NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Pazopanib for the first-line treatment of advanced and/or metastatic renal cell carcinoma

This briefing presents the key issues arising from the manufacturer's submission, Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that this briefing is a summary of the information available and should be read with the full supporting documents.

GlaxoSmithKline made an original manufacturer's submission to NICE in April 2010. This included an assessment of the cost effectiveness of pazopanib using interim overall survival data (cut-off date 23 May 2008). As these data were considered immature by the manufacturer, an addendum was submitted in July 2010 containing updated final overall survival analysis data (cut-off date 15 March 2010). The addendum also contained details of the proposed patient access scheme which was submitted simultaneously to the NICE Patient Access Scheme Liaison Unit. The original submission and addendum were reviewed by the ERG and NICE technical team and clarification questions sent to the manufacturer.

In the original manufacturer's submission the manufacturer was asked to provide:

- Clarification of the statistical issues surrounding crossover analysis (rank preserving structural failure time [RPSFT] and inverse probability of censoring weighted [IPCW] analyses).
- Further details and analysis of the clinical and cost-effectiveness data for the treatment-naive population.

In the updated submission (addendum) the manufacturer was asked to provide:

- An explanation of the clinical relevance of the non-inferiority margin (1.22) chosen to demonstrate a comparable treatment effect between pazopanib and sunitinib.
- Further cost-effectiveness data relating to the patient access scheme for a range of hazard ratios.

Licensed indication

Pazopanib (Votrient, GlaxoSmithKline) has a conditional marketing authorisation for the first-line treatment of advanced renal cell carcinoma[1] and for patients who have received prior cytokine therapy for advanced disease. Only the indication for the first-line treatment of advanced renal cell carcinoma falls within the remit of this appraisal.

As part of the conditional marketing authorisation for pazopanib, the manufacturer is required to provide further data supporting the efficacy and safety of pazopanib compared with sunitinib in patients with advanced and/or metastatic renal cell carcinoma, including the outcome of an ongoing head-to-head study of pazopanib versus sunitinib as first-line treatment (VEG108844, COMPARZ) and a pooled analysis of data from studies VEG108844 and VEG113078 (a substudy of VEG108844 in patients of Asian family origin).

Key issues for consideration

- In the trial providing the main source of evidence (VEG105192), a total of 41 (51%) treatment-naive patients in the placebo arm crossed over to receive pazopanib. To adjust for this crossover, the manufacturer used the rank preserving structural failure time (RPSFT) method to estimate overall survival. Although RPSFT is a proven method, it gave uncertain results, with wide confidence intervals around the hazard ratio derived from the RPSFT analysis. What are the implications of this in interpreting the clinical and cost effectiveness of pazopanib compared with sunitinib, interferon-α and best supportive care? Are the estimates of median overall survival used in the base case plausible (27.8 months for pazopanib, 26.8 months for sunitinib, 15.8 months for interferon-α and 12.1 months for best supportive care)?

[1] A conditional marketing authorisation is granted to a medicinal product that fulfils an unmet medical need when the benefit to public health of immediate availability outweighs the risk inherent in the fact that additional data are still required. The marketing authorisation holder is likely to provide comprehensive clinical data at a later stage.

- Of the treatment-naive population (n = 233) in VEG105192, only seven patients (3%) were from the UK. The sunitinib versus interferon-α study (Motzer et al. 2009) was multicentre, and the UK was one of 11 countries taking part. However, it was not reported how many patients were from the UK. Is the population in the VEG105192 study (and the population included in the indirect comparison) generalisable to the patient population in UK clinical practice?

- Is the indirect comparison used to generate the survival estimates robust given:
  - that some of the baseline characteristics (Eastern Cooperative Oncology Group [ECOG] performance status, cell histology) of patients participating in the included studies differed
  - the indirect comparison base case was sensitive to the source of data used to derive estimates of relative effectiveness. When only the Hancock study (MRC RE-01) was used to represent interferon-α rather the pooled data from the five interferon-α trials, there was a reduction in the relative effectiveness of pazopanib compared with interferon-α and sunitinib for both progression-free and overall survival.
  - the manufacturer assumed that medroxyprogesterone acetate and vinblastine would have no impact on progression-free survival and overall survival and could therefore be considered as palliative treatment equivalent to placebo/best supportive care.

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	Patients with advanced renal cell carcinoma who have received no prior systemic therapy
Intervention	Pazopanib
Comparators	• Sunitinib • Immunotherapy with interferon-α • Best supportive care
Outcomes	• Progression-free survival • Overall survival • Tumour response rate • Health-related quality of life and patient-reported outcomes • Adverse effects of treatment
Economic evaluation	Cost effectiveness of treatments is expressed in terms of incremental cost per quality-adjusted life year (QALY). The time horizon for estimating the clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs are considered from an NHS and Personal Social Services perspective.

1.2 Evidence Review Group comments

1.2.1 Population

In the statement of the decision problem, the manufacturer specified the population as patients with advanced renal cell carcinoma who have not received any previous treatment, in accordance with the conditional marketing authorisation. The final scope for this appraisal used 'advanced and/or metastatic' in reference to the patient population to be included. However, in the European Public Assessment Report for pazopanib, the European

Medicines Agency defines ‘advanced’ as cancer that has started to spread, meaning that the patient population stated in the decision problem is consistent with the scope of this appraisal.

The submitted evidence relates to the use of pazopanib in patients with advanced and/or metastatic renal cell carcinoma who have received no prior systemic therapy.

1.2.2 Intervention

The intervention described in the decision problem is pazopanib. The current licensed dosage of pazopanib is 800 mg once daily, with dose modifications of 200 mg increments based on individual tolerability in order to manage adverse reactions. This is consistent with the appraisal scope and the licensed indication.

The mechanism of action of pazopanib was clearly outlined, emphasising the differences in toxicity compared with sunitinib.

1.2.3 Comparators

The choice of sunitinib as the main comparator was appropriate. The manufacturer presented an indirect comparison for pazopanib versus sunitinib using interferon-α and placebo/best supportive care data for the comparative and economic evaluations in this appraisal.

1.2.4 Outcomes

The ERG stated that the choice of outcomes was appropriate and inclusive.

1.2.5 Economic evaluation

The manufacturer submitted a model analysing the cost effectiveness of pazopanib for treatment-naive patients. The ERG stated that the choice of model appeared to be appropriate given the decision problem and the data available.

