR
Lymph node	209 (57.9)	202 (55.8)	NR	NR
Other	139 (38.5)	130 (35.9)	NR	NR
Kidney	81 (22.4)	77 (21.3)	NR	NR
Brain	NR	NR	NR	NR
Pleural effusion	18 (5.0)	18 (5.0)	NR	NR
Ascites	2 (0.6)	5 (1.4)	NR	NR

Abbreviations: ECOG, Eastern cooperative oncology group; MSKCC, Memorial Sloan-Kettering Cancer Centre; NR, not reported.

Source: manufacturer's submission (table 15, page 89).

4.11 The manufacturer identified some limitations in the evidence networks from the AXIS and TARGET trials that had an impact on

the indirect comparison. In the AXIS trial, the manufacturer stated that the relative efficacy in overall survival (which was not statistically significant) may have been diluted because an active comparator (sorafenib) was used in the trial. The overall survival results may also have been confounded because of the subsequent treatments received after progression. In the prior-cytokine subgroup, 46.4% of patients in both the axitinib and sorafenib groups received subsequent treatments after progression. In the prior-sunitinib subgroup, 60% of patients in the axitinib group and 65.2% of patients in the sorafenib group received subsequent treatments. The manufacturer also stated that the overall survival analysis may have been affected by the relatively long survival post progression because of the patient heterogeneity usually seen in advanced renal cell carcinoma, the likelihood of receiving subsequent therapy, and the variability in treatment decisions made after progression.

4.12 In the TARGET trial, the overall survival result may have been confounded by crossover from the control arm to the treatment arm (sorafenib). The manufacturer stated that the method of adjusting for crossover (censoring of the patients) was not appropriate because it could lead to selection bias. The manufacturer stated that the rank-preserving structural failure time (RPSFT) method used in previous NICE appraisals of everolimus and sunitinib would have been more appropriate, as it was validated by NICE and usually improves the hazard ratio in favour of the active treatment. Another limitation with the evidence from TARGET was the absence of a prior-sunitinib group. The manufacturer stated that the prior-cytokine group (who have never received a tyrosine kinase inhibitor [TKI] such as sunitinib) and prior-sunitinib group were considered to be clinically different populations that were not interchangeable. First-line therapy was considered to have failed

more rapidly in the prior-cytokine group than in the prior-sunitinib group. Therefore, the prior-cytokine group may benefit more from second-line treatment, as shown by the higher median progression-free survival. Because of this, separate evidence was presented for the prior-sunitinib subgroup.

4.13 The indirect comparison was performed using Bayesian Markov-chain Monte Carlo sampling to determine the relative efficacy of the treatments. Sampling was performed using WinBugs. The hazard ratios from AXIS and TARGET (progression-free survival [HR 0.54, 95% CI 0.45 to 0.64] and overall survival censored for crossover [HR 0.78, 95% CI 0.62 to 0.97]) were used in a fixed effects model. Point estimates of the hazard ratio for each pair of treatments and 95% credible intervals were calculated from 5000 simulated draws from the posterior distribution after a burn-in of 20,000 iterations. The result of the indirect comparison shows a 75% reduction in disease progression (median HR 0.25, 95% credible intervals 0.17 to 0.38) for axitinib compared with placebo, (assumed here to be equivalent to best supportive care). For overall survival, the median hazard ratio for death censored for crossover was 0.63 (95% credible intervals 0.41 to 0.99).

Table 4 Summary of results – prior cytokine

AXIS	Axitinib	Sorafenib	Difference	HR (95% CI)
Median PFS (months)	12.1	6.5	5.6	0.46 (0.32 to 0.68)
Median OS (months)	29.4	27.8	1.6	0.81 (0.56 to 1.19)
Indirect comparison	**Axitinib**	**BSC**	**Difference**	**HR (95% CrI)**
Median PFS (months)	NR	NR	NR	0.25 (0.17 to 0.38)
Median OS (months)	NR	NR	NR	0.63 (0.41 to 0.99)

Abbreviations: BSC, best supportive care; CI, confidence interval; CrI, credible interval; HR, hazard ratio; NR, not reported; OS, overall survival; PFS, progression-free survival.

Source: manufacturer's submission

Prior-sunitinib group

4.14 For the subgroup of patients that were previously treated with sunitinib in AXIS, there was a statistically significant difference in the IRC-assessed median progression-free survival of 1.4 months (4.8 months in the axitinib group compared with 3.4 months in the sorafenib group). The hazard ratio for progression was 0.74 (95% CI 0.57 to 0.96, p=0.0107), adjusted for performance status. The axitinib group also had a 2-month longer investigator-assessed progression-free survival than the sorafenib group, with a hazard ratio of 0.64 (95% CI 0.49 to 0.82, p=0.0002). The hazard ratio for overall survival was 0.997 (95% CI 0.78 to 1.27, p=0.49), based on 131 deaths (67.5%) in the axitinib group and 131 deaths (67.2%) in the sorafenib group.

4.15 For the prior-sunitinib safety group (n=380) in AXIS, the treatment-emergent adverse events that occurred more frequently in the axitinib group than the sorafenib group were [redacted]. However, the following treatment-emergent adverse events occurred more frequently in the sorafenib group than the axitinib group: [redacted]. The proportion of people with any grade 3 or 4 treatment-related adverse events was [redacted].

Simulated treated comparison

4.16 The manufacturer identified 1 study in an additional systematic review of the literature where sunitinib-refractory patients received best supportive care after disease progression. This was used to provide a link between axitinib and best supportive care in a prior-sunitinib population. The study identified is known as the RECORD-1 trial (Renal Cell Cancer Treatment With Oral RAD001 Given Daily), and compared everolimus plus best supportive care with placebo plus best supportive care in patients with metastatic renal cell carcinoma who progressed after treatment with a TKI. As there was no direct link between the treatments used in the AXIS trial and those used in RECORD-1, the manufacturer performed a simulated treatment comparison (STC) to create an adjusted indirect comparison between the axitinib prior-sunitinib group from AXIS and the best supportive care prior-sunitinib group from RECORD-1. The aim of the STC was to estimate how the prior-sunitinib group from the AXIS trial would have performed if they were treated with placebo, using data from RECORD-1. Patients in RECORD-1 were allowed to cross over to the everolimus arm, although the impact of the crossover was adjusted for using the RPSFT method, which the manufacturer considered to be valid.

4.17 There were several differences highlighted between the AXIS and RECORD-1 trials. First, 14% of patients in RECORD-1 discontinued prior treatment because of intolerance, rather than progressing from prior treatment as in the AXIS trial. Second, only 43 patients in the everolimus arm of RECORD-1 had received prior sunitinib, in contrast to the 194 prior-sunitinib patients in the axitinib arm of the AXIS trial. The manufacturer noted that some of the 43 patients from RECORD-1 may have had sunitinib intolerance rather than sunitinib-refractory disease, which may lead to potential bias

because sunitinib-intolerant patients would be expected to respond better to subsequent treatment than patients with sunitinib-refractory disease. Thirdly, patients in RECORD-1 had received 1 or more prior treatments, while patients on AXIS had received just 1 first-line treatment. In RECORD-1, median progression-free survival was assessed in a prior-sunitinib subgroup (n=56). However, the overall survival and patient characteristics for this subgroup were not assessed. As a result, 2 approaches were taken in the STC to compare axitinib with best supportive care in a prior-sunitinib population. The first compared the axitinib prior-sunitinib group in AXIS with the best supportive care intention-to-treat (ITT) group in RECORD-1, and assumed that the ITT group would have the same overall survival and patient characteristics as the prior-sunitinib group in RECORD-1. The second approach compared the axitinib prior-sunitinib group with the everolimus prior-sunitinib group, and then applied the RPSFT-adjusted hazard ratio for everolimus to best supportive care to create a modelled prior-sunitinib group.