1.3 Statements from professional/patient groups and nominated experts

The clinical specialists agreed that the introduction of sunitinib represented a major advance for treating patients with metastatic renal cell carcinoma. The specialists noted that sunitinib is currently the only NICE approved tyrosine kinase inhibitor for the treatment of advanced renal cell carcinoma. However, because some patients have significant dose-limiting side effects with sunitinib, the clinical specialists stated that pazopanib would provide an alternative therapy, especially as it may have an improved side-effect profile compared with sunitinib.

The clinical specialists explained that because pazopanib will be administered by clinical teams who are already dispensing and caring for patients taking sunitinib, there will be no significant impact on resources. In addition, the degree of monitoring is the same as that required for patients taking sunitinib.

The clinical specialists suggested that it would be reasonable to consider pazopanib for a similar patient population to the one studied in VEG105192, that is, for the first or second-line treatment of patients with advanced renal cell carcinoma, with a good or intermediate prognosis. It was noted that treatments are given until disease progression.

Patient groups commented on the potential benefit of an improved side-effect profile of pazopanib compared with sunitinib. It was also noted that pazopanib would increase the therapies available to clinicians, who can then choose the most appropriate treatment with the greatest chance of success.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

Evidence on pazopanib came primarily from the treatment-naive sub-population of a phase III randomised controlled trial (VEG105192). Two non-randomised pazopanib studies (VEG102616 and VEG107769 [the unblinded extension study of VEG105192, enrolling patients on open-label pazopanib who progressed on placebo]) were provided as supportive evidence. This premeeting briefing summarises VEG105192.

VEG105192 was a multicentre, randomised double-blind study conducted in 80 centres in 23 countries across Europe, Asia, South America, Australia and New Zealand. The study compared a once-daily, oral 800 mg dose of pazopanib with placebo. A total of 435 patients with advanced or metastatic renal cell carcinoma were enrolled into the study (233 treatment-naive and 202 cytokine pre-treated patients). The treatment-naive population, which forms the focus of the manufacturer's submission, comprised 155 patients randomised to pazopanib and 78 randomised to placebo. The study was designed to be a crossover trial; patients receiving placebo with documented disease progression were allowed to receive pazopanib through the open-label extension study (VEG10776) if the treating clinician felt that they could benefit and met the eligibility criteria for the study. The primary outcome was progression-free survival, based on a blinded imaging assessment by the Independent Review Committee (IRC). Secondary outcomes were overall survival, tumour response and health-related quality of life.

The patient flow diagram of VEG105192 can be found on page 67 of the manufacturer's original submission and the baseline characteristics of the treatment-naive population are shown in table 6.7 on page 56 of the manufacturer's original submission.

Progression-free survival results

The progression-free survival data for the treatment-naive population are summarised in table 1. There was a 60% reduction in disease progression based on the blinded imaging assessment by the IRC at the 23 May 2008 cut-off date for patients receiving pazopanib compared with patients receiving placebo. The manufacturer also performed sensitivity analyses of progression-free survival based on actual scan dates and investigators' assessment to confirm the robustness of the analysis.

Although there appears to be some discrepancy between the medians reported for progression-free survival based on investigator assessment and the IRC assessment, the manufacturer suggests that this may be explained by the smaller size of the treatment-naive population. This is because the hazard ratios and the medians for progression-free survival in the overall study population for IRC and investigator assessment correlate closely. This is further explained on pages 70–1 of the manufacturer's original submission.

No further progression-free survival data were provided with the manufacturer's addendum.

Table 1 Progression-free survival in VEG105192 (23 May 2008 cut-off, taken from tables 5.12–5.14, pages 69–71 of the manufacturer's original submission)

	IRC assessment, ITT		IRC, actual scan dates, ITT		Investigator assessment, ITT	
	Pazopanib	**Placebo**	**Pazopanib**	**Placebo**	**Pazopanib**	**Placebo**
N (%)subjects progressed or died	73 (47%)	57 (73%)	73 (47%)	57 (73%)	93 (60%)	64 (82%)
Kaplan-Meier estimates for median PFS (months)	11.1	2.8	10.8	2.9	7.5	4.1
95% CI (months)	7.4 to 14.8	1.9 to 5.6	7.4 to 14.8	1.9 to 5.4	7.2 to 10.3	1.9 to 5.6
Hazard ratio (95% CI)	0.40 (0.27 to 0.60)		0.36 (0.24 to 0.55)		0.47 (0.33 to 0.68)	
Stratified log-rank p-value	$p < 0.001$		$p < 0.001$		$p < 0.001$	

IRC: Independent Review Committee; ITT: intention-to-treat analysis; PFS: progression-free survival

The median PFS values used in NICE technology appraisal guidance 169 ('Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma [Motzer 2007]) were 10.8 months versus 4.1 months (investigator assessments; hazard ratio [HR] 0.52, 95% CI 0.43 to 0.62) and 11 months versus 5.1 months (IRC; HR 0.54, 95% CI 0.44 to 0.66) for sunitinib versus interferon-α.

Overall survival results

At the time of the interim overall survival analysis (23 May 2008) 31 (40%) of treatment-naive patients randomised to receive placebo in VEG105192 had crossed over to receive pazopanib through the VEG107769 extension study. Subsequently, nine additional treatment-naive patients receiving placebo were enrolled in VEG107769. Therefore a total of 40 (51%) treatment-naive patients randomised to placebo had crossed over to receive pazopanib at the

15 March 2010 cut-off date. Details of all the post-progression therapies are provided in table 1.3 of the manufacturer's addendum.

The manufacturer highlighted that there are a number of statistical approaches to adjust for the crossover in survival analysis but none are universally accepted because each have a number of different limitations. The manufacturer undertook a number of approaches to adjust for the crossover:

- censoring at the point of crossover or when the patient receives other anticancer therapies
- inverse probability of censoring weighted (IPCW) analysis
- rank preserving structural failure time (RPSFT) analysis
- no post-study therapy analyses.

The first two approaches are minor modifications to established methods of survival analysis. Censoring at the time of crossover involves measuring survival from randomisation to the time of crossover to pazopanib or to another anticancer therapy, with all other patients having survival measured from randomisation to death or last contact. The IPCW analysis aims to adjust for crossover by recreating the population that would have been seen if crossover had not occurred. Patients who do not crossover get a greater weighting in order to correct for the resulting bias. The RPSFT method estimates the overall survival of patients randomised to receive placebo assuming that they had not crossed over, that is, as if they had remained on placebo for the duration of the trial. The RPSFT method proportionally 'shrinks' the estimated amount of additional survival given to patients who crossed over to receive pazopanib. For details of how the methods were applied see pages 11–25 of the manufacturer's addendum and pages 19–24 of the ERG report.

The final overall survival results for the treatment-naive population in VEG105192 are summarised in table 2. Overall survival for the treatment-

naive, intention-to-treat population, unadjusted for crossover was 22.9 months (95% confidence interval [CI] 17.6 to 25.4 months) for patients randomised to pazopanib and 23.5 months (95% CI 12.0 to 34.3 months) for patients randomised to placebo. The hazard ratio for overall survival was 1.01 (95% CI 0.72 to 1.42, p = 0.525). However, the results indicate that treatment with pazopanib was consistently associated with survival benefit compared with placebo across the different methodologies used to adjust for crossover. A reduction in death ranging from approximately 20–70% was seen, depending on the methodology used and whether or not adjusted for patient baseline characteristics.

Table 2 Summary of final overall survival results for treatment-naive patients in VEG105192 (15 March 2010 cut-off) adjusted for impact of crossover

Method	**HR (95% CI)**	**p-value**
ITT analysis (Log rank/Pike estimator)‡	1.01 (0.72 to 1.42)	p = 0.525
ITT analysis (Cox regression)		
Unadjusted for baseline characteristics	1.027 (0.728 to 1.447)	p = 0.8812
Adjusted for baseline characteristics	0.859 (0.602 to 1.223)	p = 0.3985
Censoring on crossover or on receiving other anticancer therapies (Cox regression)		
Unadjusted for baseline characteristics	0.797 (0.493 to 1.289)	p = 0.3553
Adjusted for baseline characteristics	0.640 (0.390 to 1.049)	p = 0.0769
IPCW (informative censoring defined as crossover to pazopanib or on receiving other anticancer therapy)		
Adjusted for baseline characteristics	0.642 (0.266 to 1.248)	p = 0.160*
RPSFT unweighted		
Unadjusted for baseline characteristics	N/A	N/A
Adjusted for baseline characteristics	0.310 (0.073 to 1.715)	0.194*
RPSFT weighted		
Unadjusted	0.501 (0.136 to 2.348)	0.548*
No post-study therapy (Log rank/Pike estimator)†		
No post-study therapy	0.300 (0.150 to 0.620)	p < 0.001
No post-study therapy, excluding patients still on study therapy	0.380 (0.200 to 0.720)	p < 0.001
Patients eligible for post-study therapy but chose not to	0.380 (0.170 to 0.820)	p < 0.001

HR: hazard ratio; CI: confidence interval; ITT: intention-to-treat; IPCW: inverse probability of censoring weighted analysis; RPSFT: rank preserving structural failure time analysis

Notes:

1. Patients with missing values for the covariates were assigned the mean for the trial population.
2. ‡Not adjusted for baseline characteristics except stratification on baseline eastern Cooperative Oncology Group (ECOG) performance status.
3. †Not adjusted for stratification factors.
4. *Bootstrap 95% CI and p-value.

The overall survival values (Motzer 2009) used in NICE technology appraisal guidance 169 ('Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma') were:
Median overall survival for ITT population was 26.4 months for sunitinib and 21.8 months for interferon-α. No adjustment was made for crossover. The HR for overall survival was taken from the no post-study therapy group and was 0.647 (95% CI 0.483 to 0.870). In this group median overall survival was 28.1 months versus 14.1 months.

The hazard ratio estimate of 0.501 for overall survival for pazopanib versus placebo, obtained using the weighted RPSFT analysis (unadjusted) was used by the manufacturer for the base case in the indirect comparison and in the economic evaluation. The manufacturer justified the choice of 0.501 on the basis that the value lies within the range of estimates obtained from the different methods used to adjust for crossover and that the RPSFT method had been considered an acceptable approach for NICE technology appraisal guidance 179 ('Sunitinib for the treatment of gastrointestinal stromal tumours') and the ongoing appraisal of everolimus for the treatment of advanced and/or metastatic renal cell carcinoma.

Indirect comparison

No head-to-head trials were available for the analysis of the efficacy of pazopanib versus the comparators in the appraisal. Therefore, the manufacturer completed searches to identify trials of comparator interventions. In the submission the manufacturer presented results of an indirect comparison that was undertaken to estimate the relative effect of pazopanib compared with sunitinib, interferon-α and best supportive care.

Seven studies were included in the indirect comparison and they included one study for pazopanib compared with placebo (VEG105192), one trial for sunitinib compared with interferon-α (Motzer et al. 2009) and five studies that directly compared interferon with a non-interferon control therapy (medroxyprogesterone acetate and vinblastine; Negrier 2007; Hancock 2000 [MRC RE01]; Kriegmair 1995; Pyrhonen 1999; Steineck 1990). The study by

Motzer et al. (2009) was a multicentre, international study that included the UK, but it was not reported how many patients were from the UK. Of the five interferon-α studies that were included in the indirect comparison, only one (Hancock 2000) took place in the UK. A summary of the seven studies can be found in tables 5.27 and 5.28 on pages 82–6 of the manufacturer's original submission.

The populations in the pazopanib (VEG105192) and sunitinib (Motzer 2009) studies were comparable, with the exception that the sunitinib study recruited a higher proportion of patients with a baseline ECOG of 0 than VEG105192 (approximately 60% versus 40%). Both studies restricted entry to patients with renal cell carcinoma with either clear cell or predominately clear cell histology. The average age of patients in both studies was 60 years and 83–91% of patients had prior nephrectomy. The patient populations in the five interferon-α studies were generally similar. All patients had advanced renal cell carcinoma. The age of patients ranged from 60–66 years and 57–100% of patients had prior nephrectomy. Three of the interferon-α studies included some patients with baseline ECOG performance status 2.

The five trials comparing interferon-α with control therapy (equivalent to placebo/best supportive care) were used to provide the indirect pathway from pazopanib to interferon α and then to sunitinib.

Details of the methodology and data sources used in the indirect comparison can be found in section 5.7 on pages 95–8 of the manufacturer's original submission.

Following the availability of final overall survival data (15 March 2010) for VEG105192, the manufacturer presented updated results for a base-case indirect analysis in the addendum to the original submission.