Table 5 Patient characteristics – AXIS and RECORD-1

	AXIS ITT sunitinib-refractory axitinib n=194	RECORD-1 Prior sunitinib everolimus n=127	RECORD-1 ITT placebo patients n=139
Male, %	74.2	79.5	76
Age, median (range)	61 (22–82)	59 (28–81)	60 (29–79)
Prior nephrectomy, %	88.1	91.3	N/A
Prior radiotherapy, %	23.2	30.7	N/A
MSKCC risk score, % Favourable (0) Intermediate (1) Poor (> 1)	 19.8 41.4 36	 28.1 54.7 17.2	 28 57 15
Clear cell RCC, %	97.9	100	
ECOG or Karnofsky performance status, % ECOG 0/ KPS 90–100 ECOG 1/ KPS 70–80 ECOG 2/ KPS 50–60 Missing	 51.6 48.4 0 0	 59.5 40.5 0 0.8	 68 33 0 0
Weeks on sunitinib, median (range)	41.4 (2.7–471)	41.3 (1.3–120)	N/A
Previous cytokine treatment, %	0	Not known but >0	Not known but >0
Target values used in STC			
Median PFS, weeks	20.8	16.9	7.8
Median OS, weeks	65.9 (15.2 months)	54.4 (12.6 months)	43.4 (10.0 months)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; KPS, Karnofsky performance status; MSKCC, Memorial Sloan-Kettering Cancer Centre; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; STC, simulated treatment comparison.

Source: manufacturer's submission (table 21, page 101)

4.18 The STC was performed by analysing patient-level data from the axitinib arm of the AXIS trial to derive parametric failure-time (survival) equations incorporating baseline predictors of the endpoints (progression-free survival and overall survival). Five distributions were examined, but only the 2 best fitting (log-normal

and Weibull) were used in the STC. The results of the STC suggested a beneficial treatment effect of axitinib compared with best supportive care, with an estimated increase in mean progression-free survival of [redacted] using the log-normal and Weibull distributions respectively for the ITT group. The STC curve for the everolimus prior-sunitinib arm of the trial also showed an increase in mean progression-free survival of [redacted] with axitinib compared with everolimus using the log-normal and Weibull distributions respectively. The result also showed a beneficial effect on mean overall survival with axitinib compared with best supportive care and with everolimus. Overall survival increased by [redacted] using the log-normal and Weibull distributions respectively for the best supportive care ITT STC curve, while the [redacted] increase for the everolimus STC curve was the same using the log-normal and Weibull distributions. The progression-free survival hazard ratio (0.34) for the prior-sunitinib group and adjusted overall survival hazard ratio (0.53) for the ITT group of RECORD-1 were applied to the everolimus STC curves to generate modelled AXIS-like, prior-sunitinib progression-free survival and overall survival curves for best supportive care.

Indirect treatment comparison

4.19 The manufacturer also provided an additional analysis, using retrospective observational data from a Swedish database (Renal Comparison; RENCOMP) to estimate the overall survival hazard ratio of people who received sorafenib or best supportive care after first-line treatment with sunitinib. Patient characteristics such as age, gender and nephrectomy status were similar between the 2 treatment groups (sorafenib and best supportive care). However, the best supportive care group seemed to be healthier in terms of

year of diagnosis, lead time between metastatic disease and first prescription of sunitinib, diagnosis of primary metastatic disease and place of treatment. A multivariate Cox proportional regression analysis was performed using variables with significance at the 5% level to adjust for uncertainty resulting from confounding. This resulted in an overall survival hazard ratio of 0.62 (95% CI 0.41 to 0.94, p=0.023). The results from RENCOMP were used in an indirect comparison with the results from the prior-sunitinib group in the AXIS trial (HR 0.997, 95% CI 0.78 to 1.27) in order to generate indirect hazard ratios between axitinib and best supportive care in the prior-sunitinib group. The results showed that axitinib was associated with an improvement in overall survival compared with best supportive care in a sunitinib-refractory population (HR 0.62, 95% credible interval 0.38 to 0.997).

Table 6 Summary of results – prior sunitinib

AXIS	**Axitinib**	**Sorafenib**	**Difference**	**HR (95% CI)**
Median PFS (months)	4.8	3.4	1.4	0.74 (0.57 to 0.96)
Median OS (months)	15.2	16.5	-1.3	0.997 (0.78 to 1.27)
RECORD-1	**Everolimus**	**Placebo**	**Difference**	**HR (95% CI)**
PFS; prior-sunitinib group (months)	3.9	1.8	2.1	0.34 (0.23 to 0.51)
Adjusted OS; ITT group (months)	14.8	10	4.8	0.53 (NR)
STC	**Axitinib**	**BSC**	**Difference**	**HR (95% CI)**
Median PFS (months)	6.3	1.7	4.6	NR
Median OS (months)	16.6	8.3	8.3	NR
RENCOMP	**Axitinib**	**BSC**	**Difference**	**HR (95% CrI)**
Median OS (months)	NR	NR	NR	0.62 (0.38 to 0.997)

Abbreviations: BSC, best supportive care; CI, confidence interval; CrI, credible interval; HR, hazard ratio; NR, not reported; OS, overall survival; PFS, progression-free survival.

Source: manufacturer's submission

Evidence Review Group comments

4.20 The ERG stated that there were a few limitations with the literature search conducted by the manufacturer, some of which were addressed by the manufacturer after clarification. Despite these limitations, the ERG considered that the search was adequate and accurately reflected the research question. The ERG was satisfied that the clinical-effectiveness evidence for axitinib was based on the subgroups of patients who were previously treated with sunitinib and cytokines only, in line with the marketing authorisation for axitinib. It stated that AXIS, TARGET and RECORD-1 were good-quality clinical trials with sound methodologies, except for the method used to adjust for crossover in TARGET (censoring of patients). The ERG considered that censoring often introduces bias

and they agreed that the method used in RECORD-1 (RPSFT) was more appropriate for adjusting for crossover. The ERG noted that although the outcomes reported in the AXIS trial corresponded with those in the final scope, only progression-free survival and overall survival outcomes were presented for the comparison of axitinib with best supportive care.

4.21 The ERG noted that baseline patient characteristics were not reported separately for the prior-cytokine groups in both the AXIS and TARGET trials. Therefore, the comparison of the trial populations for the indirect comparison was based on the ITT groups in the 2 trials. The ERG noted that the patient characteristics of the ITT groups in the AXIS and TARGET trials were reasonably similar, with slight differences observed in the MSKCC scores and number of metastatic sites. The ERG considered that the potential bias associated with the hazard ratio for overall survival in TARGET may limit the robustness of the indirect comparison in the prior-cytokine group.

4.22 The ERG noted that the comparison of patient characteristics in the AXIS and RECORD-1 trials for the prior-sunitinib group was based on the ITT group of the RECORD-1 placebo arm, in the absence of any data on patient characteristics in the prior-sunitinib group for the placebo group. The ERG also noted the differences between the AXIS and RECORD-1 trials that were highlighted by the manufacturer (see section 4.17), which could limit the evidence available to compare axitinib with best supportive care in a prior-sunitinib group. The ERG was uncertain whether an STC presents a valid and reliable estimate of the clinical effectiveness of axitinib compared with best supportive care in this group of patients. The ERG considered that there could be potential bias associated with the STC because it involves a comparison of 2 single treatment

arms and not a comparison of randomised treatment allocation. The ERG also stated that the results of the STC could not be verified because individual patient data from the AXIS trial were used; and the uncertainties around the results could not be assessed because standard errors and 95% confidence intervals were not presented. However, the ERG indicated that the analysis seemed to have been performed correctly and the reporting of methods, results and limitations was clear despite the issues identified. The ERG stated that the use of observational data (which is a lower level of evidence) from the RENCOMP database was a potential source of uncertainty because patients were not randomly allocated to receive the second-line treatments and the reasons for discontinuing first-line treatments were not known.

5 Comments from other consultees

5.1 Clinical specialists stated that sunitinib and pazopanib were generally used in clinical practice to treat people in whom cytokines have failed. They noted that very few people begin treatment with cytokines, as most people with advanced disease will be treated with the recommended VEGF drugs, which are sunitinib and pazopanib. The clinical specialists also stated that everolimus, which can be funded by the Cancer Drugs Fund in England, is currently used to treat advanced renal cell carcinoma after the failure of VEGF-targeted agents. They indicated that axitinib would be a reasonable choice for people who have received a previous cytokine and previous sunitinib. They also indicated that the choice of second-line treatment may also depend on the toxicity profile of the treatment options. Axitinib would be preferred for people with lung disease and difficult-to-treat diabetes, while everolimus would be preferred for people with cardiac disease and difficult-to-control hypertension. The clinical specialists considered that patients who

received pazopanib as first-line therapy may also benefit from axitinib (although there is no evidence for this), given the similarity of efficacy of sunitinib and pazopanib.

5.2 The clinical specialists stated that axitinib should be given by an experienced oncologist with a team of specialist nurses to support the patients. They noted that, like other TKIs and everolimus, axitinib is relatively easy to use in terms of clinical requirements and patient acceptability. The clinical specialists emphasised that axitinib would only be started after failure of first-line clinical or radiological therapy, and stopped in the presence of toxicity or disease progression. They indicated that axitinib was a well-tolerated drug except for the high occurrence of hypertension. However, they noted that hypertension was a common adverse effect associated with all TKIs used for treating renal cancer.

5.3 Patient organisations and experts stated that there was an unmet clinical need for a second-line treatment when prior systemic therapies have failed or are unsuitable for people with advanced disease. They expressed their support for axitinib as an option for this group of people, as the evidence from the AXIS trial shows that axitinib is more efficacious than other first generation VEGFR inhibitors and has fewer adverse effects. They also expressed their support for axitinib as a drug that meets all the end-of-life-criteria used by NICE when recommending drugs with incremental cost-effectiveness ratios (ICERs) above the £30,000 per quality-adjusted life year (QALY) threshold. Patient organisations and experts indicated that axitinib has the potential to extend life, enable people to enjoy a longer period of active life, delay the need for palliative care and allow people with renal cell carcinoma to enjoy a better quality of life and contribute to society. They also

highlighted its potential to delay the onset of tumour pain and postpone the need for pain management in late-stage disease.

5.4 Patient organisations emphasised that approving axitinib for use in the NHS would decrease the mental health burden of patients, carers, families and the wider community who are aware of the existence of an effective active treatment for the disease. They stated that patients were aware of and concerned about the adverse effects associated with active cancer therapies, but still prefer to receive the treatment because of the lack of other options and because the adverse effects can be managed adequately. Patient organisations also stated that patients have reacted positively to the relatively low adverse effects profile of axatinib compared with other available treatments, based on the experiences of patients in the AXIS trial and in the USA. Patient organisations recognised that the oral administration of axitinib at no extra cost would be an added advantage to patients. They expressed their concern that an approval of axitinib may have an impact on prescribing pazopanib in clinical practice, because people treated with pazopanib instead of sunitinib will be denied second-line treatment with axitinib. They also expressed their concern that people who were treated with first-line therapies other than sunitinib or cytokines in clinical trials may not benefit from axitinib, and indicated this will reduce the support and participation of patients in future renal cell carcinoma trials.

5.5 NHS organisations stated that axitinib may represent an extra line of care in the treatment pathway of advanced renal cancer, after appropriate consideration of the effectiveness, adverse effects and limitations of the clinical trial. They considered that axitinib should be used in secondary care and possibly homecare, and that it would be prescribed by a specialist. NHS organisations noted that

the lack of any clinical or economic evidence comparing axitinib with best supportive care has resulted in some difficulties in estimating the budget impact on the NHS, as axitinib is a relatively new drug. However, they highlighted that there are likely to be extra costs associated with axitinib compared with best supportive care because of the adverse effects observed in the AXIS trial and as stated in the prescribing information for axitinib. They also noted that extra costs would be incurred from managing the patient access scheme for the drug. NHS organisations indicated that NHS staff will need training on management of renal cell carcinoma with axitinib, and patients will need educating on the risks and benefits of the drug.

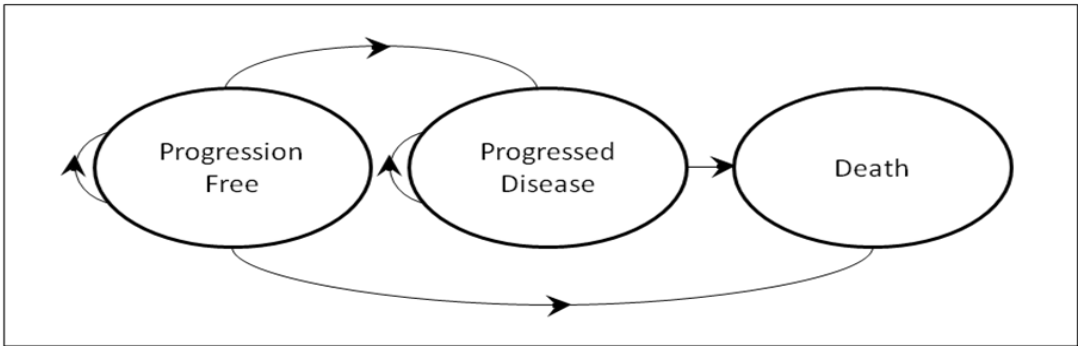
6 Cost-effectiveness evidence

6.1 The manufacturer conducted a systematic review of the literature and identified 3 studies on the cost-effectiveness of active treatments compared with best supportive care for advanced and metastatic renal cell carcinoma after failure of a systemic therapy. None of the studies identified looked at axitinib, so the manufacturer carried out a de novo analysis on the cost effectiveness of axitinib compared with best supportive care for treating advanced renal cell carcinoma after failure of prior treatment with sunitinib or a cytokine. The economic evaluation was based on the 2 separate populations specified in the marketing authorisation for axitinib (the prior-sunitinib and the prior-cytokine groups).

6.2 A 3-state Markov cohort model was developed, based on previous modelling of metastatic cancer using Microsoft Excel. All patients enter the model in the ‘progression-free’ health state and in each cycle can progress to the ‘progressed disease’ health state,

progress from either of these health states to 'death', or remain in their current health state. The model had a lifetime horizon of 10 years consisting of 4-weekly cycles, included a half-cycle correction, and both costs and benefits were discounted at 3.5%. The analysis was performed from the perspective of the NHS and personal social services.

Figure 1 Model structure



Source: manufacturer's submission (figure 29, page 132).

6.3 The proportion of patients in each health state at each point in time was calculated directly from parametric survival function equations. For the axitinib, prior-cytokine group, the Weibull model was used to extrapolate the overall survival and progression-free survival data because it was considered to provide the best model fit. Survival models based on log-logistic and Gompertz parametric distributions were used in a sensitivity analysis for overall survival, as of the 5 parametric distributions tested by the manufacturer, they provided the next best model fit. However, the log-normal and Gompertz distributions were used in the sensitivity analysis to extrapolate progression-free survival. For the best supportive care treatment group, parametric survival curves were generated by applying the hazard ratios from the indirect comparison (see section 4.13) to the parametric survival functions used to model the axitinib treatment group.

6.4 For the axitinib, prior-sunitinib group, the log-normal model was used in the base case to extrapolate overall survival data because it provided the best model fit. The Weibull and Gompertz distributions provided the next best fits, so these were explored in a sensitivity analysis. The Weibull model was used for progression-free survival data in the base-case analysis, while the log-normal and Gompertz models were explored in the sensitivity analysis. For the best supportive care group, the prior-sunitinib progression-free survival and the ITT population-adjusted hazard ratios (see section 4.18) were applied to the everolimus STC curves to generate a modelled AXIS-like, prior-sunitinib progression-free survival and overall curves. Only the Weibull option was used in the economic model for the survival curves, because the log-normal model did not support the use of hazard ratios. In a sensitivity analysis, the overall survival hazard ratio generated from the indirect comparison of the RENCOMP analysis and the prior-sunitinib overall survival analysis from the AXIS trial was applied to the axitinib parametric survival functions to generate parametric survival curves for the best supportive care group.

6.5 The utility values used in the model were derived from the AXIS trial using the EQ-5D questionnaire. The analysis was based on the full AXIS population because the p values indicated no statistically significant difference between any of the subgroups (including the prior-sunitinib and prior-cytokine subgroups). The baseline mean utility value for the axitinib group was 0.73. The mean utility value for the progression-free health state was 0.69, based on the average of the EQ-5D index value at each time point in AXIS and weighted by the number of patients still on treatment at that time point. The utility value for the progressed disease health state was 0.61, based on the weighted average of the mean utility at the end of treatment. The utility values used in the model were assumed to

reflect the adverse event profile of the treatment from the AXIS trial. In a systematic review of the literature, the manufacturer did not identify any sources reporting utility values for people with advanced renal cell carcinoma receiving best supportive care after sunitinib treatment has failed. Therefore, the manufacturer assumed that people receiving best supportive care would have the same utility value as people receiving axitinib in the model. Utility values from previous NICE appraisals, derived from a phase II study of sunitinib in a cytokine-refractory population, were explored in a sensitivity analysis. Quality of life was assumed to remain constant for each health state in the post-trial period.