Median overall survival data included in the indirect comparison were estimated using the Weibull survival model used in the economic evaluation.

In the base-case scenario (derived using the RPSFT weighted method) the median overall survival for pazopanib, sunitinib and placebo/best supportive care was 27.8, 26.8 and 15.8 months respectively, with respect to the point estimates (see table 3).

Table 3 Model projections of median overall survival for comparators

Outcome	Comparator	HR vs IFN-α	Median (months)	95% CI	
				Percentiles	Normal approximation
Overall survival	Pazopanib – weighted RPSFT	0.627	27.8	5.7 to 137.9	–43.6 to 99.2
	Pazopanib – IPCW	0.803	20.6	7.0 to 60.9	–7.7 to 48.9
	Pazopanib – ITT	1.264	11.9	7.6 to 18.8	6.3 to 17.6
	Pazopanib – no post-study therapy	0.476	38.7	17.0 to 81.9	4.5 to 72.9
	Sunitinib	0.647	26.8	18.9 to 37.9	17.0 to 36.5
	IFN-α	1.000	15.8	15.8 to15.8	NA to NA
	Placebo/BSC	1.251	12.1	9.9 to14.9	9.6 to 14.6

HR: hazard ratio; IFN-α: interferon-α; CI: confidence interval; RPSFT: rank preserving structural failure time analysis; IPCW: inverse probability of censoring weighted analysis; ITT: intention-to-treat; BSC: best supportive care.

Table 4 Indirect comparison of overall survival (base-case results)

	Overall survival	
	HR	95% CI
Data inputs		
Pazopanib vs. placebo/BSC	0.501	0.140 to 2.350
IFN-α vs. placebo/BSC‡	0.799	0.674 to 0.948
Sunitinib vs. IFN-α	0.647	0.483 to 0.870
Results of indirect comparison		
Pazopanib vs. IFN-α	0.627	0.173 to 2.269
Pazopanib vs. sunitinib	0.969	0.359 to 2.608

HR: hazard ratio; CI: confidence interval; BSC: best supportive care; IFN-α: interferon-α.

† HR adjusted for crossover using weighted unadjusted RPSFT method with imputation for missing data

‡ Includes all 5 IFN-α trials: MRC RE-01 (Hancock 2000 data); Negrier 2007; Steineck 1990; Kriegmair 1995; Pyrhonen 1999

$ Patients with no post-study cancer therapy (Motzer 2009)

Table 4 shows that pazopanib is associated with a decreased risk of death (37% reduction) compared with interferon-α and pazopanib appears to have comparable efficacy with sunitinib in terms of overall survival. The manufacturer highlighted that the 95% confidence intervals around the hazard ratios were wide, indicating a level of uncertainty with the estimates. The manufacturer stated that this was a result of the uncertainty in the RPSFT-derived overall survival hazard ratios for VEG105192.

The manufacturer undertook a number of sensitivity analyses, which included varying the hazard ratio for overall survival in VEG105192 by using the different methods for adjusting for crossover and varying the interferon α studies included. The results of the sensitivity analyses can be found in tables 1.19–1.32 on pages 27–30 of the manufacturer's addendum. The manufacturer concluded that the results of these sensitivity analyses of the indirect comparison were similar to those of the base-case analysis.

Safety

At the 23 May 2008 cut-off, 91% of pazopanib patients (141/155) had experienced an adverse event, of which 87% (135/155) were related to study medication, 37% (57/155) were grade 3 and 6% (9/155) were grade 4. In the placebo group the rates were 74% (58/78), 37% (29/78), 13% (10/78) and 6% (5/78), respectively.

The indirect comparison (using interferon-α data [Steinbeck 1990]) of specific adverse events for pazopanib relative to sunitinib showed generally lower rates for pazopanib, although these were statistically significant only for fatigue (hazard ratio [HR] 0.21, 95% CI 0.06 to 0.77). Rates for alopecia (HR 3.63, 95% CI 0.05 to 253.99) and hypertension (HR 2.69, 95% CI 0.11 to 63.56) were on average lower for sunitinib. A summary of the indirect comparison of adverse events for pazopanib versus sunitinib is presented in table 5.

Table 5. Indirect comparison of adverse events for pazopanib versus sunitinib

Class	Outcome	HR (95% CI)
Gastrointestinal disorders	Diarrhoea	0.60 (0.02 to 16.11)
	Vomiting	-
	Nausea	0.56 (0.02 to 14.32)
	Mucositis/stomatitis	-
General disorders and administration site conditions	Fatigue	0.21 (0.06 to 0.77)
Skin and subcutaneous tissue disorders	Alopecia	3.63 (0.05 to 253.99)
	Hand-foot syndrome/PPE	-
	Rash	0.23 (0.02 to 2.91)
Investigations	Total bilirubin increased	0.05 (0 to 2.55)
Vascular disorders	Hypertension	2.69 (0.11 to 63.56)
Metabolism and nutrition disorders	Anorexia	0.4 (0.13 to 1.29)
Respiratory, thoracic and mediastinal disorders	Epistaxis	0.09 (0 to 7.68)
Infections and infestations	Flu-like symptoms	-
Blood and lymphatic system disorders	Anaemia	0.28 (0.07 to 1.08)
	Leucopenia	0.14 (0 to 7.66)
	Thrombocytopenia	0.46 (0.01 to 17.29)

Health-related quality of life

Only VEG105192, which compared pazopanib with placebo, and the study by Motzer et al. (2009), which compared sunitinib with interferon-α, reported health-related quality of life (HRQoL) data.

For VEG105192, there was no statistically significant difference between pazopanib and placebo for any of the instruments used (EORTC-QLQ-C30, EQ-5D, EQ-5D-VAS). For the comparison of sunitinib with interferon-α, sunitinib patients had a statistically significantly better quality of life than interferon-α patients, as measured by the EQ-5D, EQ-5D-VAS and the Functional Assessment of Cancer Therapy (FACT) Kidney Symptom Index Disease-related Symptom (FKSI-DRS) Index, FACT-Kidney Symptom Index – 15-item scale (FKSI-15 Index) and the FACT-General Scale (FACT-G). No indirect comparison was made for this outcome.

2.2 Evidence Review Group comments

Overall, the ERG noted the substantial amount of evidence on the efficacy and safety of pazopanib submitted by the manufacturer. In addition, it was noted that a great deal of effort had gone into providing these data and the methods were generally well reported.