6.6 The average cycle (4 weeks/28 days) cost of axitinib [redacted] using the proposed patient access scheme was based on the recommended dosing schedule of 5 mg twice daily until disease progression. The cost was adjusted for the relative dosing intensity observed in the AXIS trial, which was 102%. A dosing intensity of 80% was explored in a scenario analysis to reflect the lower intensities observed in clinical practice and previous NICE appraisals. Drug discontinuation occurred because of disease progression or adverse events. The probabilities of discontinuation per cycle applied in the model were 0.80% and 1.26% for the prior-cytokine and prior-sunitinib groups respectively, although the discontinuation rates from adverse events alone were assumed to be the same. No administration cost was included in the model because axitinib is administered orally and the patient access scheme is a flat net discount applied at the point of invoice. No drug costs were assumed for best supportive care.

Table 7 Unit costs associated of therapies in the economic model

Items	Value
Axitinib cost per 56 tablets (without PAS)	£3517/cycle (28 days)
Axitinib cost per 56 tablets (with PAS)	[redacted]
Dosing intensity (base case)	102.0% (SD 35.2%)
Dosing intensity (scenario analysis)	80%
Best supportive care costs	none
Administration costs	none

Abbreviations: PAS, patient access scheme; SD, standard deviation.

Source: manufacturer's submission (table 43, page 158).

6.7 The costs associated with routine medical monitoring were based on those used in previous NICE appraisals and validated with expert clinical opinion to ensure consistency with current clinical practice. These costs were applied equally to the axitinib and best supportive care groups because patients are assumed to receive the same management regardless of their treatment. For the progression-free state, the total cost per cycle (£109.69) was based on 1 GP visit per cycle, 1 tumour scan per 3 cycles and 1 blood test per cycle. The total cost per cycle for the progressed disease state was £319, and this included 1 GP visit per cycle, 3 visits by a specialist community nurse every 2 cycles, and 28 vials of pain medication per cycle. A scenario analysis was explored where patients visited an oncologist rather than their GP. This resulted in a total management cost per cycle of £176.69 for the progression-free state and £386 for the progressed disease state. Costs associated with adverse events were included in the model for the progression-free state only, and were assumed to be similar for the prior-sunitinib and prior-cytokine groups. Only the costs for grade 3 and 4 adverse events (which occurred in over 5% of the patient population) were considered. For the axitinib group the relevant adverse events were hypertension (£424 per episode) and diarrhoea (£544 per episode), and the cost of anaemia (£2368.47

per episode) was applied to the best supportive care group in a sensitivity analysis.

Table 8 List of health states and associated costs in the model

Health states	Items	Mean frequency or duration	Unit cost (£)	Cost per cycle (£)
Progression free – base case	GP visit[a]	1 visit per cycle	£53.00/visit	£53.00
	CT scan[b]	1 scan per 3 cycles	£160.00/scan	£53.33
	Blood test[c]	1 test per cycle	£3.36/test	£3.36
Total cost per cycle – progression-free state				**£109.69**
Progressed disease - base case	GP visit[d]	1 visit per cycle	£53.00/visit	£53.00
	Specialist community nurse[d]	3 visits per 2 cycles	£84.00	£126.00
	Pain medication[e]	28 vials per cycle	£5.00/dose	£140.00
Total cost per cycle – progressed disease state				**£319.00**
Progression free – scenario analysis assuming oncologist visits	Oncologist visit[f]	1 visit per cycle	£120/visit	£120.00
	CT scan	-	-	As above
	Blood test	-	-	As above
Total cost per cycle – progression-free state (scenario analysis)				**£176.69**
Progressed disease – scenario analysis assuming oncologist visits	Oncologist visit[f]	1 visit per cycle	£120/visit	£120.00
	Specialist community nurse[e]	-	-	As above
	Pain medication[e]	-	-	As above
Total cost per cycle – progressed disease state (scenario analysis)				**£386.00**

[a] GP visits: Curtis L (2011) Unit Costs of Health and Social Care 2011. [b] Code RA14Z Computerised Tomography Scan, more than three areas.
[c] Code DAP823 Haematology [Excluding Anti-Coagulant Services].
[d] Code 202AF Band 2 Palliative/respite care: adult face-to-face NHS Trust and PCT combined Reference Costs 2007-08.
[e] BNF section 4.7.2 Opioid analgesics (morphine sulphate 1 mg/mL, net price 50-mL vial = £5.00 (http://www.medicinescomplete.com/mc/bnf/current/3502.htm#_3502).
[f] Medical Oncology Code 370 for the 'National Schedule of Reference Costs Year : 2010-11 - NHS Trusts and PCTs combined Consultant Led: First Attendance Non-Admitted Face to Face'.

Source: manufacturer's submission (table 44, page 159).

Prior-cytokine group

6.8 The results of the economic analysis showed that most of the additional QALY gains from axitinib treatment were observed in the progression-free state. The base-case results showed an incremental cost of [redacted] and an incremental QALY gain of [redacted] for axitinib compared with best supportive care after failure of a prior cytokine. This resulted in an ICER of £65,326 per QALY gained. The manufacturer also presented the ICER without the patient access scheme, which was [redacted] per QALY gained.

Table 9 Summary of QALY gain and costs by health state (patient access scheme)

Health state	QALY (axitinib)	QALY (BSC)	Increment	Absolute increment	% absolute increment
Progression free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state	**Cost (axitinib)**	**Cost (BSC)**	**Increment**	**Absolute increment**	**% absolute increment**
Progression free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; QALY, quality-adjusted life year.

Source: manufacturer's submission (tables 52 and 53, page 166).

Table 10 Base-case results – prior cytokine (patient access scheme)

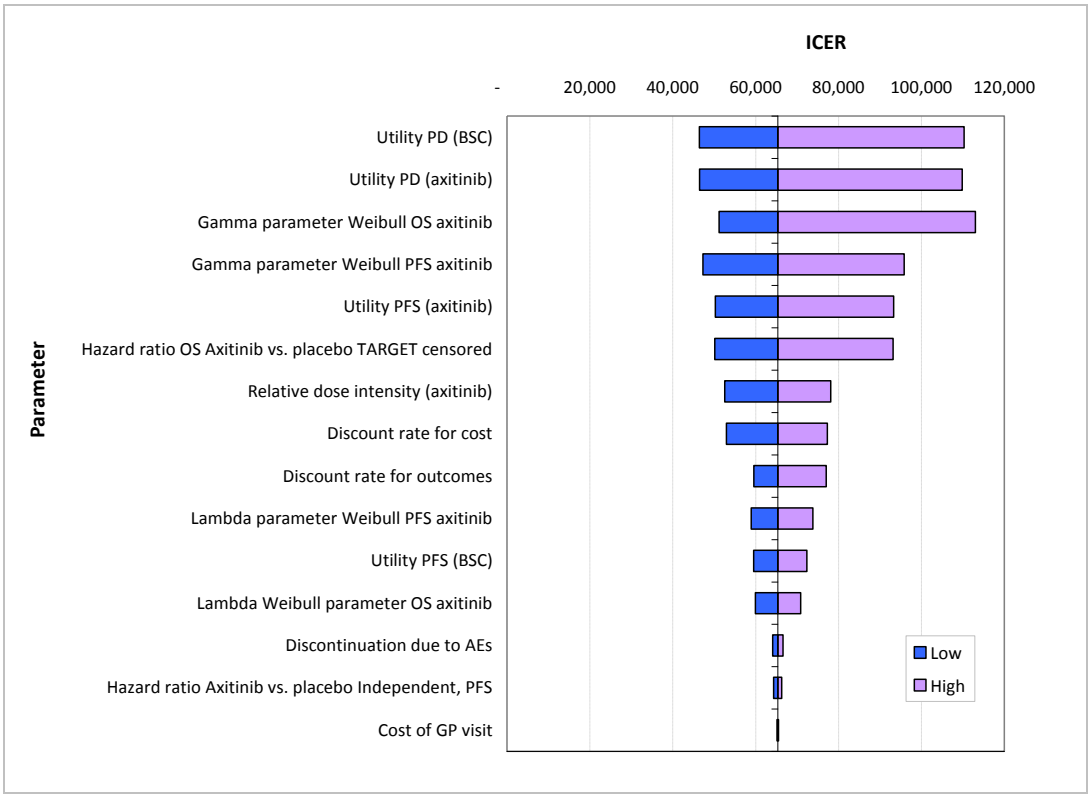
Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) (QALYs)
Best supportive care	[redacted]	[redacted]	[redacted]	–	–	–	–
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	65,326

Abbreviations: LYG, life years gained; QALY, quality-adjusted life year.