The manufacturer's inclusion criteria were limited to randomised controlled trials, resulting in a smaller, but higher quality evidence base than if non-randomised studies had been included. Overall, the methodological quality of the included studies was good.

Although the ERG identified a few additional reports that might have been considered relevant, there was no evidence that any important data had been omitted from the submission. However, the ERG stated that potentially relevant studies may have been excluded by the manufacturer based on their definition of what could and could not be included in terms of best supportive care and the exclusion of studies reporting interleukin-2.

The ERG noted that the RPSFT method used to deal with crossover of placebo-treated patients to pazopanib in VEG105192 was an appropriate method to use. However, the ERG had concerns with some aspects of the RPSFT analysis. The timing of the final analysis meant that data may not have been mature enough for an effect size to be estimated with sufficient accuracy. The ERG highlighted that the chosen statistical method is sensitive to the maturity of the data. The ERG also noted that the manufacturer had presented an unweighted RPSFT analysis for overall survival results in the VEG105192 study in the original submission but had presented weighted RPSFT analyses in the addendum. The ERG stated the weighted RPSFT advocated by the manufacturer may not have been appropriate given the lack of an adequately developed methodology required to analyse the data robustly. The RPSFT weighted method provided a higher hazard ratio than

the unweighted method, and although this does affect the results, the change in method has not necessarily been favourable to pazopanib.

The ERG commented that in the absence of a trial directly comparing pazopanib with sunitinib, the manufacturer attempted to provide an informative estimate of the relative effectiveness and safety of pazopanib by a formal indirect comparison between sunitinib and interferon-α studies. The ERG commented that there was uncertainty surrounding the estimates reported by the indirect comparison, relating to the data used to derive the hazard ratios used to estimate relative effectiveness. While the pazopanib and sunitinib studies limited inclusion to patients with ECOG performance status 0 or 1, three of the interferon studies included some patients with ECOG performance status 2 (that is, a worse prognosis). The ERG stated that theoretically, this might make the relative performance of pazopanib and sunitinib compared with interferon-α appear better than it actually is. However, the manufacturer stated that there is no evidence that the effects of treatment with pazopanib, sunitinib or interferon-α, measured in terms of hazard ratios, differ in subgroups of patients defined on the basis of performance status.

2.3 Statements from professional/patient groups and nominated experts

Regarding the relevance of VEG105192 to patients in the UK, clinical specialists noted that the endpoints of the study were clinically relevant and appropriate for patients in the UK with advanced and/or metastatic renal cell carcinoma. The clinical specialists also commented that experience with other drugs of the same class indicates that the benefit seen in clinical trials was similar to that seen in the wider population, and this could also be the case for pazopanib.

Clinical specialists stated that progression-free survival is a meaningful surrogate measure of outcome in advanced renal cell carcinoma and is widely

accepted. They also considered that it is the most relevant outcome measure in a patient population that has access to second-and third-line therapies.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

The manufacturer's updated economic submission incorporated a proposed patient assess scheme and the final overall survival data for VEG105192 (cut-off date 15 March 2010). Under the proposed access scheme, a straight discount of 12.5% will apply at the point of invoicing from the time of positive NICE guidance (part A of the patient access scheme). No additional criteria will need to be met. In the event that pazopanib does not meet non-inferiority in the head-to-head trial (the COMPARZ study, results expected in 2012), the manufacturer proposes a future financial rebate for the specialised population and subsequent list price reduction (part B of the patient access scheme).

The economic model presented in the addendum was based on the model in the original submission. The manufacturer submitted a de novo model analysing the cost effectiveness of pazopanib for treatment-naive patients. The model compared pazopanib with interferon-α, sunitinib and best supportive care. The model was described by the manufacturer as a 'partitioned survival' model, characterised by three mutually exclusive health states: alive pre-progression, alive post-progression and dead.

Unlike a Markov model, which models transitions between health states explicitly using transition probabilities, the partitioned survival model calculates the proportion of patients in each treatment arm at any time after starting treatment, using parametric survival curves fitted to empirical data on overall survival and progression-free survival over time. The proportion of patients in the 'alive post-progression' health state at any given time was calculated as the difference between overall survival and progression-free survival.

In the model, pazopanib was assumed to be administered until disease progression or death (if occurring before progression). After starting treatment, patients were assumed to be in an 'alive pre-progression' health state, and to be at risk of disease progression and/or death over time. Patients who experienced disease progression were assumed to discontinue treatment and transition to an 'alive post-progression' health state and to stay in that state until death. A description of the model can be found on pages 150–1 of the manufacturer's original submission. Tables of the summary key features of the analysis and assumptions made in the economic model can be found on pages 153–71 of the manufacturer's original submission.

Effectiveness data

Most of the effectiveness data were based on the pivotal study VEG105192, but relative effectiveness data were based on the indirect comparison. In the model the underlying effectiveness of treatments was assessed compared with the effectiveness of interferon-α. Clinical effectiveness data (progression-free and overall survival) used in the economic model for the base-case analysis are summarised in table 6 below (updated values from the original submission are in bold). The resulting survival curves are shown in figures 2.1–2.3 on pages 37–8 of the manufacturer's addendum. Survival curves were obtained by applying estimated hazard ratios to parametric survival curves for interferon-α. These survival curves had been fitted to Kaplan-Meier data for investigator assessed progression-free survival for patients receiving interferon-α in the sunitinib pivotal trial as reported by Motzer et al. (2009). A comparison of the model and clinical trial results is provided in table 7.

Table 6 Effectiveness estimates used in the economic model (updated values in bold)

		Progression-free survival			Overall survival			Sources
		Estimated HR	95%CI		Estimated HR	95%CI		
IFN-α	λ	0.154			0.070			PFS: Motzer 2007 ASCO
Weibull distribution	γ	0.895			0.830			OS: TA169/Figlin 2008
HR vs. BSC	Pazopanib	0.360	0.240	0.550	**0.501**	**0.140**	**2.350**	PFS: VEGF105192 IRC scan dates **OS: VEGF105192 RPSFT weighted unadjusted model**
	IFN-α	0.704	0.580	0.854	0.799	0.674	0.948	Pooled analysis PFS: Negrier (2007), Hancock/MRC (2000) and Pyrhonen (1999) OS: Negrier (2007) , Hancock/MRC (2000), Pyrhonen (1999), Kriegmair (1995), Steineck (1990)
HR vs. IFN-α	Pazopanib	0.512	0.326	0.802	**0.627**	**0.173**	**2.269**	**Indirect comparison** **HR Pazopanib vs. BSC ÷ HR IFN-α vs BSC**
	Sunitinib	0.539	0.431	0.643	0.647	0.483	0.870	PFS: Motzer JCO 2009 (Final analysis) OS: Motzer JCO 2009 (Final analysis-patients with post-study treatment excluded.)

IFN-α: interferon-α; PFS: progression-free survival; OS: overall survival; HR: hazard ratio; BSC; best supportive care

Table 7 Summary of economic model base-case results compared with clinical data

	Pazopanib		Sunitinib		IFN-α		Best supportive care	
Outcome (months, median)	**Clinical trial result**	**Model result ¥**	**Clinical trial result**	**Model result**	**Clinical trial result***	**Model result**	**Clinical trial result****	**Model result**
Progression-free survival	11.1	11.3	11.0	10.7	4.0	5.4	2.8	5.6
Post-progression survival	11.8	16.5	15.4	16.1	5.0	10.4	20.7	6.5
Overall survival	22.9	27.8	26.4	26.8	9.0	15.8	23.5†	12.1

IFN-α: interferon-α
¥ Rank preserving structure failure time (RPSFT) method, weighted unadjusted (base case)
*from Hancock 2000. **from placebo arm of VEG105192.†not adjusted for cross over (ITT)

Estimation of costs

Costs considered in the economic model included acquisition costs for study medications, drug administration costs for infusions, costs of treating grade 3+ adverse events, routine follow-up costs, costs of progression, and supportive care costs (supportive care costs included inpatient, day case and outpatient treatments). Details of the costs can be found in tables 6.21 and 6.24, pages 194–5 of the manufacturer's original submission.

The revised economic model submitted in the addendum incorporates a straight discount of 12.5 % acquisition cost from the pazopanib list price (£74.73). Costs of study medications were adjusted using relative dose intensities reported in randomised controlled trials of the study treatments. For example in the model, it was assumed that the mean relative dose intensity of pazopanib was 0.86, equivalent to 688 mg per day per patient. Therefore, the cost of pazopanib per day was £56.24. Similar dose intensities were used for sunitinib (0.86) and interferon-α (0.84).

Only the costs of treating adverse events that were grade 3 or higher, with an incidence of at least 5%, were considered for any treatment based on the

indirect comparison. The cost per event was assumed to be independent of treatment. Assumed services and costs of treatment for grade 3+ adverse events are presented in table 6.25 on page 186 of the manufacturer's initial submission.

Utility data

Health-related quality of life measures were derived from VEG105192 using the EQ-5D questionnaires completed at weeks 8,16,24 and 48 of the follow-up period. For the model, the utility value for progression-free survival without adverse events was based on the mean EQ-5D utility value for patients who did not suffer an adverse event in VEG105192. Post-progression survival data were obtained from Remark (2008) and Parasuraman (2008) because the manufacturer considered these data to be consistent with the results of the VEG105192 and the Oxford outcomes study. Utility decrements for adverse events were also obtained from VEG105192. The manufacturer stated that as a result of the lack of published data in this patient population, a health state preference study was commissioned to generate utility values for progression-free survival and post-progression survival and disutilities for treatment-related adverse events such as anaemia, diarrhoea and fatigue.

For the model a utility value of 0.70 was assumed for patients who had no progression of disease and no adverse events, based on the mean EQ-5D utility value among patients without adverse events in the VEG105192 study. Disease progression was assumed to be associated with a decrement in utility of 15% (that is, a post-progression utility value of 0.59). These utility values are summarised in table 8. These values were used for all the interventions in the model.

Table 8 Summary of quality-of-life values used in the cost-effectiveness analysis

State	Utility value	Confidence interval	Reference	Justification
Progression free (no adverse events)	0.70	0.68 to 0.72	VEG105192	Best available estimates
Post progression	0.59	N/A	Remark (2008) Parasuraman (2008)	Best available published estimates
Utility values used in NICE technology appraisal guidance 169 ('Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma') **Sunitinib** Progression-free survival 0.77, progressive disease 0.72 **Interferon-α** Progression-free survival 0.79, progressive disease 0.69				

Results from the manufacturer's de novo economic model

Two base-case analyses were presented; one using the interim overall survival data for VEG105192 (cut-off date 23 May 2008) and another using the updated analysis of the overall survival data for VEG105192 (cut-off date 15 March 2010). The manufacturer's updated analysis also incorporated a proposed patient access scheme. Under the proposed scheme, a straight discount of 12.5% will apply at the point of invoicing from the time of positive NICE guidance (part A of the patient access scheme). The premeeting briefing summarises only the updated analysis.

The manufacturer presented disaggregated incremental quality-adjusted life years (QALYs) and costs by health states, and base-case cost-effectiveness and incremental results using the list price of pazopanib and with the 12.5% discount. A summary of the QALY gain and costs by health states for pazopanib compared with sunitinib, interferon-α and best supportive care can be found in tables 2.4 and 2.5 on page 39 of the manufacturer's addendum.

The incremental base-case cost-effectiveness results with no discount and with 12.5% discount are presented in tables 9 and 10. The manufacturer used the weighted unadjusted RPSFT estimate for the economic base case (that is, HR 0.627, pazopanib versus interferon-α). Including the 12.5% discount, sunitinib was extendedly dominated by a combination of pazopanib and interferon-α. As a result, the incremental cost per QALY gained for pazopanib versus interferon-α was £38,925 (table 10).

Table 9 Incremental base-case results without discount

	Total cost (£)	Total QALYs	Incremental cost (£)	Incremental QALY	ICERs versus baseline	Incremental analysis
BSC	4085	0.987				
IFN-α	8379	1.249	4294	0.262	16,395	16,396
Sunitinib	36,179	1.898	27,799	0.649	35,231	42,832
Pazopanib	40,441	1.966	4263	0.068	37,126	62,414
QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; BSC: best supportive care; IFN-α: interferon-α						

Table 10 Incremental base-case results with 12.5% discount

	Total cost (£)	Total QALYs	Incremental cost (£)	Incremental QALY	ICERs versus baseline	Incremental analysis
BSC	4085	0.987				
IFN-α	8379	1.249	4294	0.262	16,395	16,395
Sunitinib	36,179	1.898	27,799	0.649	35,231	extendedly dominated by pazopanib
Pazopanib	36,301	1.966	122	0.068	32,898	38,925
QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; BSC: best supportive care; IFN-α: interferon-α						

The manufacturer conducted a series of one-way deterministic sensitivity analyses which included varying:

- the hazard ratio for progression-free and overall survival for pazopanib versus interferon-α
- the cost of interferon-α administration

- the utility value for progression-free survival
- the decrement utility value for adverse events and
- the method used to adjust for the crossover (see pages 44–6 of the manufacturer's addendum).