Source: manufacturer's submission (table 55, page 167).

6.9 The manufacturer performed a univariate deterministic sensitivity analysis by varying some of the model input parameters by ±20% of their base-case value. The cost-effectiveness result for the prior-cytokine group was most sensitive to changes in the progressed disease utility values for the axitinib and best supportive care groups and progression-free utility value for the axitinib group, with ICERs ranging from £46,402 to £110,317 per QALY gained. The base-case ICER was also sensitive to changes in the values of the survival parameters for the axitinib group, the overall survival hazard ratio of axitinib compared with best supportive care, and the relative dose intensity of axitinib. Changes in the cost estimates (such as GP visits, specialist nurse visits, and tumour scans), discontinuation because of adverse events, changes in the progression-free utility for the best supportive care group, and changes in the IRC-assessed progression-free survival hazard ratio from the AXIS trial showed very little sensitivity to the base-case results. The ICERs ranged from £59,530 to £72,373 per QALY gained.

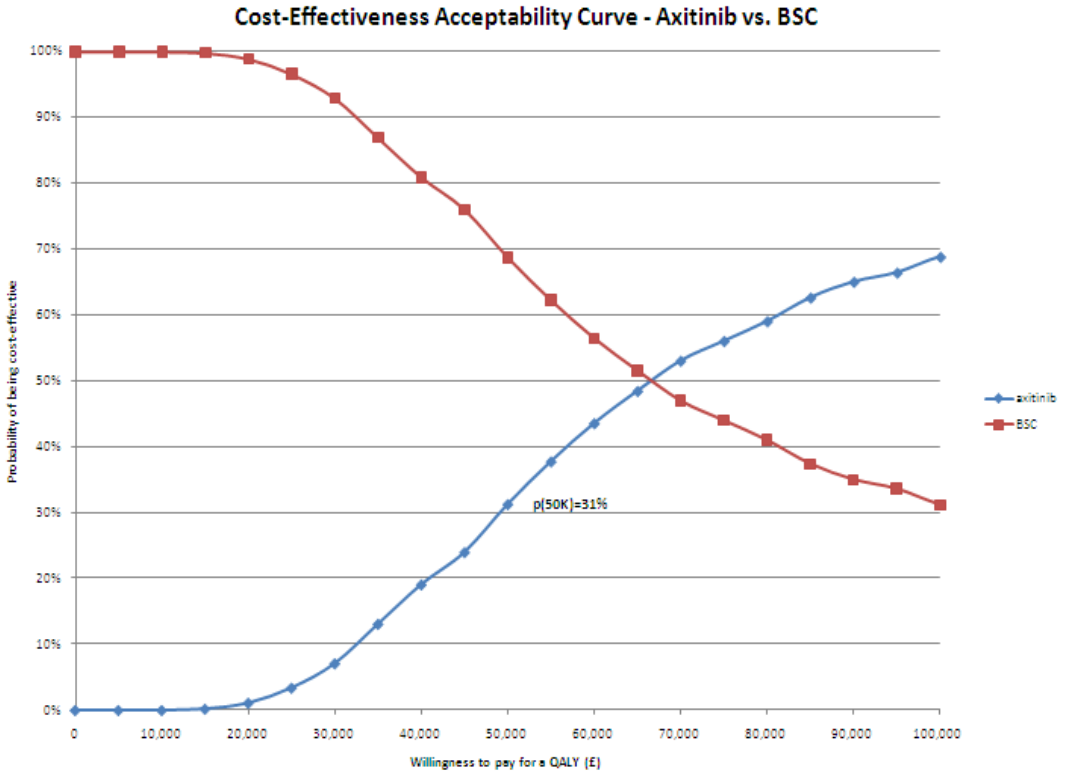
Figure 2 Tornado diagram – prior cytokine (patient access scheme)



Abbreviations: AE, adverse effect; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PFS, progression-free survival.
Source: manufacturer's submission (figure 36, page170).

6.10 The probabilistic sensitivity analysis indicated that axitinib would have a 31% and [redacted] chance of being cost effective compared with best supportive care, if the maximum acceptable ICER was £50,000 per QALY gained for the prior-cytokine group in the patient access scheme and non-patient access scheme scenarios respectively.

Figure 3 Cost effectiveness acceptability curve – prior cytokine (patient access scheme)



Abbreviations: BSC, best supportive care; QALY, quality-adjusted life year.
Source: manufacturer's submission (figure 38, page 172).

6.11 The manufacturer also explored various scenario analyses to account for the uncertainties associated with some of the assumptions in the base-case model. The scenario analyses explored the effect on the ICER of: using alternative parametric distributions (log-normal, log-logistic and Gompertz) to extrapolate survival, using external data to estimate utility values, reducing the dosing intensity of axitinib to 80%, assuming an oncologist visit instead of a GP visit for estimating costs in the progression-free state, assuming time horizons of 5 and 10 years, and using alternative discount rates of 0% and 6%. The scenario analyses all resulted in ICERs ranging from £51,546 to £84,255 per QALY gained. The ICER was most sensitive to the use of the Gompertz

distribution for extrapolating overall survival (£84,255 per QALY gained), use of a 5-year time horizon (£83,752 per QALY gained), and reduction in the dosing intensity of axitinib (£51,546 per QALY gained). It was least sensitive to the use of a 15-year time horizon and costing based on oncologist visit (£64,359 and £66,410 per QALY gained respectively).

Table 11 Scenario analysis results – prior cytokine (patient access scheme)

Parameter	Base case	Scenario analysis	ICER
Base case			£65,326
Method of PFS extrapolation	Weibull	Log-normal Gompertz	£71,535 £63,702
Method of OS extrapolation	Weibull	Log-logistic Gompertz	£52,260 £84,255
Axitinib and BSC utility estimates	AXIS trial	Second-line utilities (advanced and mRCC appraisal and everolimus appraisal)	£59,654
Axitinib relative dosing intensity	AXIS trial	Estimated real-world dosing intensity (everolimus appraisal)	£51,546
Ongoing medical management in pre-progression state	GP Management	Oncologist management	£66,410
Time horizon	10 years	5 years 15 years	£83,752 £64,359
Discount rate	3.5% costs and QALYs	0% 6%	£60,015 £69,164

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; mRCC, metastatic renal cell carcinoma; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year.
Source: manufacturer's submission (table 57, page 174).

Prior-sunitinib group

6.12 The results of the economic analysis showed that there were additional QALY gains with axitinib before and after progression, although more than half of the additional QALYs gained were

observed before progression. The incremental cost and incremental QALYs gained from treating advanced renal cell carcinoma with axitinib compared with best supportive care in the prior-sunitinib group were [redacted] and [redacted] QALYs respectively. This resulted in an ICER of £40,933 per QALY gained for the prior-sunitinib group. The ICER without the patient access scheme discount was [redacted] per QALY gained.

Table 12 Summary of QALY gain and costs by health state (patient access scheme)

Health state	QALY (axitinib)	QALY (BSC)	Increment	Absolute increment	% absolute increment
Progression free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state	**Cost (axitinib)**	**Cost (BSC)**	**Increment**	**Absolute increment**	**% absolute increment**
Progression free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; QALY, quality-adjusted life year.
Source: manufacturer's submission (tables 52 and 53, page 166).

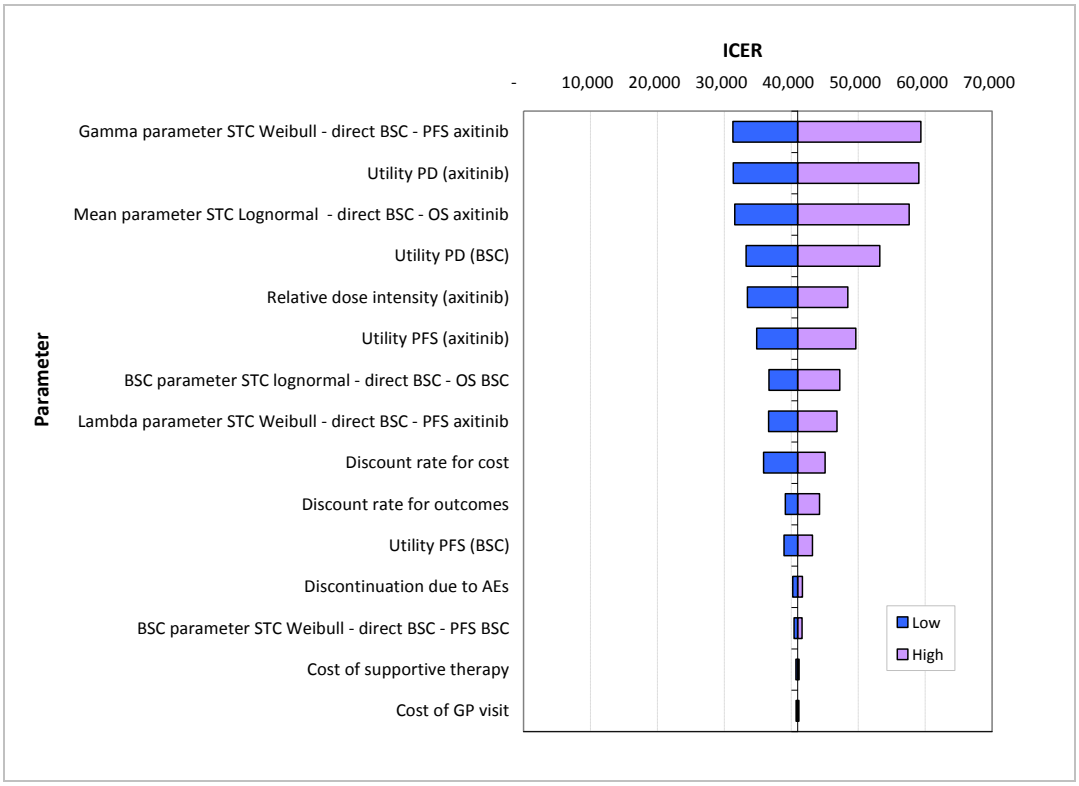
Table 13 Base-case results – prior sunitinib (patient access scheme)

Technology	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) (QALYs)
Best supportive care	[redacted]	[redacted]	[redacted]	–	–	–	–
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	40,933

Abbreviations: LYG, life years gained; QALY, quality-adjusted life year.
Source: manufacturer's submission (table 55, page 167).

6.13 The univariate sensitivity analysis performed for the prior-sunitinib group showed that the ICER was most sensitive to changes in the survival parameter values for the axitinib group, with ICERs ranging from £31,271 to £59,373 per QALY gained. The base-case ICER was also sensitive to changes in the progressed disease utility values for the axitinib and best supportive care groups and progression-free utility value for the axitinib group, the resulting ICERs ranging from £31,324 to £59,044 per QALY gained. Changes in the relative dosing intensity of axitinib also showed some sensitivity to the base-case results (£33,434 to £48,432 per QALY gained). Changes in the cost estimates (such as GP visits, specialist nurse visits, and tumour scans), discontinuation because of adverse events, and changes in the progression-free utility for the best supportive care group showed very little sensitivity to the base-case results. The ICERs ranged from £38,927 to £43,157 per QALY gained.

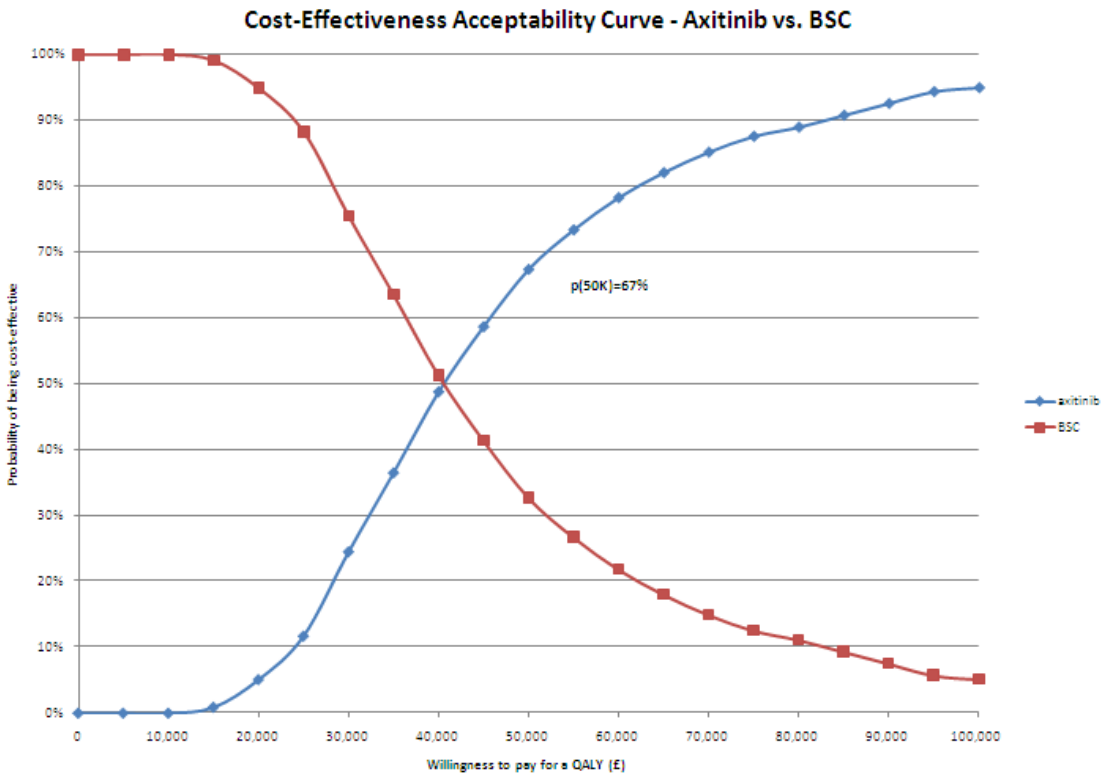
Figure 4 Tornado diagram – prior sunitinib (patient access scheme)



Abbreviations: AE, adverse event; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PFS, progression-free survival; STC, simulated treatment comparison.
Source: manufacturer's submission (figure 37, page 171).

6.14 The probabilistic sensitivity analysis showed that axitinib would have a 67% and [redacted] chance of being cost effective compared with best supportive care if the maximum acceptable ICER was £50,000 per QALY gained for the prior-sunitinib group in the patient access scheme and non-patient access scheme scenarios.

Figure 5 Cost effectiveness acceptability curve – prior sunitinib (patient access scheme)



Abbreviations: BSC, best supportive care; QALY, quality-adjusted life year.
Source: manufacturer's submission (figure 40, page 173)

6.15 Several scenario analyses were also performed to explore the effect on the ICER of: using alternative parametric distributions to extrapolate survival, methods of comparison with best supportive care, using external data to estimate utility values, reducing the dosing intensity of axitinib to 80%, assuming an oncologist visit instead of a GP visit for estimating costs in the progression-free state, time horizons of 5 and 10 years, and using alternative discount rates of 0% and 6%. The scenario analyses all resulted in ICERs ranging from £32,846 to £56,113 per QALY gained. The ICER was most sensitive to the use of the Weibull and Gompertz distribution to extrapolate overall survival using the RENCOMP method of comparison (£56,113 and £54,851 per QALY gained

respectively), use of a 5-year time horizon (£48,283 per QALY gained) and reducing the dosing intensity of axitinib (£32,846). It was least sensitive to the use of alternative distributions to extrapolate progression-free survival using the STC method of comparison, use of a 15-year time horizon, use of a 6% discount rate, and costing based on oncologist visit (ICERs ranged from £39,207 to £42,806 per QALY gained).