The manufacturer provided additional cost-effectiveness analyses using alternative methods of adjusting for the crossover. The results of the analyses are presented in table 11.

Table 11 Summary of cost-effectiveness estimates for all final overall survival analyses incorporating a 12.5% discount from list price of pazopanib (see table 2.11 in addendum)

Final overall survival analysis	HR vs. IFN-α	Pazopanib			ICER (£/QALY) vs.		
		Costs (£)	LYs	QALYs	Sunitinib	IFN-α	BSC
ITT	1.264	32,099	1.581	1.071	4936†	Dominated	322,237
Cox model censored on crossover on receiving other anticancer therapy	0.801	34,676	2.503	1.616	5327†	71,648	48,638
IPCW	0.803	34,661	2.497	1.613	5139†	72,274	48,877
RPSFT weighted unadjusted*	**0.627**	**36,301**	**3.097**	**1.966**	**1790**	**38,925**	**32,898**
RPSFT unweighted adjusted	0.388	39,689	4.335	2.697	4394	21,625	20,824
No post-study therapy	0.476	38,241	3.806	2.385	4238	26,293	24,438

HR: hazard ratio; IFN-α: interferon-α; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; LYs: life years; BSC: best supportive care; ITT: intention-to-treat; IPCW: inverse probability of censoring weighted analysis; RPSFT: rank preserving structure failure time

***** Base-case analysis

†Comparator is more costly and more effective than pazopanib. Ratio is cost effectiveness of comparator versus pazopanib.

The results of the sensitivity analyses showed that the key drivers of cost effectiveness were the efficacy estimates for pazopanib versus interferon-α, which contribute to the relative efficacy of pazopanib and sunitinib.

Specifically, the model is sensitive to the method used for adjusting for crossover for overall survival data from VEG105192.

Results of the manufacturer's probabilistic sensitivity analyses incorporating a 12.5% discount are summarised on pages 47–50 of the manufacturer's addendum.

The manufacturer indicated that the results of these analyses suggested that there was a high degree of uncertainty about the incremental costs and benefits of pazopanib compared with sunitinib. There was relatively less uncertainty about the incremental costs and benefits of pazopanib compared with interferon-α or best supportive care. In the pairwise comparisons, given a threshold value of cost effectiveness of £30,000 per QALY gained, there was a 54% probability that pazopanib was preferred to sunitinib, a 40% probability that pazopanib was preferred to interferon-α, and a 47% probability that pazopanib was preferred to best supportive care. In the incremental analysis (that is, multiway comparison), given a threshold of £30,000 per QALY gained, there was a 41% probability that pazopanib was preferred, a 6% probability that sunitinib was preferred, a 48% probability that interferon-α was preferred, and a 6% probability that best supportive care was preferred. Changes in monitoring costs, the cost of treating adverse events and utility values had little impact on cost effectiveness. A similar pattern was seen for comparisons of pazopanib with interferon-α and best supportive care.

In addition to providing cost-effectiveness estimates incorporating a 12.5% discount (part A of the proposed patient access scheme) the manufacturer also provided incremental analysis for cost-effectiveness results if pazopanib does not meet the terms of the conditional marketing authorisation (part B of the proposed patient access scheme). Under part B of the proposed access scheme, [redacted], the manufacturer has proposed a patient access scheme that will provide a rebate and subsequent list price reduction.[redacted]

[redacted]

Table 12 [redacted]

	Total cost (£)	Total QALYs	Incremental cost (£)	Incremental QALY	ICERs versus baseline	Incremental analysis
Best supportive care	[redacted]	[redacted]				
IFN-α	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sunitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pazopanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						

3.2 Evidence Review Group comments

The ERG noted that the evidence base was not ideal for this appraisal as there are currently no data from head-to-head comparisons of pazopanib with sunitinib or interferon-α.

However, the ERG commented that the choice of model appeared to be appropriate given the decision problem and the data available. The time horizon appeared to be appropriate, although there are some concerns that it may overestimate survival, as the median age of diagnosis is 60–65 years and constant all-cause mortality was assumed, rather than taking data from life tables which would have the impact of mortality increasing over time. The ERG stated that the results appeared valid in terms of the methods used. Most of the model analyses performed could be replicated, however this was not true for all sensitivity analyses.

One major concern that the ERG had with structural uncertainty was with the hazard ratios used to estimate the cost effectiveness and in particular with the way the crossover data were handled. In the manufacturer's original submission the base-case analysis was based on the estimates from the model using the RPSFT method to adjust for crossover and pooled interferon-α studies. In the updated analysis (addendum) the method used for adjusting for crossover was the weighted RPSFT method, unadjusted. The ERG acknowledged that the manufacturer had presented a set of analyses which comprehensively covered the range of methodologies available to adjust for crossover. However, the ERG stated that care should be taken when assessing trials that have used relatively new methods because there is no consensus on the best approach to use and these methods still require further development.

The ERG also highlighted a concern about the manufacturer's assumption that as soon as a patient's disease progressed they stopped treatment. The ERG considered that in practice, it is unlikely this will happen immediately

because the patient will only know the status of their disease when they have their next review, which may not be at the exact time the disease progresses. This assumption may create a small bias in favour of the more costly treatments such as pazopanib.

The ERG also stated that there was some uncertainty around the utility value estimate used. The estimate used by the manufacturer was based on the EQ-5D utility value among all patients without adverse events in VEG105192. This value was also assumed to be similar for all interventions.

ERG's exploratory analyses

The ERG undertook additional exploratory analyses on the revised economic model submitted with the manufacturer's addendum submission, taking into account the proposed 12.5% discount on the pazopanib list price. Full details of the exploratory analysis can be found in section 6.14 pages 105–18 of the ERG report.