Table 14 Scenario analysis results – prior sunitinib (patient access scheme)

Parameter	Base case	Scenario analysis		ICER
Base case				£40,933
Method of PFS comparison	STC Weibull via ITT RECORD-1 BSC population	STC lognormal via ITT RECORD-1 BSC		£42,428
		STC Weibull via everolimus sunitinib refractory – BSC PFS		£40,509
Method of OS comparison	STC lognormal via RECORD-1 ITT BSC population	STC Weibull via RECORD-1 ITT BSC		£39,906
		STC Weibull via everolimus sunitinib refractory – BSC RPSFT		£33,268
		RENCOMP	Weibull	£56,113
			Log-normal	£43,384
			Gompertz	£54,851
Axitinib and BSC utility estimates	AXIS study	Second-line utilities (advanced/mRCC appraisal and everolimus appraisal)		£37,059
Axitinib relative dosing intensity	AXIS study	Estimated real-world dosing intensity (everolimus appraisal)		£32,846
Medical management pre-progression	GP management	Oncologist management		£42,074
Time horizon	10 years	5 years 15 years		£48,283 £39,207
Discount rate	3.5% costs and QALYs	0% 6%		£38,254 £42,806

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; mRCC, metastatic renal cell carcinoma; OS, overall survival; PFS,

progression-free survival; QALY, quality-adjusted life year; RPSFT, rank preserving structural time failure; STC, simulated treatment comparison.
Source: manufacturer's submission (table 58, page 174).

6.16 After a clarification request, the manufacturer used separate dosing intensities of [redacted] and [redacted] for axitinib in the prior-cytokine and prior-sunitinib groups respectively. This resulted in ICERs of £66,955 and £40,639 per QALY gained with the patient access scheme. After clarification, the manufacturer also provided the results of a univariate sensitivity analysis, where the model input parameters for the 2 groups were varied using the 95% confidence interval. The results showed that the base-case results were most sensitive to the utility values, with some of the scenarios resulting in negative ICERs. However, the manufacturer stated that the results should be interpreted with caution because some of the univariate scenarios could be clinically implausible. No subgroup analysis was performed by the manufacturer because the economic evaluation was based on 2 subgroups from the main AXIS study.

Evidence Review Group comments

6.17 The ERG was satisfied with the manufacturer's modelling approach, which was consistent with other published economic studies of advanced renal cell carcinoma and used a population that was reflective of the actual clinical population. It re-emphasised that approximately 94% of the renal cell carcinoma population will receive sunitinib for first-line treatment, and 6% will receive cytokines. The ERG was satisfied that the best supportive care comparator used in the model reflected recommended UK clinical practice and was in line with the final scope for this appraisal. The ERG was concerned that the lifetime time horizon of 10 years used in the base-case model may not be in line with real life expectancy. Nevertheless, it considered the time horizon to be acceptable because the sensitivity analysis performed by the manufacturer

showed that increasing the time horizon to 15 years had minimal impact on the base-case results (see section 6.11 and 6.15).

6.18 The ERG accepted the manufacturer's choice of the distributions used in the base-case and scenario analysis. However, it noted that in some cases, the method of selection of the distributions was unclear and contradictory, and in one instance the decision was based on expert opinion of clinical plausibility. The ERG also noted the manufacturer's clarification that patients who withdrew from treatment prematurely because of adverse events were still followed up in the trial, and were included in the estimation of progression-free survival and overall survival curves for the axitinib arm rather than the best supportive care arm. The ERG stated that this approach will only be valid if the patients were followed up for progression as well, and not for survival only. The ERG considered that the estimate of the QALYs in the axitinib group may have been affected if they were not followed up for progression, because these patients are expected to progress earlier once they stop treatment. It also noted that, because of earlier progression to the progressed disease state, the overall costs would be higher for the axitinib group compared with the cost in the model, which was set at 'zero' for these patients. The ERG indicated that making this adjustment in the model would increase the base-case ICERs, although the impact would be limited by the relatively small group of patients withdrawing from the treatment prematurely.

6.19 The ERG was satisfied with the manufacturer's assumption that the utility value was the same for people receiving axitinib and those receiving best supportive care. They agreed that while people on axitinib may experience utility decreases from adverse events, those receiving best supportive care would experience utility decreases from actively progressing uncontrolled disease. The

ERG was concerned that the utility value applied in the progressed disease state remained constant after entry into that state, when it should actually decline as patients near the end of life. It noted that applying declining utility values would increase the ICER slightly if axitinib patients stay in the progressed disease state for longer than best supportive care patients (prior-sunitinib group), but no impact would be observed if the time spent in the progressed disease state is the same for both treatment arms (prior-cytokine group). The ERG noted from the AXIS clinical study report that health states were based on US valuation. It stated that the utilities used in the model appear to be too high because studies have shown that the US valuation was consistently higher than UK valuation. The ERG noted that standard errors should have been used with the utility values in the analysis instead of standard deviation because the reported utility values were sample means. The ERG stated that it could not reproduce the original utility for the progression-free state; a higher utility value of 0.73 was produced instead using the method described in the manufacturer's submission.

6.20 The ERG noted that the percentage of people with hypertension was less than 1% in the TARGET study, rather than the 2% which was applied in the model. However, the impact on the ICER was negligible given the small costs associated with treating this adverse event. The ERG also noted that the relative dosing intensity of axitinib was based on a sample mean from the trial, so standard error should have been used rather than standard deviation. The ERG considered that the assumption that the cost of death is a fixed cost in the model underestimates the uncertainty associated with the cost in the model. Therefore, it calculated the standard error for the cost of death (104.3) from the reference provided by the manufacturer and conducted an exploratory analysis.

6.21 The ERG concluded given the result of the sensitivity analyses that the model for the prior-cytokine group was not very robust to most of the structural assumptions. However, the ERG agreed that the model for the prior-sunitinib group was robust to the majority of the assumptions, with most of the scenarios producing ICERs lower than £50,000 per QALY gained. Although it noted that the evidence for this population was derived from an STC which was not based on randomised treatment allocation, so there is potential bias in the evidence.

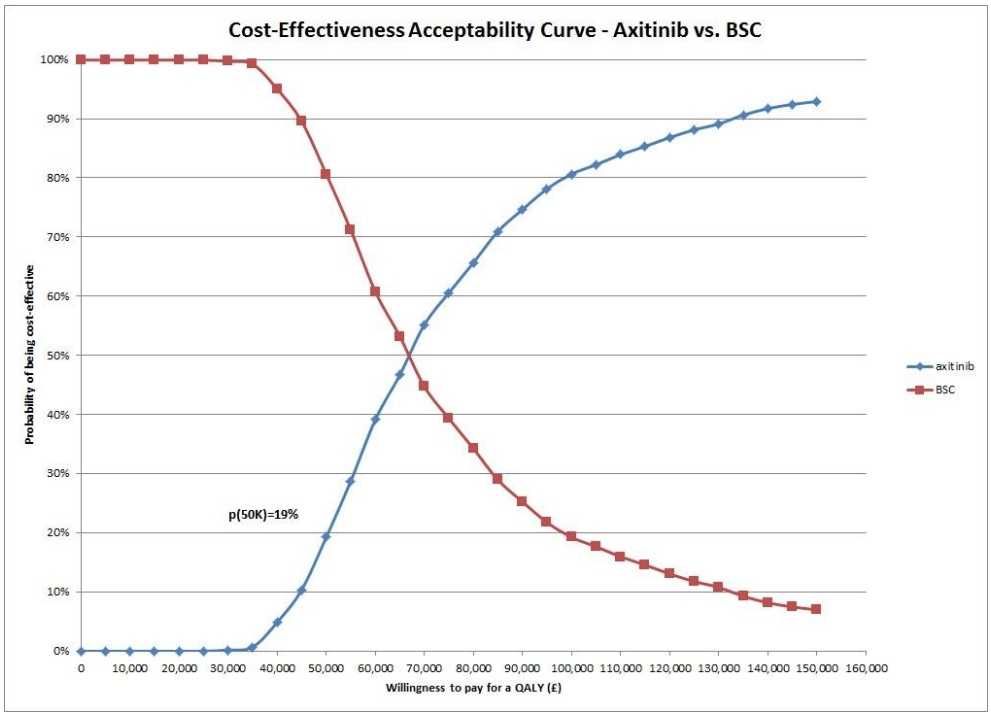
ERG's exploratory analyses

6.22 The ERG undertook exploratory analyses within which adjustments were made to some of the parameters used in the manufacturer's base-case sensitivity analysis. It varied the model input parameters using the 95% confidence intervals provided by the manufacturer during clarification. The most obvious difference from the manufacturer's analysis was observed when the overall survival hazard ratio for the prior-cytokine group was varied. It showed very high sensitivity compared to the base-case result, with an upper limit ICER of £423,083 per QALY with the patient access scheme. The prior-sunitinib group results were still relatively stable compared to the base-case ICER.