To address concerns with the weighted unadjusted RPSFT results for overall survival being used for the base-case analysis, the ERG undertook exploratory analyses to assess the potential impact of a robust weighted analysis on the results, particularly with a model adjusted for baseline covariates, for which methods are still in development. The ERG considered the impact of weighting by comparing the unweighted analyses with the weighted analyses when the models were unadjusted for baseline. This was done by examining the p-value distribution plots from the log-rank tests in the RPSFT analyses. For further details of the analysis undertaken by the ERG, see pages 103–5 of the ERG report. The ERG concluded from the analysis that overall it seems clear that weighting does have an impact on the hazard ratio, but it is difficult to establish the direction and magnitude of this effect.

The ERG also performed one-way sensitivity analysis around the progression-free and overall survival estimates. This was done by varying the hazard

ratios estimates for pazopanib from 0.3 to 1 in 0.05 increments. The ICERs were sensitive to the overall survival hazard ratios (see figure 6.4, page 108 of the ERG report). For both interferon-α and best supportive care the ICER increased as the hazard ratio increased. However, for sunitinib the ICER decreased as the hazard ratio increased until it reached 0.65, at which point pazopanib dominated sunitinib. As the hazard ratio increases from 0.65 the ICER value represents the cost effectiveness of sunitinib versus pazopanib, because pazopanib costs less and is less effective than sunitinib. The ICERs were also sensitive to changes in progression-free survival (see figure 6.5, page 109 of the ERG report). For both interferon-α and best supportive care the ICER decreased as the hazard ratio increased. However, for sunitinib the ICER was above £100,000 when the hazard ratio was 0.3 and decreased quickly until the hazard ratio increased to 0.55, at which point pazopanib dominated sunitinib.

The ERG undertook multiway sensitivity analyses around the cost estimates by increasing and decreasing the costs associated with treatment initiation, administration, other costs of progression-free survival, post-progression survival and adverse events by 50%. This analysis indicated the lack of sensitivity of the results to changes in cost other than the cost of pazopanib and sunitinib.

The ERG also undertook multiway sensitivity analyses around the utility estimates for progression-free survival, utility decrement for progression and duration of utility with adverse events. The full results of the multi-way sensitivity analysis performed on the utility values can be found in table 6.2, page 107 of the ERG report.

The ERG also undertook multiway sensitivity analysis combining:

- increase in cost, decrease in utility, increase in time horizon, increase in discount rate with a hazard ratio for overall survival of 0.6, 0.7 and 1

- decrease in cost, increase in utility, decrease in time horizon, no discount rate with hazard ratio for overall survival of 0.4 and then 0.3.

The results of the sensitivity analyses can be found in tables 6.7 and 6.8 on pages 113–4 of the ERG report.

Because the manufacturer only reported pairwise probabilistic sensitivity analysis, the ERG took the base-case work and, using net benefit, compared all four options. An additional net benefit approach analysis was performed excluding interferon-α, because the ERG considered that there may be some doubt about the relevance of this treatment to current practice. The analysis showed that up to a cost per QALY gained threshold of approximately £15,000, best supportive care was likely to be cost effective. Between a cost per QALY gained threshold of £15,000 and £35,000, interferon-α was most cost effective and beyond that threshold and at least up to £50,000 per QALY gained, pazopanib was most likely to be considered cost effective. However apart from best supportive care, when the cost per QALY gained threshold was less than £10,000, no treatment had much more than a 50% chance of being cost effective. Excluding interferon-α resulted in pazopanib being most likely to be cost effective when the cost per QALY gained threshold was above £30,000.

The ERG highlighted that the probabilistic sensitivity analyses had essentially taken the base-case analysis at face value. The uncertainties highlighted by the ERG in terms of the technique used to deal with cross over and the point estimates of relative effectiveness derived from the indirect comparison extends into consideration of the distributions associated with the various input parameters The ERG stated that it had not been possible to explore this uncertainty with additional probabilistic analyses because of the limited data available for some parameters.

4 Equalities issues

No major equality issues were raised during the scoping process. The consultees suggested discussions should take into account that renal cell carcinoma is an orphan disease. However, rarity of a disease does not provide a basis to use equality issues to justify treatment.

Technology Appraisal, No. 169, March 2009. 'Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma' Recommendation 1.2 states when using ECOG performance status score, clinicians should be mindful of the need to secure equality of access to treatments for people with disabilities. Clinicians should bear in mind that people with disabilities may have difficulties with activities of daily living that are unrelated to the prognosis of renal cell carcinoma. In such cases clinicians should make appropriate judgements of performance status taking these considerations into account.

5 Authors

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Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A The Evidence Review Group (ERG) report for this appraisal was prepared by Aberdeen Health Technology Assessment Group:

- Kilonzo M et al. Pazopanib for the first line treatment of patients with advanced and/or metastatic renal cell carcinoma: A Single Technology Appraisal. September 2010.

B Submissions or statements were received from the following organisations:

I Manufacturer/sponsor:

- GlaxoSmithKline

II Professional/specialist, patient/carer and other groups:

- James Whale Fund
- Kidney Cancer UK
- NHS Waltham Forest
- Royal College of Nursing
- Royal College of Physicians

C Additional references used:

None.

Appendix B: Related NICE recommendations

Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma. NICE technology appraisal guidance 169 (March 2009)

1.1 Sunitinib is recommended as a first-line treatment option for people with advanced and/or metastatic renal cell carcinoma who are suitable for immunotherapy and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

1.2 When using ECOG performance status score, clinicians should be mindful of the need to secure equality of access to treatments for people with disabilities. Clinicians should bear in mind that people with disabilities may have difficulties with activities of daily living that are unrelated to the prognosis of renal cell carcinoma. In such cases clinicians should make appropriate judgements of performance status taking these considerations into account.

1.3 People who are currently being treated with sunitinib for advanced and/or metastatic renal cell carcinoma but who do not meet the criteria in 1.1 should have the option to continue their therapy until they and their clinicians consider it appropriate to stop.

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 (August 2009).

1.1 Bevacizumab, sorafenib and temsirolimus are not recommended as first-line treatment options for people with advanced and/or metastatic renal cell carcinoma.

1.2 Sorafenib and sunitinib are not recommended as second-line treatment options for people with advanced and/or metastatic renal cell carcinoma.

1.3 People who are currently being treated with bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for advanced and/or metastatic renal cell carcinoma should have the option to continue their therapy until they and their clinicians consider it appropriate to stop.