6.23 The ERG replaced the standard deviations used for the utilities and relative dosing intensity of axitinib with standard errors in the probabilistic sensitivity analysis. The standard errors used (0.0035, 0.0175 and 1.86%) reduced the uncertainty in the ERG's progression-free utility (section 6.19), the progressed disease utility and the dosing intensity of axitinib. The ERG also specified the cost of death as an uncertain parameter by providing a standard error of 104.43 in the probabilistic sensitivity analysis. The revised results showed that axitinib has a 20% (■) and 83% (■) chance of being

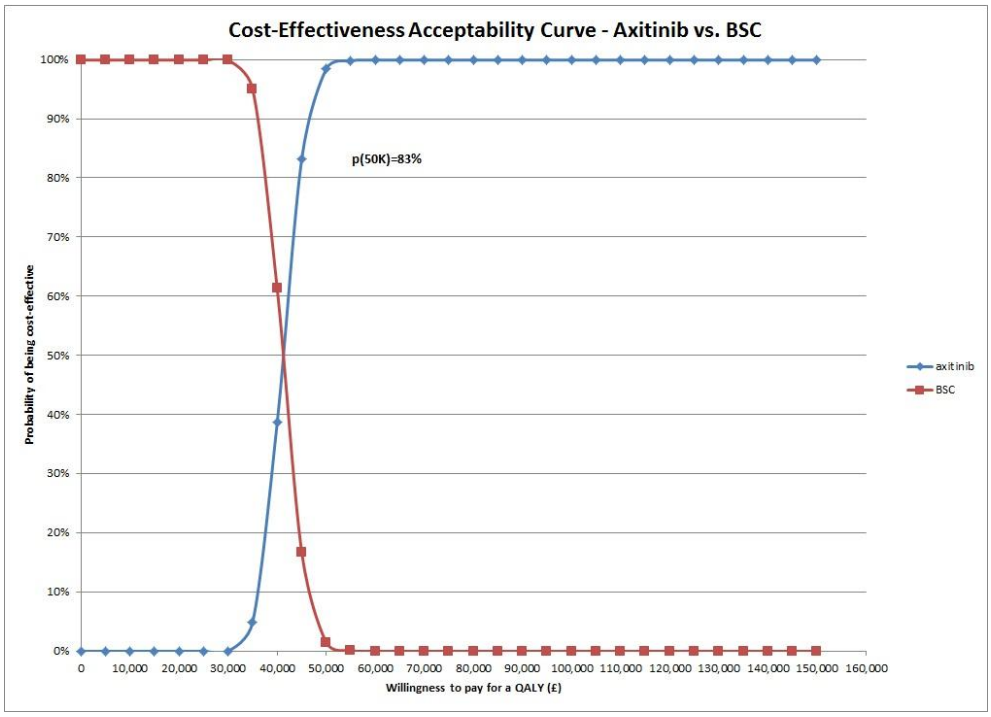
cost effective if the maximum acceptable ICER was £50,000 per QALY gained for the prior-cytokine and prior-sunitinib groups respectively, in the patient access scheme and (non-patient access scheme) scenarios. The ERG emphasised that the results for the prior-sunitinib group should be interpreted with a level of caution because the assumptions for the STC estimates could not be quantified (that is, no measures of uncertainty were provided for the adjustment factor for the best supportive care arm). In addition, the source of evidence for the prior-sunitinib group was limited compared with the prior-cytokine group.

Figure 6 Cost effectiveness acceptability curve – prior cytokine (patient access scheme)



Abbreviations: BSC, best supportive care; QALY, quality-adjusted life year.
Source: ERG report (figure 5.28, page 107).

Figure 7 Cost effectiveness acceptability curve – prior sunitinib (patient access scheme)



Abbreviations: BSC, best supportive care; QALY, quality-adjusted life year.
Source: ERG report (figure 5.30, page 108)

6.24 The ERG further explored several scenarios using different assumptions for the utility estimates with the patient access scheme. First, the ERG used separate utility values for the prior-cytokine and prior-sunitinib groups based on the data provided by the manufacturer during clarification. This resulted in a slightly lower ICER for the prior-cytokine group (£62,885 per QALY gained) and a slightly higher ICER for the prior-sunitinib group (£42,095 per QALY gained). Secondly, lower utility values were applied for progression-free (0.66) and progressed disease (0.54) based on the assumption of lower UK valuation. The ICERs increased slightly to £68,433 and £44,125 per QALY gained for the prior-cytokine and prior-sunitinib groups respectively. Finally, a higher utility value of 0.72 was assumed for the best supportive care group in order to test the impact of treatment-specific utility estimates before

progression (that is, the progression-free health state). This also had very minimal impact on the ICERs: £66,639 per QALY gained for the prior-cytokine group and £41,363 for the prior-sunitinib group with the patient access scheme.

7 End-of-life considerations

7.1 The manufacturer considers that axitinib may be eligible for appraisal as an 'end-of-life' treatment.

Table 15 End-of-life criteria for axitinib

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	All model cases examined for sunitinib-refractory patient population result in mean best supportive care survival estimates of less than 24 months. In addition, the systematic review of survival after sunitinib failure carried out to support this submission indicates that real-world survival times in the absence of second-line treatment are expected to be less than a year.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Axitinib results in expected survival gains of greater than 3 months over best supportive care in all model cases evaluated.
The treatment is licensed or otherwise indicated for small patient populations	The annual number of patients eligible to receive axitinib in the sunitinib- or cytokine-refractory patient population is 1580 in year 1, rising to 1743 in year 5.

Source: manufacturer's submission (table 59, page 177).

7.2 The ERG noted that the manufacturer's submission and previous NICE technology appraisals indicated that approximately 4000

people are diagnosed with advanced renal cell carcinoma in England and Wales every year. The ERG stated that there was no direct evidence to suggest that axitinib increases survival by more than 3 months compared with best supportive care. However, it noted that the indirect comparison performed for the prior-cytokine population suggested that axitinib increased overall survival compared with best supportive care by 4.2 months and 5.1 months when using uncensored and censored data respectively from TARGET. Based on these considerations, the ERG agreed that axitinib meets the 3 end-of-life criteria above.

8 Equalities issues

8.1 The patient expert stated that younger and healthier patients may benefit more from axitinib than older patients with additional health issues, who may find the adverse effects more difficult to tolerate. Patient organisations stated that people with rare cancers such as kidney cancer often feel unfairly treated because the shortage of recommended treatments for rare cancers means they do not have equity of access to NHS-funded treatments. Patient organisations also stated that approving axitinib will avoid the inequalities associated with access of second-line therapies through the Cancer Drugs Fund. The NHS organisations stated that the scope does not specify consideration of axitinib for people whose condition is unsuitable for first-line immunotherapy.

9 Innovation

9.1 The manufacturer and patient organisations stated that there was an unmet need for people with advanced renal cell carcinoma whose disease had progressed after first-line treatment. This is because there is currently no second-line drug recommended by NICE for this group of people. The manufacturer stated that the

availability of axitinib was expected to offer a step-change in the second-line management of advanced renal cell carcinoma by improving survival beyond what is expected with best supportive care, while maintaining health-related quality of life. The manufacturer highlighted that axitinib is the first and only VEGFR-TKI proven to be superior to an active comparator in a second-line patient population. The manufacturer also stated that the knowledge that there is a treatment available will provide patients with renewed hope and optimism, and may help in alleviating the psychological burden associated with the disease which would normally have an impact on quality of life.

10 Authors

Nwamaka Umeweni
Technical Lead

Dr Bhash Naidoo
Technical Adviser

with input from the Lead Team (Stephen O'Brien, Rachel Elliott and David Chandler).

Appendix A: Supporting evidence

Related NICE guidance

Published

- Everolimus for the second-line treatment of renal cell carcinoma. NICE technology appraisal guidance 219 (2011). Available from www.nice.org.uk/guidance/TA219
- Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma. NICE technology appraisal guidance 178 (2009). Available from www.nice.org.uk/guidance/TA178

Under development

There is no related guidance under development for this technology.

Appendix B: Clinical efficacy section of the draft European public assessment report

The European public assessment report for axitinib was published on 13 September 2012; it is available from:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002406/human_med_001573.jsp&mid=WC0b01ac058001d124